



Improving Pediatric Trials in Antibacterial Drug Development: No Sick Child Left Behind

Multi-Stakeholder Expert Meeting

Summary of the Meeting held April 5, 2016

Sheraton Silver Spring Hotel
8777 Georgia Avenue | Silver Spring, Maryland

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

Meeting materials, including agenda, participant list, and presentations, are available on the Clinical Trials Transformation Initiative (CTTI) website at: <https://www.ctti-clinicaltrials.org/improving-pediatric-trials-in-antibacterial-drug-development-no-sick-child-left-behind/>

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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.

MEETING BACKGROUND

Pediatric patients should have access to antibacterial drugs that have undergone appropriate evaluation for safety and efficacy. Antibacterial drug development programs should include pediatric studies when pediatric use is anticipated. Although legislation such as the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) have been enacted to facilitate pediatric drug development, many of the antibacterial drugs commonly used to treat children still lack adequate pediatric use information in drug labeling for all of the age groups. This is particularly true for the neonatal age group. In addition to economic disincentives, even for those sponsors who wish to comply and study drugs in children, trials have been very difficult to enroll and complete. When pediatric studies have been completed, the interval from approval in adults to updating labeling for the pediatric population can be as long as 5 years, and a number of antibacterial drugs have yet to complete pediatric studies more than 5 years post approval. The goal of this CTTI Antibacterial Drug Development Program (ABDD) project is to identify and address barriers/challenges in conducting antibacterial drug trials in neonates and children with a focus on enrollment, clinical trial design/conduct and feasibility issues (see [CTTI Pediatric Trials in Antibacterial Drug Development](#) for the project plan and other background materials). In that regard, a multi-stakeholder project team was convened and after collecting data from a literature review, focus groups and interviews with stakeholders, an expert meeting was held on April 5, 2016 to obtain feedback and generate recommendations.

MEETING EXECUTIVE SUMMARY

The **legal/regulatory** framework for pediatric development in the US and European Union (EU) was discussed by representatives from the Food and Drug Administration (FDA) and European Medicines Agency (EMA). Elements of the 2002 Best Pharmaceuticals for Children Act (BPCA) and 2003 Pediatric Research Equity Act (PREA) and aspects of pediatric labeling were highlighted. See *Table 1* for an outline of US Pediatric Legislation and Regulation. See also links below to pertinent FDA, EMA and International Conference on Harmonization (ICH) guidance.¹

¹ See additional information regarding pediatric product development at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm> and http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp and the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Clinical Investigation of Medicinal Products in the Pediatric Population. ICH 11 is being updated, see link at <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/clinical-investigation-of-medicinal-products-in-the-pediatric-population.html>.

Meeting agenda and presentations can be viewed at <https://www.ctti-clinicaltrials.org/briefing-room/meetings/improving-pediatric-trials-antibacterial-drug-development>. Included is information about the methodology utilized and summaries of interviews and surveys done with key clinical trial enterprise stakeholders including parents and caregivers, community providers, investigators and pharmaceutical industry staff involved in pediatric clinical development programs. Barriers to implementing pediatric clinical trials were identified, as well as ethical, logistical and protocol-related issues ([CLICK HERE](#) to view data set slides). In addition, in order to characterize the **landscape**, a review was conducted of pediatric antimicrobial drug trials in ClinicalTrials.gov utilizing the Aggregate Analysis of Clinical Trials.gov ([AACT](#)) database.² This database was then compared with pediatric studies submitted to the FDA with attention to studies conducted to satisfy BPCA requests and PREA commitments. Presentations were also made regarding **sustainable clinical trial infrastructure and networks** and the value added by initiatives such as the global Pediatric Trials Consortium ([PTC](#)) and the International Neonatal Consortium ([INC](#)); Pediatric Trials Network ([PTN](#)) and the EU's Global Research in Pediatrics ([GRiP](#)); the Paediatric European Network for Treatment of AIDS – Infectious Disease (PENTA-ID) which is part of the Innovative Medicines Initiative's (IMI) Combatting Bacterial Resistance in Europe ([COMBACTE](#)) program; and the European Network of Paediatric Research at the EMA ([EnprEMA](#)).

Major themes and issues discussed in open sessions and later in meeting breakout groups are included below. Considerations are provided and where consensus was achieved, draft recommendations will be developed.

1) Ethical considerations that apply to this vulnerable population and suggestions on how to improve recruitment, the informed consent process, and retention were discussed.

- **How to assist parents contemplating study participation for their child:**
 - Design questions that could be used during the informed consent (IC) process to help empower parents (who may feel overwhelmed) to get the information they need to better understand and frame the decision to participate in the clinical trial (e.g., include a “Frequently Asked Questions” resource).
 - Apply “reasonably available” criteria to obtaining informed consent when one parent is not physically present.³ Also consider using other methods of communication (e.g., telephone) to get IC from the parent who is not physically present.
 - Consider offering an online resource about the disease and clinical trials since the internet can empower parents seeking information to guide decisions.
 - Find parents to contact (e.g., using social media), who can share their experience of having a child enrolled in a clinical study, in order to facilitate peer-to-peer communication about the benefits and risks of clinical trial participation.

² See also http://www.ctti-clinicaltrials.org/files/State_of_Clinical_Trials/AACT-Background-2016-03-10.pdf.

³ See the [Draft Guidance: Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors](http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm) at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm>.

- Look for ways to enhance and improve “shared decision-making” about participating in a study. Have available an independent advocate with whom parents could discuss issues about clinical trial participation.
 - Explore whether better education of the public and outreach about the basics of clinical research and informed consent could add value.
 - Consider more interviews with parents whose newborn child went directly to the NICU and consider doing more focus group work with children down to age 7 years who have participated in trials to get their perspective.
- **How to assist clinical study staff conducting the trial:**
 - Improve the timing of the Informed Consent discussion in sensitive situations where the child is critically ill.
 - Provide recommendations regarding tools to improve the informed consent process (e.g. electronic informed consent, [CTTI's Informed Consent Recommendations and Tools](#)).
 - Create and provide sensitivity training; avoid “down-delegating” the informed consent process to inexperienced or peripheral personnel. Task persons with greater expertise in sensitivity and attributes necessary to good communication with parents (good interpersonal skills) to obtain informed consent. Explore the institution’s willingness to build infrastructure and provide adequate salary support for such personnel.
 - Encourage role playing/training (incorporating video feedback) as an approach to “rehearsing” approaching parents and obtaining consent; use experienced coordinators and patient advocates to forge effective approaches. Obtain feedback on the informed consent and recruitment processes.
 - Explore use of role-playing, electronic tools, and the use of video to explain to children what is involved when participating in a clinical study.

2) Clinical trial design and conduct issues, including safety data collection and pharmacokinetic studies, were discussed.

There was consensus that:

- Simultaneous enrollment of all age groups above two years may be possible, based on the safety profile of the class, safety data in adults, and toxicology data in juvenile animals.
 - Sequential enrollment should be done in children under two years.
- When efficacy in children can be extrapolated based on the demonstration of efficacy in adults, safety and pharmacokinetic (PK) studies should not exclude the collection of efficacy endpoints, but these may not necessarily have to be collected at the same time-points or at the same frequency as the endpoints in adult efficacy trials.
 - Some exclusion criteria needed for a non-inferiority trial to demonstrate efficacy, such as limiting prior antibacterial drug treatment, may not be necessary in the pediatric setting.
- Sparse sampling and population opportunistic PK (Pop-PK) sampling is acceptable.
- Sponsors suggested that in some cases, pediatric PK trials could begin simultaneously with phase 3 trials in adults.

3) Challenges in antibacterial drug development for Neonates

Consensus among pediatricians is that knowledge of cerebrospinal fluid (CSF) penetration is very important for the treatment of sick neonates, but the reality is that many antibacterial drugs used in clinical practice are lacking CSF penetration data.

- There is a rabbit model of meningoencephalitis, but additional validation work may be needed.
- A CSF opportunistic sampling sub-study could be done at sites participating in a larger study. Patients could be enrolled in the sub-study when a lumbar puncture is being done for clinical reasons.
- There is also value in sampling ventricular reservoirs; this could be done perhaps via a single dose study in these infants and, if done in a study network, the efficiency could be enhanced.
- It is unclear whether FDA issuing a Pediatric Written Request for neonatal CSF data would be helpful – some thought it might be helpful if the request was also part of an EMA Pediatric Investigational Plan (PIP). There was no consensus on whether CSF data was critical for neonatal labeling going forward, but it is certainly desirable.
- It could be helpful to standardize adverse event (AE) reporting and approaches to capturing common AEs such as the “morbidity of prematurity” (e.g. seizures). Sample size considerations for safety will depend on the drug, whether the drug is first in class, and any safety issues in adult studies. Comparative arm studies are desirable, but the tradeoff is that fewer neonates will be exposed to study drug. A focus on adverse events that are plausibly related to study drug might be helpful.
- In the few successful examples of master protocols, an independent group takes the lead and sponsors participate during the time their investigational drug is being studied. Questions about ownership of data have been resolved in the oncology and other settings. A Biomedical Advanced Research and Development Authority (BARDA) Request for Information (RFI)⁴ has prompted ongoing discussions in the context of adult trials.⁵ Nimbleness and efficient administrative structure will be important.
- Regarding whether neonates should be enrolled at the same time as older children in PK trials or only after safety/PK is assessed in older children:
 - Concurrent enrollment seems very reasonable if the drug class is one with which physicians have substantial experience. There may be concerns with a new drug class, particularly if there were safety concerns in adults.
- Regarding whether PK trials should be single or multiple dose in neonates:
 - From a clinical pharmacology perspective, it is desirable to conduct a single dose PK trial first and then follow up with a multiple dose study with sparse PK sampling per subject. Multiple samples per individual neonate will be

⁴ For more information, see the [Clinical Trial Network for Antibacterial Drugs RFI](https://www.fbo.gov/index?s=opportunity&mode=form&id=c49bbf90a77767a69c9cdf148879f711&tab=core&_cview=0) at

https://www.fbo.gov/index?s=opportunity&mode=form&id=c49bbf90a77767a69c9cdf148879f711&tab=core&_cview=0

⁵ See the University of Maryland School of Pharmacy [Pediatric Master Protocols Meeting Agenda and Video Recordings](http://pharmacy.umaryland.edu/centers/cersievents/master-protocols/agenda/) at

<http://pharmacy.umaryland.edu/centers/cersievents/master-protocols/agenda/> and [Innovations in Breast Cancer Drug](http://www.fda.gov/downloads/Drugs/NewsEvents/UCM423368.pdf)

[Development – Next Generation Oncology Trials](http://www.fda.gov/downloads/Drugs/NewsEvents/UCM423368.pdf) available at

<http://www.fda.gov/downloads/Drugs/NewsEvents/UCM423368.pdf>.

helpful to evaluate the intra- and inter-individual variability at different time points.

4) Labeling:

A final theme centered on optimizing labeling information. In addition to including as much high-quality data as possible, educational efforts may be needed to ensure that both patients and providers understand how to read, interpret, and find specific information in labeling. There was also a question regarding whether it was possible to include dosing information in labeling based on PK studies for pediatric age groups *prior to completion of safety studies* in situations where efficacy can be extrapolated or if this might be seen as a “back door” or implied indication. FDA representatives acknowledged that this was a complex scenario and noted that if a product is not approved for a pediatric indication, PK data from pediatric subjects will not be included in the dosing and administration information (label section 2). However, depending on the product and the information available for FDA review, the PK data may be added to other sections of the label. Please see FDA guidance regarding placement and content of pediatric information in human prescription drug and biological products labeling when available data do not support a pediatric indication (i.e., data are negative or inconclusive).⁶

Recommendations and Next Steps:

Further explore the challenges and issues related specifically to antibacterial drug development for the neonatal population in an FDA-sponsored workshop. Develop consensus working group recommendations to improve the design and conduct of antibacterial trials for pediatric and neonatal populations. These recommendations will be reviewed by the CTTI Executive Committee, and once endorsed, can be disseminated to stakeholders and the community.

MEETING SUMMARY

Welcoming Remarks

Introduction to the Clinical Trials Transformation Initiative (CTTI)

Jamie Roberts (for Pamela Tenaerts), CTTI

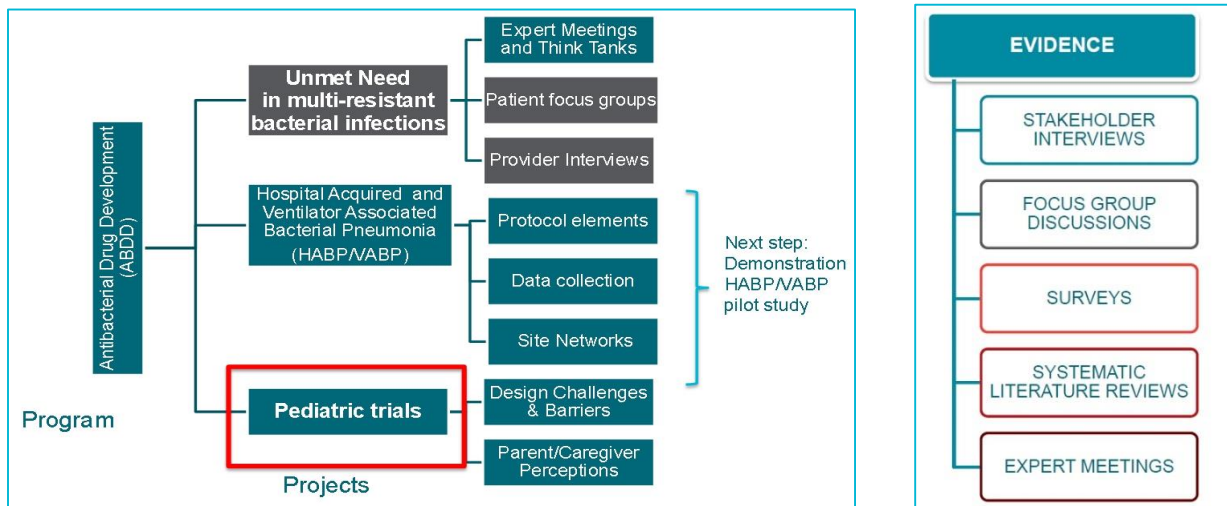
CTTI Project Manager, Jamie Roberts, welcomed the meeting participants on behalf of Director Dr. Pamela Tenaerts and provided a [brief overview of CTTI](#), including the key elements of the group’s approach:

- 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; and
- Create and share knowledge, tools & resources to facilitate change that improves clinical trials.

⁶ See FDA [Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling \(Good Review Practice/Labeling\)](#), February 2013 available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf>

CTTI projects⁷ are focused on creating actionable, evidence-based, consensus-driven recommendations that are designed to improve the conduct of clinical trials by accelerating trial startup activities, leveraging new technologies for improved efficiency, enhancing trial quality without adding undue burdens, and identifying streamlined strategies for meeting regulatory requirements. CTTI's projects are characterized by a distinct methodological approach:

1. Identify research impediments
2. Identify gaps and barriers
3. Analyze and interpret findings
4. Develop recommendations and tools
5. Disseminate and implement findings and recommendations



CTTI's Evidence-Based Approach

CTTI projects employ both quantitative and qualitative methods (including interviews, focus groups, surveys, systematic literature reviews, and expert meetings) according to how well-suited they are for a given project's objectives. The essential aims are to:

- Identify or describe a phenomenon to gain a better understanding of it; and
- Move beyond individual views and opinions to a more complete, objective understanding of the incentives and disincentives for change.

Once data have been gathered and analyzed, CTTI project groups challenge assumptions, identify barriers, and develop recommendations and tools designed to change the ways people think about and conduct clinical research.

CTTI Antibacterial Drug Development (ABDD) Program

Increasing antibacterial resistance, particularly of multidrug-resistant (MDR) pathogens, and a corresponding shortfall in new agents capable of treating MDR infections, represent a serious and growing public health problem. In partnership with the FDA, CTTI is working to improve capacity to respond to a number of different facets of this issue through its [Antibacterial Drug](#)

⁷ Clinical Trials Transformation Initiative website. Mission statement. Available at: <http://www.ctti-clinicaltrials.org/who-we-are/mission>. Accessed March 28, 2016.

[Development Program](#), including by addressing improvements in the design and conduct of [pediatric ABD trials](#).

Background

Under the Pediatric Research Equity Act (PREA),⁸ new drug applications (NDAs) and biologics licensing applications (BLAs) (or supplements to applications) 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 with PREA, most antibacterial drug (AB) developers are required to conduct pediatric trials to determine dosing, efficacy, and safety in children. However, designing and conducting such trials in children and neonates presents significant challenges:

- Estimating a dose regimen for children based solely on the pharmacokinetics (PK) of a drug in adults can result in inappropriate dosing.
- Clinical trials involving children are generally more difficult to complete than adult trials.
 - Typically have smaller sample sizes and thus smaller effect size,
 - Small sample sizes raise concern about the robustness of the conclusions, and
 - More difficult to conduct due to ethical considerations and challenges in obtaining parental consent.

There is a need to identify **scientific and operational challenges in clinical trial conduct in pediatric antibacterial trials**.

Project 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 antibacterial drug trials performed under Best Pharmaceuticals for Children Act (BPCA)⁹ or PREA.

Project 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, and
 - 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 ABD trials, achieved through:

⁸ Pediatric Research Equity Act. Available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf>. Accessed May 5, 2016.

⁹ Food and Drug Administration Amendments Act of 2007. Title V – Best Pharmaceuticals for Children Act. Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf>. Accessed May 5, 2016.

- Better design and conduct,
- More efficient enrollment, and
- Increased compliance with BPCA and PREA.

Specific Meeting Objectives

- Present findings from data gathered over previous year,
- Identify any remaining gaps that may require deeper dives,
- Obtain feedback on draft considerations that may be developed to improve the successful conduct and execution of pediatric antibacterial clinical trials, and
- Develop initial consensus on mechanisms that can improve the conduct and execution of pediatric antibacterial clinical trials.

Session I: The Challenge

Facilitator: John Bradley, MD; Rady Children's Hospital; University of California, San Diego

Dr. Bradley provided an overview of the current landscape of ABDD for pediatric applications from the perspective of an academic infectious disease specialist. He noted that ABDD has changed markedly since the 1970s and 1980s, an era when multiple cephalosporins were being evaluated and antibiotic clinical trial design was far less sophisticated and clinical trials easier to conduct. Since that time, ABDD has become increasingly sophisticated and difficult, but the challenges presented for drug development in neonates, infants and children are especially profound and create different sets of issues.

Addressing the Challenges of Antibacterial Drug Development

Edward Cox, MD, MPH; FDA, CDER

Trials typically involve patients with acute illness and diagnostic uncertainty, and are difficult scientifically and operationally. In addition, the economics of ABDD in particular are not attractive for the pharmaceutical industry. Issues of stewardship add further complexity, as do the challenges of obtaining informed consent/assent from parents/guardians and children. Despite these problems, the field has made significant progress in the last decade and a half. The field has worked through significant issues in clinical trial design, and collaborative groups such as CTTI are important to achieving workable solutions. One key to further progress is getting a clear understanding of the breadth of ideas in the field and the challenges faced in implementing them—working from the evidence to get to viable solutions. One of our current challenges is the time gap between initial study approval and study completion in pediatric clinical trials. It is important to set realistic goals and see if we can narrow the gap between the time that drugs are approved in adults and time that information is available to guide pediatric use.

Pediatric Product Development in 21st Century

Lynne Yao, MD; FDA, CDER

Dr. Yao provided an overview of the laws and regulations (see Table 1) governing pediatric drug development in the current era, beginning by outlining a pair of general principles that apply to pediatric therapies:

1. Pediatric patients should have access to products that have undergone appropriate evaluation for safety and efficacy; and

2. Medical product development programs should include pediatric studies when pediatric use is anticipated.

Laws Affecting Pediatric Drug Development

In 1938, the Federal Food Drug and Cosmetic Act was passed. [Table 1](#), below, is provided as a summary outline of U.S. pediatric legislation and regulation.

Table 1 Laws Affecting Pediatric Drug Development

Year	U.S. Pediatric Legislation & Regulation	Highlights: Labeling, Modernization, Rules, Carrots, Sticks, Reauthorizations, Exclusivities, Safety and Innovations
1994	Pediatric Labeling Rule	Requires manufacturers to survey existing pediatric data and add labeling and introduced “pediatric extrapolation”.
1997	Food Drug and Modernization Act (FDAMA)	1 st incentive program for pharmaceutical companies to conduct pediatric studies on drugs to receive an additional 6 months of market exclusivity and created the Written Request (WR) process
1998	Pediatric Rule	1 st requirement for manufacturer to conduct pediatric studies in certain drugs. The "Rule," effective April 1, 1999, modified 21 CFR Parts 201, 312,314, and 601.It specifies "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients." Sunset date was 2002.
2002	Best Pharmaceuticals for Children Act (BPCA)	BPCA provides an incentive (the “Carrot”). Re-authorized FDAMA incentive program for companies to conduct pediatric studies on drugs and receive additional exclusivity. BPCA also provided a mechanism for study of off-patent drugs. NIH was directed to establish a program for pediatric drug development through Section 4091(a) and (b) of the Public Health Service Act and establish a Priority List of drugs needing study. The goal of this initiative is to help provide pediatric labeling for off-patent drugs or for drugs for which a WR was issued and declined by the sponsor.
2003	Pediatric Research Equity Act (PREA)	PREA is the “Stick” and applies to Drugs and Biologics. Section 505b of Federal Food, Drug and Cosmetic Act requires companies to assess safety and effectiveness of certain products in pediatric patients if application is for a new indication, new dosing regimen, new active ingredient including a new combination, new dosage form or new route of administration. Not subject to PREA are products granted orphan designation for that indication and devices are not subject to PREA (see below <i>Title III FDAAA 2007</i>).
2007	FDA Amendments Act (FDAAA)	Reauthorized BPCA and PREA, required that Labeling include information on pediatric studies and whether or not studies demonstrated safety or efficacy and if studies were inconclusive in pediatric populations, NIH may submit a Proposed Pediatric Study Request (PPSR) to initiate the WR process and NIH mandated to update the Priority List of needs in pediatric therapeutic areas every 3 years. Devices for use in children now included with drugs/biologics for children.

2010	Patient Protection and Affordable Care Act (ACA) ¹⁰	Includes biosimilars and adds 6 months of Pediatric Exclusivity for biologics .
2012	Food Drug Administration Safety and Innovation Act (FDASIA)	Permanent reauthorization of PREA and BPCA , enforcement/deferral extensions (DE) and Pediatric Study Plan (PSP) requirements outlined.

Best Pharmaceuticals for Children Act (BPCA) & Pediatric Research Equity Act (PREA)

The BPCA provides financial incentives for sponsors to voluntarily conduct pediatric studies. BPCA also provides a mechanism for study of off-patent drugs. The FDA and the National Institutes of Health (NIH) partner to obtain data to support pediatric labeling for products used in pediatric patients. Please see [Table 1](#) and this [link](#) for additional details regarding the BPCA off-patent process.¹¹

PREA requires sponsors to assess the safety and effectiveness of products in pediatric patients if an application is for a new indication, new dosing regimen, new active ingredient including a new combination, new dosage form or new route of administration. Importantly, PREA and BPCA do not provide for a different evidentiary standard for approval in children compared to adults. However, there are special considerations related to pediatric drug development that must often be addressed, including ethical and feasibility issues. Under certain circumstances, adequate and well-controlled trials may not be needed to provide substantial evidence of effectiveness to support approval of a product in children. The use of pediatric extrapolation of efficacy from adequate and well-controlled data in adult populations may be considered. However, even when pediatric extrapolation is acceptable, dosing and safety information must be collected. There has been progress in pediatric product development: as of 2016, with greater than 600 products that now include pediatric-specific labeling. Remaining challenges for the 21st century include:¹²

- **Pediatric-specific diseases.** There is a desperate need for product development for neonatal indications. Only 35% of products used in the neonatal intensive care unit (NICU) are approved by the FDA (out of 409 drugs with pediatric-specific labeling changes from 1997-2010, only 28 included information on use in neonates).
- **Information on long-term safety of therapeutics.** A number of initiatives, programs and networks are working to fill these gaps. These include the ADEPT (Adapting the Development of Pediatric Therapeutics) public workshops¹³ sponsored by the FDA, which are exploring the long-term safety of pediatric therapies, as well as initiatives underway through CTTI, Critical Path (International Neonatal Consortium “INC”, Pediatric Trials Consortium “PTC”), and the European Union’s [Global Research in Pediatrics \(GRiP\)](#) network. There are also international collaborations, such as the

¹⁰ The Affordable Care Act, Section by Section at <http://www.hhs.gov/healthcare/about-the-law/read-the-law/>. See also the Biologics Price Competition and Innovation Act (BPCIA) which was included in the PPACA (PL111-148) <https://www.dpc.senate.gov/healthreformbill/healthbill27.pdf>.

¹¹ NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development Best Pharmaceutical for Children Act at <https://bpcanichd.nih.gov/clinical/Pages/index.aspx>

¹² See the Pediatric Trials Consortium at <https://c-path.org/programs/inc/> and the International Neonatal Consortium at <https://c-path.org/programs/ptc/>

¹³ For example, see: <http://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm477639.htm>

monthly [Pediatric Cluster](#) Conferences (co-sponsored by the FDA, the European Medicines Agency, and other national regulatory agencies) and the International Council on Harmonisation's ICH E11 pediatrics addendum.¹⁴

- **Improving efficiency of pediatric clinical trials.** Now that we know we can get pediatric trials done, how can they be done efficiently? Dr. Yao noted that children are protected *through* research, not from it, and that there needs to be commitment and collaboration across the community of stakeholders to increase availability of safe, effective therapeutics for children. She also emphasized that the FDA is committed to working with external stakeholders to improve the efficiency of clinical trials.

Pediatric Trials Consortium – Public-Private Partnerships to Support Pediatric Trials

Ed Connor, MD, MBE; Critical Path Institute

Dr. Connor began by noting the impressive history of legislation and regulatory efforts aimed at encouraging or mandating clinical research to support pediatric indications, including the FDA Modernization Act ([FDAMA](#)), ICH Harmonised Tripartite Guideline-Clinical Investigation of Medicinal Products in the Pediatric Population ([ICH E11](#)),¹⁵ BPCA, PREA, EU pediatrics regulations, the FDA Amendments Act ([FDAAA](#)), and the FDA Safety and Innovation Act ([FDASIA](#)). He remarked that given such a significant body of regulatory effort, the onus was on the pediatric research community to ensure that the necessary research gets done. Dr. Connor noted that substantial progress has been made in creating pediatric labeling, with 608 new labels created since the enactment of BPCA and PREA. However, significant gaps remain: over 50% of available therapeutics lack pediatric labeling and more than 90% have not been studied at all in neonates.

Key Issues to Move Trials Forward

The following major issues currently affect attempts to conduct more efficient, clinical trials to support pediatric use:

- Multiple age-based population segments (with potentially significant differences across age cohorts) create obstacles from the perspective of accruing adequate trial populations—how many populations are there?
- How do we go about creating and incentivizing child-friendly drug formulations?
- Due to restrictive enrollment criteria, many pediatric clinical trials see fewer enrollment per site compared with adult trials (averaging 1-2 enrollments per site per year).
- Compared with adult trials, time to study start-up is longer on average (6-8 months) and trial operational costs are higher.

¹⁴ ICH Harmonised Tripartite Guideline. Clinical investigation of medicinal products in the pediatric population. E11. Step 4 version, 20 July 2000. Available at:

<http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106621.htm>. Accessed May 2, 2016.

¹⁵ See European Medicines Agency Paediatric medicines: Overview at

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp and

ICH Harmonised Tripartite Guideline. Clinical investigation of medicinal products in the pediatric population. E11. Step 4 version, 20 July 2000. Available at:

<http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106621.htm>.

Developing Sustainable Practices and Infrastructure

The pediatric trials community needs to focus on developing sustainable infrastructure for conducting pediatric clinical research, as opposed to going to the effort and expense of creating trial-specific or disease-specific infrastructure and then dismantling it at trial's end. The pediatric trials community needs validated endpoints, but there is currently a disconnect among what sponsors, regulators, and academics want and need in this regard, and getting the approach right on the first attempt is important to overall success. We have to find ways to solve each of these problems on an individual basis; the focus now needs to turn to institutionalizing this knowledge and sustaining it across multiple projects, and awareness and commitment are key. We have seen recent progress, but the enterprise as a whole still struggles in many respects. We also need awareness of and commitment to this kind of work, including “buy-in” from the academic community.

The Pediatric Trials Consortium

Following the landmark American Academy of Pediatrics (AAP) forum,¹⁶ the community has turned attention toward improving the system through a shared new vision of trial infrastructure and established a global pediatric clinical trials network. The Critical Path Institute ([C-Path](#)) established a Pediatric Trials Consortium ([PTC](#)) to catalyze such an initiative. C-Path, which was created as a public-private partnership ([PPP](#)) with the FDA, has gained significant expertise in creating trusted neutral forums for convening stakeholders, and over the past 10 years has created a dozen global consortia.

The PTC is committed to enabling the creation of sustainable solutions that assure timely, efficient evaluation of innovative drugs for pediatric use. The consortium now has 32 diverse global stakeholders to guide and inform programs, and multiple participating organizations. Its vision and mission overlap those described in the 2004 Critical Path Initiative.¹⁷ The PTC's key principles allow it to be accountable for regulatory quality and for meeting timelines, as well as those principles important to PPPs more generally. The consortium's scope and focus include not just resources and funding, but creating buy-in that allows the group to succeed in its primary mission.

Opportunities: Pediatric Trials Network

P. Brian Smith, MD, MPH, MHS; Duke Clinical Research Institute (DCRI)

Dr. Smith noted that among the 100 drugs most commonly used in the NICU, 87 lack labeling information to guide use in premature infants; of the remaining agents, many of the exposures seen in practice are off-label, involving the wrong indication, wrong population, and/or wrong dosage. The Pediatric Trials Network ([PTN](#)) is working to bridge this gap by creating infrastructure for studies that will provide data to support pediatric labeling and children's health.

¹⁶ Bogue C, DiMeglio LA, Maldonado S, et al. Special article: 2014 Pediatric Clinical Trials Forum. *Pediatr Res.* 2016 Apr;79(4):662-9. doi: 10.1038/pr.2015.255.

¹⁷ US Food and Drug Administration website. FDA's Critical Path Initiative. Available at: <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm>. Accessed May 2, 2016.

How the PTN Works

The PTN develops projects through the following process: 1) The NIH creates a priority listing for unmet needs; 2) investigators submit study concept sheets to the PTN; 3) the administrative core reviews for scientific merit and feasibility and renders an approval decision; 4) approved projects form a protocol development team comprising a chair and thought leaders and experts in pharmacology; 5) the NIH provides a small funding package for study development; 6) PTN sends a scope of work and budget to the NIH; and 7) PTN selects sites from a rapid-startup network. Since 2010, the PTN has enrolled >5,000 participants in studies across a broad array of therapeutic areas—a number the PTN hopes to double within the next year.

Problems Identified from PTN Experience

- Blood volume limitations (possible solution: more sensitive drug assays).
- Needle sticks (possible solution: sparse sampling and/or scavenge sampling).
- Study startup difficulty/delays (possible solution: Duke rapid-start network).
- Funding limitations: large efficacy studies likely to overwhelm budget (possible solution: perform opportunistic phase 1, phase 2, and pharmacokinetic/pharmacodynamic (PK/PD) studies).

Lessons Learned

PTN has found that it helps to consult with FDA up-front and identify existing needs. Keeping research protocols simple has been another major factor in success: make entry criteria as broadly inclusive as possible (and minimize exclusion criteria), minimize blood draws, utilize laboratory procedures done as part of the standard of care, and, where possible, work with sites experienced in performing clinical trials.

Open Discussion

A recurring theme during this discussion session revolved around “three cogs on the wheel”—dosing, efficacy, and safety. Participants noted that clinicians faced challenges related to the time and costs needed to provide definitive data for all three aspects. There was also a question regarding whether it was possible to include dosing information in labeling based on PK studies without efficacy/safety information for a specific pediatric indication, or if this might be seen as a “back door” or implied indication. FDA representatives acknowledged that this was a complex scenario and noted that if a product is not approved for a pediatric indication, PK data from pediatric subjects will not be included in the dosing and administration information (section 2 of the label), but might be included in the section devoted to PK/PD findings (label section 8.4).¹⁸ It was suggested that just the inclusion of PK data for different age groups would help clinicians better understand the characteristics of drug exposure in children. If a clinician felt that the drug needed to be used for a neonate, infant or child, it would more likely result in a more appropriate drug exposure, compared with extrapolation from adult PK data.

¹⁸ Please see FDA guidance regarding placement and content of pediatric information in human prescription drug and biological products labeling when available data do not support a pediatric indication (i.e., data are negative or inconclusive). [Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling \(Good Review Practice/Labeling\) February 2013](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf) available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf>.

Other themes included how to broaden perspectives on approaches and lower barriers to clinical trial participation for both patients and clinicians, as well as how to include smaller groups that have succeeded in this research space into much larger global networks. Regarding this latter point, it was noted that different diseases often create differing needs and priorities; in addition, there may be varying levels of investigator experience with these diseases. **What is most important is adapting to these conditions and finding opportunities for synergy and filling in gaps, while also ensuring the longer-term sustainability of efforts (including both research infrastructure and researcher engagement), possibly by developing models that specifically address sustainability issues.**

A final theme centered on optimizing labeling information. In addition to including as much high-quality data as possible, educational efforts may be needed to ensure that both patients and providers understand how to read, interpret, and find specific information in labeling.

Session II: The Landscape

Facilitator: Gary Noel, MD; Johnson & Johnson

Dr. Noel noted that many of the challenges being faced in antibacterial drug development are translatable to other therapeutic areas and these challenges need to be addressed in hopes of improving development of new medicines for children. He then introduced the Session II topics and speakers, whose presentations were focused on describing the overall landscape of pediatric ABD development.

Pediatric Anti-bacterial and Anti-fungal Trials from 2007 to 2015: A Systematic Review of ClinicalTrials.gov

Joshua Thaden, MD, PhD; Duke University

Dr. Thaden provided a description and high-level summary of a project undertaken to characterize the current state of pediatric trials of antibacterial (AB)/antifungal (AF) agents, as reflected in data collected in the ClinicalTrials.gov repository. Goals of this study included identifying gaps in the clinical trials enterprise (including by agent, disease area, and/or population) and informing efforts to address disparities in the development of these drugs. Data on interventional pediatric AB/AF trials from September 27, 2007 to September 27, 2015 were examined.¹⁹

Studies registered during the study interval were downloaded and identified for inclusion in the analysis using an algorithm supplemented with manual review. A total of 142 interventional studies in pediatric ID were identified: 110 antibacterial agents; 33 antifungal agents; and one that examined both AB and AF therapies (vaccines, antimalarials, and tuberculosis drugs were excluded from analysis). Nearly 50% of all trials involved one of three conditions: otitis media, pneumonia, and skin infections, while very few studies focused on central nervous system (CNS) or bacteremia/central line infections. Studies classified as “other/not specified” accounted for 36%-37%. Among antifungal trials, about two-thirds were for candidiasis and invasive fungal (e.g., *Aspergillus*) infections. Other attributes included:

¹⁹ The start date was chosen to coincide with enactment of provisions in FDAAA that mandated reporting of top-level summary data to ClinicalTrials.gov for any trial conducted under U.S. regulations.

- No clear upward or downward trend in numbers of studies observed over time (Fig.1)
- Few studies enrolled neonates
- AB trials tended to be larger than AF trials
- Most trials (AB and AF) involved multiple sites
- Industry accounted for majority of trial sponsorship and funding
- Relatively few AB studies collected PK data; this typically involved 1-2 samples from plasma. A larger proportion of AF trial reported PK data.
- AF trials tended to take longer, with a median duration of 33 months vs 26 for AB studies
- Reporting of results after trial completion (whether through peer-reviewed publication and/or reporting to ClinicalTrials.gov) tended to be poor (only ~40% reported results to ClinicalTrials.gov for the entire 8-year interval)

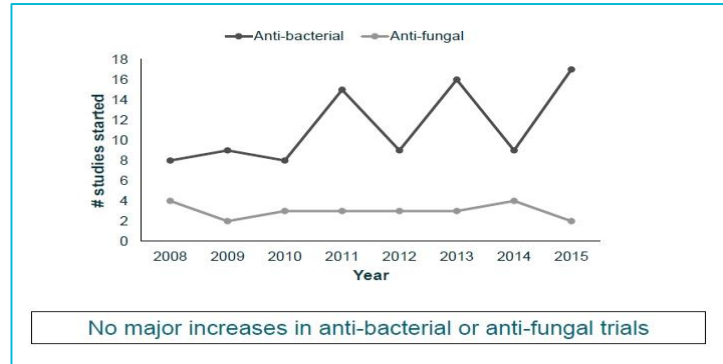


Figure 1. Antibacterial & Antifungal Studies by Year

Summary

- A very low number of pediatric AB/AF trials overall
- No upward trends in number of trials per year
- Very few studies in neonates
- Most funding/support provided by industry

Quantifying BPCA and PREA Submissions: Pediatric Labeling for Antibacterial and Antifungal Drugs

John Farley, MD, MPH; FDA, CDER

Dr. Farley offered a “crash course” in pediatric labeling, which should contain the essential information needed for safe and effective use of medical products in children. When data support the use of a drug in a pediatric population for a given indication, that information must also be placed in a relevant section of the product labeling. When evidence is insufficient to support a pediatric indication, that information must also be communicated in labeling. In addition, other information, such as inactive ingredients that could pose risks to children and data from studies in juvenile animals, may need to be included.

Particularly important sections of the label are:

- Indications and usage (#1) – will give the age range for which use is supported;
- Dosage and administration;
- Contraindications;
- Warning and precautions;
- Adverse reactions;
- Use in specific populations (including for pediatric use) (#8.4);
- Clinical pharmacology;
- Clinical studies (#14) – reserved for “adequate, well-controlled studies”; and
- Patient counseling.

Landmark regulation regarding pediatric trials can be reviewed in [Table 1](#) above. Importantly, tempo for AB drug submissions had slowed in the latter 90s, with many antibacterial drugs coming off patent.

A recent example of required studies under PREA:

- *Conduct an open-label dose ranging PK safety and tolerability study of drug in pediatric subjects less than 18 years of age with suspected confirmed bacterial infections.* This allows the sponsor the flexibility of determining how to conduct the study (age range divisions not stipulated, but PREA requirements extends down to birth).
- *Conduct a multicenter evaluator-blinded randomized study to evaluate the safety and tolerability of a new drug vs. vancomycin for the treatment of pediatric subjects less than 18 years of age with acute bacterial skin and skin structure infection (ABSSSI).* Note that the size of the database is not stipulated in PREA in order to provide latitude for feasibility, although there are discussions of sample size during initial pediatric study plan and other iterative discussions.

Importantly, the extrapolation of *efficacy* in children based on studies in adults is common across some or all age groups, as the disease process and putative benefits of the drug are expected to be the same—what FDA is looking for is PK and safety data.

Labeling for Recently Approved AB Drugs

Table. PREA Requirement Initial Approved Indications

Drug	Approval Year	Pediatric Indication/Dosing	Neonatal Indication/Dosing
Linezolid	2000	From birth	Variable (CSF)
Ertapenem	2001	3 months and older	No data; CSF concern
Daptomycin	2003	Avoid use < 23 months; neuromuscular effects observed in dogs	
Telithromycin	2004	Pediatric trials halted	adverse hepatic reactions in adults
Tigecycline	2005	Pediatric trials not conducted	mortality risk in adults
Doripenem	2007	Safety/efficacy in pediatric patients not established	
Telavancin	2009	Safety/efficacy in pediatric patients not established	
Ceftaroline	2010	Safety/efficacy in pediatric patients not established	
Fidaxomicin	2011	Safety/efficacy in pediatric patients not established	
Dalbavancin, Tedizolid, Oritavancin, Ceftolozane/Tazobactam, Avibactam/ Ceftazidime	2014-2015	Safety/efficacy in pediatric patients not established	

Referring to the table above, Dr. Farley pointed to the example of linezolid, which accomplished pediatric labeling in the shortest period of time, having started with a pediatric written request prior to requirements enacted by PREA. The drug has labeling information by age from birth and data on CSF penetration.²⁰

Dr. Farley also provided an overview of statuses of ABDs that have a PREA requirement related to their initial approved indications. He noted that for drugs with labeling complete or a supplement submitted the interval from approval in adults to submission of a pediatric labeling supplement has ranged from 2-5 years, with the upper range likely to increase as ongoing studies are completed. Some drugs have been granted extensions due to slow trial accrual. He

²⁰ See package insert for linezolid at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021130s030,021131s029,021132s034lbl.pdf or <http://labeling.pfizer.com/showlabeling.aspx?id=649>.

also provided a number of examples that can “trigger” PREA and thus require pediatric labeling studies, including a new indication or dosage. Examples included:

- Azithromycin oral suspension for children >6 months,
- Piperacillin/tazobactam for children with appendicitis/peritonitis >2 months,
- Cefepime in children >2 months, and
- Meropenem for children >3 months

Antifungal Drugs and PREA Requirements

AF drugs have been even more challenging in terms of PREA than have ABDs. For those with labeling complete or supplement submitted, the interval between approval for adult indications to submission of a pediatric labeling supplement ranges from 7–12.5 years. For those that do have pediatric labeling, there is not a neonatal indication or dosing information. Citing slow enrollment, sponsors have requested waiver or deferral extension requests, and recruitment of preadolescent children seems particularly challenging.

Summary

The lag between approval for adult indications and pediatric indications is very long for many drugs and must be addressed. Extrapolation of pediatric efficacy on the basis of adult information is common for anti-infective agents but completion of PK and safety trials for pediatric labeling is slow and challenging and scientific questions affecting pediatric trial initiation may arise in pre- or post-market settings. Finally, when pediatric labeling information is available, it rarely includes information for neonates.

PENTA-ID

Professor Mike Sharland, MD; St. George’s University, London

Professor Sharland provided an introduction to the Paediatric European Network for Treatment of AIDS ([PENTA-ID](#)), a European pediatric HIV clinical trials network. Over the past 20 years, PENTA-ID has completed 11 trials and enrolled more than 1,500 participants; it currently has 2 trials open and another in follow-up. Recognized in 2012 by the European Networks of Pediatric Research at the European Medicines Agency ([EnprEMA](#)) as a Level 1 Pediatric Clinical Trials Network, it conducts trials in pediatric antimicrobial agents, including antibiotics, antivirals, and antifungals, with a particular focus on strategic trials. A total of 106 sites participate in the PENTA-ID network, of which 40 are currently recruiting. The network conducts observational, PK, and interventional trials and is a pediatric partner of the Combatting Bacterial Resistance in Europe ([COMBACTE](#)) network. Education has been a major focus of PENTA-ID, including ensuring that clinical practitioners are aware of and have access to data to guide pediatric dosing and administration.

Professor Sharland noted that there is significant variation in the use of antimicrobial drugs worldwide in terms of both dosing and indication, some of which is inappropriate or problematic. Efforts are underway to improve this through World Health Organization (WHO) surveillance programs designed to monitor antimicrobial use in neonates and pediatric patients. WHO is also planning to produce guidance (NOT guidelines): short, evidence-based summaries that include information about optimal drug choice and dosing for a given condition to guide clinical practice. New EU guidelines in the form of updates to the *Manual of Childhood Infections* (“[Blue Book](#)”) will provide evidence-based guidance for all common infection syndromes.

Professor Sharland also described a forthcoming analysis of clinical antibacterial trials from 2000-2016 that shows problems with reporting and quality, and suggests trials may be getting increasingly difficult to combine in reviews and pooled analyses. He also noted that there may be interest in pooling strategic trials with ones focused on regulatory approval.

Open Discussion

Discussion of these presentations was opened with the question, “are these data surprising, or are they what you expected to see?” Some meeting participants indicated that current circumstances could be shocking to some parents, who might be unaware that many drugs have not been tested in children. It was noted that EU researchers seem to have an easier path to conducting trials and establishing networks and infrastructure, possibly thanks to up-front investment, although as that funding is expended networks must adapt to new funding approaches (on a per-study basis), which can create vulnerabilities. It was also noted that a positive sign is the degree of “cross-talk” among global colleagues that can potentially lead to collaboration and synergy, particularly interoperability can be leveraged to provide access across geographical regions.

A possible problem of perception was also noted, in that despite PREA, investors may view pediatric testing as “wasting” resources because, over the years, practitioners have been conditioned to accept using drugs off label to treat children as the norm. Some meeting participants voiced that more social/cultural change is still needed regarding pediatric drug development. Without approved drug doses for children, pediatricians have to use drugs off label and they prefer to have data on dosing information incorporated in the drug label making it readily available. Even if pediatric studies are completed and published they may not be submitted to FDA for review leaving pediatricians without adequate accessible information. Additional challenges noted included: the need for flexibility in acquiring safety data and embracing the dynamic nature of data; conducting research in very small or rarefied populations; and logistical issues leading to delays when companies change hands. In the case of the latter, an FDA representative noted that in the case of a company being purchased, the original timeline would still apply unless an extension is provided for another reason.

Finally, it was noted that even with critical infrastructure in place, challenges arising from logistics, study design issues, and patient perspectives may still make trials difficult to enroll. Greater interaction with agencies and regulators might help expedite this, particularly with a shared understanding of clinical exigencies and workflows.

Session III: Findings from Focus Groups and Surveys²¹

Facilitator: Rose Tiernan, MD, MPH; FDA, CDER

Parental Decision-Making about Enrolling Children in Clinical Trials: An In-Depth Interview Study

Diane Bloom, PhD, MPH; InFocus Research

Dr. Bloom reported on a qualitative study conducted to provide insight into the decision-making processes of parents deciding whether to enroll a child into a clinical trial. Twenty-four in-depth interviews were conducted with parents who had been approached about enrolling their children in clinical trials. The study group included parents whose children ranged in age from

²¹ For additional data regarding the survey participants and findings, please see individual presenters’ meeting slides at <https://ctti-clinicaltrials.org/our-work/novel-clinical-trial-designs/antibiotic-drug-development/abdd-peds-trials/>

neonates to teenagers, were from a national geographical mix, and represented a wide variety of health conditions.

Research Goals

The goals of the research were to understand the factors that affected parents' decisions to enroll or not enroll their child in a clinical trial; to gain insight into why some parents chose to enroll while others did not; and to identify barriers to participation in pediatric clinical trials and gain insight into strategies for overcoming those barriers.

Key Findings

- **Initial contact** between study personnel and parents was particularly important and should include attention to **trust** (learning about a study from a provider engaged in and providing care to their child), **timing** (attending to the overwhelmingly stressful period for parents and timing approach accordingly), and **empathy** (showing sensitivity and compassion for the child's circumstances as a patient, not a research subject).
- **Conveying the right messages** when seeking parental consent including the need to **be clear about the direct benefits** of study participation, offering assurance that the child's safety and well-being are paramount, **and providing full and transparent disclosure** of risks and side effects in plain language.

Investigator Perspectives

Amy Corneli, PhD, MPH; Clinical Trials Transformation Initiative

Dr. Corneli presented findings from an online survey of investigators of pediatric ABD trials (see topics and factors in Table 2 below).

Survey Topics

Survey participants were asked to indicate how important the particular issues were to successfully conducting ABD trials (or how severe the barrier) using a Likert scale of Very Important to Unimportant, Not sure and Not Applicable. Topics and factors are presented in Table 2.

Table 2

Topic 1: Factors related to the successful conduct of ABD Trials	Topic 2: Barriers related to conduct of pediatric ABD trials	Topic 3: Investigator Comments on...
<ul style="list-style-type: none"> • Access to potential study participants 	<ul style="list-style-type: none"> • Ethics and regulatory issues 	<ul style="list-style-type: none"> • Prevalence of pediatric infections
<ul style="list-style-type: none"> • Staff support 	<ul style="list-style-type: none"> • Study protocol 	<ul style="list-style-type: none"> • Impact of institutional policies on reporting
<ul style="list-style-type: none"> • Clinic space 	<ul style="list-style-type: none"> • Parental concerns 	
<ul style="list-style-type: none"> • Finance 	<ul style="list-style-type: none"> • Parent and child logistics • Colleague's concerns • Miscellaneous 	

Study Findings

For additional detailed data from the findings, please [CLICK HERE](#) to view the meeting slides.

Topic 1: Factors Important to Successful Trials²²

Five factors were reported as very important to successful implementation of pediatric ABD trials by large majorities of respondents, including having site research personnel available to assist with enrollment, receiving adequate funding to cover implementation costs, having staff with regulatory, budget and IRB expertise.

Topic 2: Barriers²³ to Conducting Pediatric ABD Trials

Investigators cited parental concern factors that were identified as barriers including the number of blood draws and invasive study procedures, side effects, use of investigational agents, risks of harm and insufficient benefit, length and complexity of the consent and the possibility of receiving a placebo.

Other factors considered by investigators to be major barriers were overly narrow eligibility criteria and the high frequency of patient visits, the logistics of obtaining consent from both parents, especially when disagreement is evident. Investigators also identified their colleagues' concerns about the number of blood draws and insufficient budgets to cover costs of participation as barriers (altogether, 67% of respondents did not believe they were fairly compensated for their time and effort in implementing a pediatric ABD trial).

Topic 3: Infection Prevalence and Reporting

All infections that were inquired about (blood stream infections, including central line associated blood stream infection (CLABSI); complicated urinary tract infections (cUTI); hospital acquired pneumonia, and ventilator associated pneumonia (HABP/VABP)) had been seen by the majority of investigators in the previous year with varying degrees of frequency; least often seen were complicated urinary tract infections and HABP/VABP, which may have been impacted by the type of investigators answering the survey and their practice setting. The majority of participants indicated that the number of pediatric patients diagnosed with infections has not changed since 2010 and a large number (82%) were aware of policies penalizing hospitals for nosocomial infections. Of these, there was an even split between those who agreed or strongly agreed and those disagreed or strongly disagreed that reported incidence rates of these infections in children are likely lower than the true incidence since these policies were enacted.

Perspectives from Community Providers caring for Potential Study Subjects

Rachel G. Greenberg, MD; Duke University

Study Design and Overview

Dr. Greenberg presented results from an online survey conducted to elucidate factors to consider when referring patients for pediatric clinical trials and the specific barriers that may prevent community pediatric providers from participating in clinical trials as site investigators. The study population included community-based providers who treat children, including those with and without previous experience as trialists and those with and without pediatric/infectious diseases/pediatric hospitalist training. The final sample size of "community providers" was 136:

²² Each factor presented to investigators was reported as "very important" or "somewhat important" for the successful implementation of pediatric AB drug trials by a high percentage (>70%)

²³ Each factor presented to investigators was reported as a barrier ("major," "moderate," or "somewhat") by a considerable percentage of participants (48% to 99%)

40% practiced family medicine, 33% general pediatrics, 15% Pediatric Hospitalist and 11% Pediatric Infectious Diseases. Eighty-three percent had been practicing for more than 10 years.

Survey Topics

Participants were asked to identify the severity of barriers (Major, Moderate, Somewhat, or Not a Barrier) to pediatric ABD trials according to four major categories including study implementation, ethics and regulatory issues, parental concerns and parental and child logistics.

Study Findings

[CLICK HERE](#) to view the meeting slides for additional detailed data regarding the survey participants and findings.

Patient Referral

In terms of referring patients to trials, 38% had referred pediatric patient to clinical trial, with 52% of those having referred to an ABD trial. Of those who had not previously referred to trials, 92% were not aware of any drug trials to refer and 77% were interested in learning more about referring patients to trials. A number of considerations were cited by a majority as at least somewhat if not very important when deciding to whether to refer their patients to trials, including risks and benefits, distance to study site, and the time needed to discuss the study with parents.

Barriers to Implementing ABD Trials

All topic factors were considered barriers by the majority of providers.²⁴ All subfactors for study implementation were considered to be barriers, with the top 5 major barriers including funding to cover research costs, initial research training required for site staff, availability of staff for enrollment assistance, reaching accrual targets and the impact of participation on clinic work flows.

Regarding ethical and regulatory concerns, top major barriers were preparing the required regulatory documents and addressing IRB questions and concerns.

Regarding parental concerns, the top 5 major barriers were concerns about side effects, taking a drug not yet tested in children, the number of invasive procedures and blood draws, and increased risk of physical harm.

Finally, with regard to parent and child logistics, top 5 major barriers included parents' work schedules, insufficient compensation for time and transportation, children's school schedules, transportation difficulties and childcare concerns.

Effect of Experience and Background

Interestingly, previous experience as an investigator was significantly associated with a higher likelihood of classifying several potential issues as "not a barrier," including obtaining adequate funding to cover research costs (Investigators: 3/14 (21%); non-investigators: 5/113 (4%); $P=0.04$) and perception of insufficient study benefits for the child (Investigators: 4/15 (27%);

²⁴ Major, moderate, or somewhat.

non-investigators: 7/112 (6%); $P=0.02$). This may reflect some degree of overestimation of these barriers by community providers who do not have previous experience as investigators. Respondent subspecialty did not seem to have any significant effect on perceptions of barriers.

Summary

Referral by community providers to clinical trial centers is vital to ensuring clinical trial recruitment. Targeting community sites has been shown to increase trial recruitment rates, particularly in minority/underserved populations. There is an imperative to establish trust between PIs and community providers. Reducing barriers will require a multifaceted approach, including improving site compensation to overcome logistical challenges, addressing widely variable compensation for providers and the participants' families, educating providers about potential pediatric drug trials in progress and developing strategies to improve feasibility, including mobile/web-based technology, and master protocols.

Industry Perspective

Gary Noel, MD; Johnson & Johnson

Dr. Noel presented qualitative findings from in-depth interviews conducted with 12 industry representatives currently or recently involved in their respective companies' ABD development programs, including chief medical officers, executives, research program leads, and a payer associate. Both large and small companies were represented. Participants were asked various questions related to ABD development, including why such trials take so long to conduct, and how the process can be improved.

Study Findings

[CLICK HERE](#) to view the meeting slides for additional data from the findings.

Extrapolation from Adult Efficacy Data

Most respondents supported the practice of extrapolating from adult efficacy data to guide pediatric use across indications and age groups, although caution was expressed regarding extrapolating to neonates and older infants. The practice was generally regarded as beneficial, one that can be used to avoid unnecessary pediatric studies or to design better studies. Challenges to extrapolation include unclear rules about when it is appropriate to pursue pediatric labeling, timing of pediatric studies which are often done last on the tail end of the adult study, understanding risk tolerance in younger children and the level of data needed for FDA approval. In addition, there can be conflicting regulator and payer requirements with the payer asking "Where is the phase 3 pediatric trial to support use in children?" Smaller adult studies make extrapolation of efficacy from adults to children more difficult because they may not generate sufficient information to establish an exposure-response relationship that could be the foundation upon which extrapolation may be based.

Reasons for Slow Progress in ABD Trials

Interview participants identified factors related to recruitment and enrollment as the chief challenges, including parents who are strongly risk averse and less trusting of physicians in general, as well as the ease of obtaining drugs as part of the standard of care versus participating in trials. Participants also cited the differences in enrollment rates between the US and international sites, with enrollment being far easier outside the US due to differences in

parental attitudes toward trial participation with respect to trust that the studies were important and necessary.

Suggestions for Simplifying Pediatric ABD Trials

Interview participants suggested several strategies for simplifying antibacterial pediatric trials including: extrapolating pediatric efficacy from adult data, reducing the burdens of trial participation (especially reducing blood draws and invasive procedures wherever possible), easing investigator burdens and eligibility requirements (e.g., reexamining requirements for the number of days of prior effective antibiotics, allowing evaluator blinding, using larger non-inferiority margins for pediatric trials than those used in completed successful adult studies), rethinking study designs to accomplish more with a single protocol (e.g., allowing multiple indications to be combined in a single trial), and selecting sites with proven track records.

Experience with Pediatric Antibacterial Clinical Trials Sites

Interview participants indicated that it is important to select experienced sites, especially with pediatric PK studies. A challenge in tapping more experienced sites is that there may be increased competition for access to the same patient population; hence, research networks may be an important component of site selection.

Utility of Providing Pediatric PK Data through Peer-Reviewed Publications

Respondents were asked about the mechanisms for providing PK data for new drugs. Respondents indicated peer-reviewed publications would not serve as a good standalone source for PK data for new drugs as many pediatricians in general practice might lack familiarity with the literature and there are other well-established sources for prescribing information available (e.g., [Lexicomp](#)) as well as drug labeling that provides prescribing information.

Potential Reasons for Delay in Submitting Pediatric Trial Results to FDA

Interview participants were asked about reasons for delays in submitting trial results to the FDA but had difficulty in definitively identifying circumstances that would warrant submission delays. Possible reasons offered included that the results do not support the use of the drug in a pediatric population, that they may be unable to recommend a dose to put on the label, that there is significant time spent preparing the submission package in order to avoid numerous follow-up questions, that there have been no unexpected safety findings, that there is limited interest in submission and that there may be a perception that data could not be submitted piecemeal to FDA (rather, must wait until studies of all age ranges are completed), or that a substantial charge to the sponsor accompanied each partial submission, suggesting that it is more cost-effective for the sponsor to wait until the package is complete.

Open Discussion

Following the presentations, discussion began with an acknowledgment of the complex issues raised, including burdens on sites/researchers, difficulties in referring patients for trials, and limitations imposed by the need to keep turnover volume in practices high (meaning that many practitioners lack resources and sufficient time to discuss trials with patients and parents in depth). Several participants noted that enrolling patients in pediatric trials is substantially

easier in Europe than in the United States, largely due to differing attitudes toward research. It was noted that regardless of the geographic location of trial sites, it is critical for a successful site lead to clearly and compassionately communicate the importance of the planned research to staff (medical, nursing, pharmacy, etc.), parents and patients, to be willing to share information about the outcome and conclusions of the trial and to appreciate parents' and patients' reasons for wanting to join a research trial. Barriers that might exist for contributing to a clinical trial, including those that academics might face by investing their time on efforts not valued by those assessing the progress of their career, need to be identified and addressed. Effective site leads should be comfortable using all forms of communication, including social media, and be open to, and be resourced for developing new ways to interact with all stakeholders involved in developing and conducting a clinical trial. Creating a sense of true collaboration and partnership with the medical community, parents and patients was recognized as being characteristic of most successful research sites.

Session IV: Considerations

Facilitator: Chris Wheeler, PharmD, FDA; CDR, USPHS

CDR. Wheeler noted that this section would be devoted to building on the findings presented in the previous session and identify some key themes and considerations that could inform more detailed recommendations as well as setting the stage for breakout session discussions.

Communicating with Parents: Approaches to Informed Consent

Breck Gamel, Patient Representative

Approach and Consent

Approach and consent represent critically important steps. Success boils down to three critical dimensions:

- **Who:** a trusted source, familiar with and already involved in the child's care.
- **When:** Especially in situation of critical illness or medical fragility, if immediacy is not a factor, consider a participant finding website to introduce the study to parents. When immediate decisions are needed, provide parents with a single-page summary to review and encourage them to return to discuss questions and concerns with study staff.
- **How:** Staff should be sensitive, compassionate, and empathetic; they should show concern for and familiarity with the child's care and the family situation.

Questions for Discussion

- How should site staff be trained to approach parents, especially in critical care environments and in circumstances involving very ill or medically fragile children?
- Are specialty certification and sensitivity training needed?
- What tools are needed?

Protocol and Logistical Concerns

- Engage parents and primary care providers during study design to ensure that they will support and even champion the trial.
- Consider the age and perspective of child during trial design (age differences may be significant in how study procedures are perceived).
- Minimize painful or scary procedures (and consider this from the child's perspective).

- Consider age-appropriate motivators for children.
- Consider flexible scheduling for appointments and procedures (remote visits and digital technology may be helpful).

Questions for Discussion

- How can we engage care providers and parents?
- How can we make trials more child-friendly and reduce burdens on both patients and parents?

Communication Issues

- Describe the current uses of the study drug; using the trade name when possible
- Use lay/non-technical language.
- Make the child's own doctor and advocate/champion for the study.
- Create a mechanism for parents to engage with other parents about trials in general or specific studies (Patient Advocate Team?).
- Always clearly convey:
 - How the child will benefit;
 - That the child's well-being and safety are of primary importance;
 - Risks, based on the parent's desired level of knowledge;
 - Potential for furthering the common good;
 - Appreciation for the contributions being made by patients and parents; and
 - Study results in timely fashion.

Questions for Discussion

- How can trial champions be made of community providers (pediatricians, family practitioners, etc.) and parents?
- Should someone develop a standard glossary of procedures and tests, described in lay language, which can be used in pediatric study consent and other informational documents? And if so, who?
- What is the best mechanism for rapidly sharing study results with parents of participants?
- What tools are needed?

Addressing Challenges in Neonatal Infection Studies

P. Brian Smith, MD, MPH, MHS; DCRI

Why Are Studies So Difficult to Perform in Infants?

- Limited populations of patients with a given disease.
 - Competition for trial participants at research centers, and
 - Limitations on trial co-enrollment.
- No such thing as a "healthy baby volunteer" to provide phase 1 data;
- Low rates of parental informed consent;
- Perceived risks of research;
- Limited blood volume available for tests;
- Increased variability with sick populations;

- Safety and PK data
- Lack of clinical pharmacology expertise;
- Clinicians' beliefs and attitudes about therapies and trials (lack of equipoise?); and
- What conditions can efficacy be extrapolated from adult data (e.g., meningitis, necrotizing enterocolitis, cUTI)

Problems

- Differential enrollment at 20 clinical sites (Fig. 2). Enrollment at several sites is zero and even the last quintile has only a few enrollments.
- Large variability in antibiotic prescribing practices across sites.
- Limited number of eligible subjects.
 - Solution: adopt strictly limited eligibility criteria, as in PTN and POPS examples.

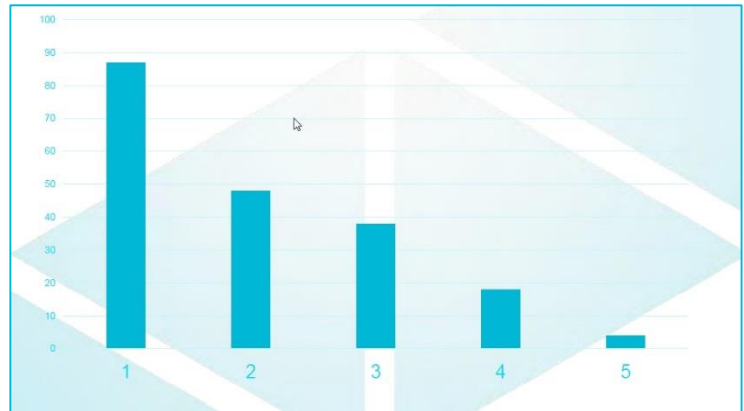


Figure 2. Enrollment for 200-patient, 20-site meropenem study by enrollment by quintiles (each representing 4 sites). (Source: P.B. Smith)

Questions for Discussion

- What would you recommend to improve the feasibility of conducting neonatal PK trials and obtaining CSF samples?
 - How could opportunistic sampling studies be improved?
 - What could networks do that they are not doing at present?
 - Could in-vitro and animal model data better inform the design of neonatal CSF PK trials?
- Should neonates be enrolled at the same time as older children in PK trials or only after safety/PK is assessed in older children?
- Should PK trials be single or multiple dose in neonates?
- What would you recommend to streamline neonatal safety trials (e.g., changes in eligibility criteria, data collection requirements, sample size, comparator arm, timing of endpoints, logistics)?
- How long should safety follow-up be for neonatal trials (e.g., weeks, months, years)?
- Are master protocols feasible for any indications in this population?
- If the available data for neonates does not include CSF data, should dosing recommendations based on that data be included in the labeling? What are the pros and cons in terms of usefulness for pediatricians?

Improving Clinical Trial Design: Meeting the Needs of Investigators

John Bradley, MD; Rady Children's Hospital, UCSD

Meeting the needs of children treated by clinicians is investigators' ultimate goal

Investigators' responsibilities include:

- Providing high-quality data to sponsor/NICHD and FDA on children treated per protocol for PK or for specific indications
- Oversee programs that include site-specific research coordinators, research nurses, pharmacists, and administrators, as well as accountants, lawyers, IRBs, parents, grandparent and children, all the while assuring the availability of research beds and clinic space
- Performing clinical duties for subjects within the context of standard care
- Interacting with all healthcare providers, integrating research into the care for the subjects
- Not interfering with workflow/care provision, especially in NICU

Meeting Investigators' Needs – Questions for Consideration

- Screening for trial participation 7 days a week would be optimal, but may incur expense.
- Securing approval of primary care provider before approaching parents is helpful.
- Consenting processes for labs and for trial should be streamlined.
 - Discussing parental concerns such as safety, risk, cultural issues, incentives
- Randomized comparative study issues for parents and primary care physicians:
 - Did patients receive active agent or comparator, particularly if they do not appear to be responding to investigational treatment?
- Obtaining consent for PK study:
 - There is no clinical benefit for patients but does involve risk and pain, especially in infants/neonates.
 - This involves an appeal to altruism and raises potential ethical issues.
- Pharmacy, lab, and ward/ICU nursing support for research (in addition to dedicated research staff) may be an issue.
- Administration of research drug:
 - Difficult for double-blinded, double-dummy trials and can lead to problems
- Need study physicians (blinded and unblinded) and research coordinators available to answer questions 7 days a week, but creates expense/staffing issues.
 - Often a contracting issue with the CRO for increasing the budget to meet needs, based on a CRO business model that minimizes expense (to maximize profits).
- Managing subject with primary team physician per protocol management.
- Determining causality: what if the child's condition doesn't improve? Is it the infection or the drug?
- Funding for research nurses and physicians, data entry, regulatory documentation compliance training.
- Conflict of interest for investigators:
 - Funding information for investigators is now publicly available (Sunshine Act).²⁵ Does this create perceptions of bias if an investigator is paid to conduct a study?
- More efficient clinical trial designs:
 - Decrease the number of days needed on study drug; long investigational drug treatment courses may create problems relative to allowable hospital stay
 - Most patients will not stay longer than necessary.

²⁵ Centers for Medicare and Medicaid Services. Open Payments. Available at: <https://www.cms.gov/openpayments/>. Accessed June 29, 2016.

- Simplify and standardize case reporting and research compliance requirements across all sponsors.

Breakout Reports

Group 1: Addressing Challenges in Conducting Neonatal Studies

Facilitator: P. Brian Smith, MD, MPH, MHS; DCRI

Scribe: John Farley, MD; FDA

This group addressed the overarching question: *What would you recommend to improve the feasibility of conducting neonatal PK trials and obtaining CSF samples?* Below, detailed questions and responses are provided:

- Should neonates be enrolled at the same time as older children in PK trials or only after safety/PK is assessed in older children?
 - **Response:** Concurrent enrollment seems very reasonable if the drug class is one with which physicians have substantial experience. There may be concerns with a new drug class, particularly if there were safety concerns in adults.
- Should PK trials be single or multiple dose in neonates?
 - **Response:** In cases of multiple doses, physicians may need to be able to escalate doses during the trial, or have a way to know that they are administering a therapeutic dose. Variability within an individual neonate is commonly observed. From a clinical pharmacology perspective, it is desirable to conduct a single dose PK trial first with intensive PK sampling and then follow up with a multiple -dose study with sparse PK sampling (e.g., 3 microsamples via blood stick per subject which would require the presence of a lab capable of handling microsamples).
- If available data for neonates does not include CSF data, should dosing recommendations based on that data be included in the labeling?
 - **Response:** The consensus among pediatricians is that knowledge of CSF penetration relative to minimum inhibitory concentration (MIC) is very important for the treatment of sick neonates, but the reality is that many antibacterial drugs used in clinical practice are lacking CSF penetration data. There is a rabbit model of meningoencephalitis, but additional validation data may be needed. A CSF opportunistic sampling sub-study could be done at sites participating in a larger study. Patients could be enrolled in the sub-study when a lumbar puncture (LP) is being done clinically. There is value in sampling ventricular reservoirs; this should be done more often, perhaps via a single dose study in these infants. It is unclear whether FDA issuing a Pediatric Written Request (PWR) for neonatal CSF data would be helpful – maybe if it was also part of a Pediatric Investigational Plan (PIP) and coordinated submission to the EMA. There was no consensus on whether CSF data was critical for neonatal labeling going forward, but it is certainly desirable.
- What would you recommend to streamline neonatal safety trials?
 - **Response:** Adverse event reporting could be more consistent, as could approaches to common AEs and AEs of special interest as well as the anticipated “morbidity of prematurity” (e.g., seizures) – perhaps through standardized case report forms. Sample size considerations will depend on the

drug, whether the drug is first in class, and any safety issues in adult studies. Comparator arm studies may be desirable, but the tradeoff is that fewer neonates will be exposed to study drug. A focus on adverse events that are plausibly related to study drug might be helpful and should be discussed with FDA.

- How long should safety follow-up be for neonatal trials?
 - **Response:** Depending on the individual study drug, the size of the safety database and duration of follow-up should be discussed with FDA.
- Are master protocols feasible for any indications in this population?
 - **Response:** In the few successful examples of master protocols, an independent group takes the lead and sponsors participate during the time their investigational drug is being studied. Questions about ownership of data have been resolved in the oncology and other settings. A BARDA RFI²⁶ has prompted ongoing discussions in the context of adult trials,²⁷ focused on changes in standard of care over time, and access to data for sponsors to meet reporting requirements. Nimbleness and efficient administrative structure will be important. An independent entity may be needed to lead this effort.

Group 2: Addressing Challenges in Informed Consent for Children

Facilitator: Rose Tiernan, MD, MPH; FDA

Scribe: Diane Bloom, InFocus Research

This group examined possible ways to improve informed consent processes in pediatric ABD trials, with a particular focus on the following dimensions:

- **Trust** – How best to foster trust between parents, providers and research staff?
- **Timing** – How best to ensure sensitivity to the stressful situation of a critically ill/medically fragile child?
- **Tools** – What tools have been most helpful in conducting the informed consent process with parents of fragile/ill children?
- **Trial** – What accommodations have been successful in improving study participation/retention with regard to a more meaningful informed consent process?
- **Training** – What type of training is needed to improve the process of obtaining informed consent in sensitive situations?

Recommendations for Enhancing Trust between Providers, Investigators, Study Staff and Parents

- Design discussion questions and prompts to empower parents to get the information they need to better understand and frame the decision to participate in the clinical trial.
 - Place prompts (phrased as questions) in the consent or other materials that are designed to provide parents with a basic “starting point” of questions in order facilitate informed discussion with study staff.

²⁶ For more information, see the [Clinical Trial Network for Antibacterial Drugs RFI](https://www.fbo.gov/index?s=opportunity&mode=form&id=c49bbf90a77767a69c9cdf148879f711&tab=core&_cview=0) at

https://www.fbo.gov/index?s=opportunity&mode=form&id=c49bbf90a77767a69c9cdf148879f711&tab=core&_cview=0

²⁷ See the University of Maryland School of Pharmacy [Pediatric Master Protocols Meeting Agenda and Video Recordings](http://pharmacy.umaryland.edu/centers/cersievents/master-protocols/agenda/) at

<http://pharmacy.umaryland.edu/centers/cersievents/master-protocols/agenda/> and [Innovations in Breast Cancer Drug](http://www.fda.gov/downloads/Drugs/NewsEvents/UCM423368.pdf)

[Development – Next Generation Oncology Trials](http://www.fda.gov/downloads/Drugs/NewsEvents/UCM423368.pdf) available at

<http://www.fda.gov/downloads/Drugs/NewsEvents/UCM423368.pdf>.

- Look for ways to enhance and improve “shared decision-making” about participating in a study.
 - Consider the development of a Frequently Asked Questions document designed to empower parents with information that will allow them to engage in shared decision-making.
- Parents identify with each other—facilitate their connection to others who chose to participate in the clinical trial they are considering.
 - Identify parent “influencers” (perhaps through social media) with whom to partner who can share the experience of having a child enrolled in a clinical trial in order to facilitate peer communication about the value of participation.
 - Develop/employ unbiased Family/Parent/Peer advocates or navigators who can explain the benefits and risks of participation, provide peer support and answer questions that parents contemplating participation may not know to ask.
- Explore whether better education and outreach about the basics of clinical research and informed consent could add value.
- Consider offering an online resource since the internet can empower parents seeking information to guide decisions.

Recommendations for Improving the Timing of Consent in Sensitive Situations

- Provide recommendations regarding necessary tools to improve informed consent processes in sensitive situations, for example electronic informed consent processes that may allow for reduced pressure and anxiety as information is incrementally absorbed and supplemental information provided.
- Apply “reasonably available” criteria to obtaining physical consent (i.e., a signature) when one parent is physically present while the other is not physically present but informed.
 - The Code of Federal Regulations supports the acceptability of obtaining informed consent from one present parent while the other is informed (e.g., via telephone).²⁸
- Encourage role playing (incorporating video feedback) as an approach to “rehearsing” approaching parents and obtaining consent; use coordinators and patient advocates to forge effective approaches.
- Create and provide sensitivity training; avoid “down-delegating” to inexperienced or peripheral personnel.

Recommendations for Talking with Parents and Children about Study Participation

- Task persons with greater expertise in sensitivity and attributes needed for good communication with parents (good interpersonal skills).
- Explore institution’s willingness to build infrastructure and provide adequate salary support for such personnel.
- Explore use of role-playing, electronic tools, and encouraging kids to take video (“I-cam”).

²⁸ See the [Draft Guidance: Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors](http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm) at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm>.

Recommendations for Training to Improve the Informed Consent Process in Sensitive Situations

- Engage in role playing with patient coordinators and patient advocates.
- Ask for and provide feedback on recruitment processes and techniques – consider engaging parents in evaluating the process.

Additional Recommendations

- More focus group work, including with more specific patient types
 - Greater preparation and planning for a parent-engaged/patient-centric clinical trial may necessitate additional qualitative work such as focus groups during study question design and protocol development.
- Talk to parents in the NICU (a possible opportunity for ad-hoc interviews and focus groups).
- Gather perspectives from children who have participated in clinical trials.
- Work with nurses (e.g., NICU and Pediatric) to obtain their input on trial design.

Group 3: Making Pediatric Antibacterial Drug Trials More Feasible & Efficient

Facilitator: Jamie Roberts, CTTI; with Hasan Jafri and John Bradley

Scribe: Ethan Hausman, FDA

This group was tasked with addressing issues related to streamlining pediatric ABD trials for greater feasibility and efficiency. In particular, they discussed the following concerns and questions:

How could PK trials in children be made more efficient and provide adequate data?

- What strategies could be used to reduce the number of blood draws/burden of enrollment (e.g., sparse sampling, single vs. multiple dose, opportunistic blood sampling, filter paper sampling, other)?
- Could pediatric PK trials begin earlier in drug development (e.g., after an adult phase 2 trial, or after a single phase 3 trial is completed in adults)?
- Are there circumstances in which PK data can be obtained in all pediatric age groups simultaneously rather than sequentially?

How could comparative trials in children be made more efficient and provide adequate data (assuming efficacy is extrapolated)?

- Are there changes in eligibility criteria that could be made (e.g. prior ABDs; concomitant medications)?
- Are there other changes in study design and conduct that could be made (e.g., data collection requirements, visit windows, comparator arm, timing of endpoint, use of biomarkers, and other logistics)?
- What are the factors that impact sample size? Can sample size be reduced?
- Are there circumstances in which comparative trials can be conducted in all age groups simultaneously?
- If an ABD is approved for two indications in adults, are there circumstances in which children with both diseases could be enrolled in the same comparative trial?
- How can we most efficiently address unmet needs for multidrug-resistant pathogens in children?

Are there changes to clinical trial infrastructure and administration that would be helpful?

- What is the best mechanism for educating hospitalists, neonatologists, surgeons, and referring physicians about the value of new antibiotics and the need for clinical trials?
- How could the potential advantages of a clinical trial network be realized (e.g., would companies be willing to use a common protocol and network of sites for both PK and comparative safety and rotate drugs in and out)?
- How could the need for better funding for clinical trial sites be addressed?
 - How can sites be better supported in both understanding their real costs of participation and obtaining the necessary training to efficiently negotiate appropriate study budgets?
 - What is the best way to ensure that families are adequately compensated for the time and travel necessary for participation?
- How can we achieve better buy-in and alignment?
 - Are there opportunities for obtaining payer buy-in earlier in the development process, such that regulators and payers accept the same level of evidence of efficacy?
 - Are there opportunities to achieve alignment between global regulatory agencies with regard to pediatric study plans?

Preliminary Recommendations based on Meeting Discussion for Improving the Efficiency and Feasibility of Pediatric Antibacterial Drug Trials

Study Design

- Simultaneous enrollment of all age groups above two years is acceptable provided there are no safety concerns.
 - Sequential enrollment of children under two years.
 - Initiating PK studies concurrently with adult phase 3 trials may be appropriate in some cases and should be considered.
- Assuming efficacy can be extrapolated from adult trials, proceed with safety trials for pediatrics.
- When efficacy in children can be extrapolated based on the demonstration of efficacy in adults, safety and PK studies should not exclude the collection of efficacy endpoints, but these may not necessarily have to be collected at the same time-points or at the same frequency as the endpoints in adult efficacy trials.
- Reduce the burden of participation through the use of sparse sampling, single dose studies, opportunistic blood sampling, filter paper sampling.
- Critically assess the study design for logistical barriers that will impact efficiency, including inclusion/exclusion criteria, visit windows, comparators, use of biomarkers or surrogates, as well as the length of the study and endpoint timing.
- Build and support efficient trial networks and the use of master protocols, especially for neonatal studies.

Communication

- Improve communication and dissemination of current FDA thinking regarding pediatric antibacterial drug studies to stakeholders including Patients, Providers, Academia and Industry.
- Communicate to community providers the importance of clinical research to the children they treat.
- Improve the informed consent document and process, including sensitivity training for those obtaining consent in acute and/or critical situations.
- Facilitate the interaction and engagement of parents who have had children participate in clinical research with those considering participation (e.g., train and support Parent or Peer Navigators).
- Apply “reasonably available” criteria to obtaining physical consent (i.e., a signature) when one parent is physically present while the other is not physically present but available and informed (e.g., by phone).²⁸

Conclusions

Improving the efficiency and feasibility of pediatric antibacterial trials is critical to ensuring that pediatric patients have access to antibacterial drugs that have undergone appropriate evaluation for safety and efficacy. While challenges to pediatric antibacterial drug development are multifactorial, this multi-stakeholder expert meeting formulated consensus recommendations focusing on study design and communication that may be helpful to address these challenges. Study design recommendations focus on streamlining and efficiency including support for clinical trial networks. Communication recommendations focus on more effective communication with and education of multiple stakeholders including the pharmaceutical industry and site investigators, parents, and community providers. Additional evaluation will be needed to operationalize and implement these consensus recommendations.

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ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership to identify and promote practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

For more information, contact the Pediatric Trials in Antibacterial Drug Development Project Manager, Jamie Roberts, at jamie.Roberts@duke.edu or visit <http://www.ctti-clinicaltrials.org>.

Appendix A. Meeting Agenda

TUESDAY, APRIL 5, 2016

8:00 Welcoming Remarks

- 8:00 Introduction to the Clinical Trials Transformation Initiative and the ABDD Program
Pamela Tenaerts, Clinical Trials Transformation Initiative
- 8:15 Opening Remarks, Housekeeping
Jamie Roberts, Clinical Trials Transformation Initiative

8:30AM SESSION I: The Challenge

Facilitator: John Bradley, Rady Children's Hospital / UCSD

Topics:

- ▶ Progress in antibacterial drug development – Perspectives from the FDA
- ▶ Mechanisms intended to foster pediatric drug development (BPCA/PREA)
- ▶ Infrastructure and networks supporting clinical trials for pediatric populations

- 8:30 Addressing the Challenges of Antibacterial Drug Development
Edward Cox, Food and Drug Administration
- 8:45 PREA & BPCA: The Details
Lynne Yao, Food and Drug Administration
- 9:00 Public/Private Partnerships to Support Pediatric Trials
Ed Connor, Critical Path Institute
- 9:15 Opportunities: Pediatric Trial Networks
P. Brian Smith, Duke Clinical Research Institute (DCRI)
- 9:30 Open Discussion

10:15AM SESSION II: The Landscape

Facilitator: Gary Noel, Johnson & Johnson

Objectives:

- ▶ Present and discuss findings from the AACT database review of Pediatric Trials of Antimicrobials
- ▶ Present and discuss findings from the FDA review of PREA and BPCA submissions
- ▶ Present and discuss US and global approaches to pediatric clinical trials

- 10:15 Quantifying Pediatric AB Trials in Clinical Trials.Gov
Joshua Thaden, Duke University
- 10:30 Quantifying BPCA and PREA Submissions
John Farley, Food and Drug Administration
- 10:45 US and Global Initiatives for Pediatric Trials in Antibacterials
Pamela Tenaerts, CTTI
Hasan Jafri, MedImmune
Mike Sharland, St. George's University, London
- 11:00 Discussion

TUESDAY, APRIL 5, 2016 (Continued)

12:00PM SESSION III: The Findings

Facilitator: Rosemary Tiernan, Food and Drug Administration (CDER)

Objectives:

- ▶ Present and discuss findings from interviews with parents
- ▶ Present and discuss findings from surveys of providers and investigators
- ▶ Present and discuss findings from interviews with industry personnel

12:00 Parent and Caregiver Perspectives
Diane Bloom, InFocus Research

12:15 Investigator Perspectives
Amy Corneli, Clinical Trials Transformation Initiative

12:30 Community Provider Perspectives
Rachel Greenberg, Duke University

12:45 Industry Perspectives
Gary Noel, Johnson & Johnson

1:00 Discussion

1:45PM SESSION IV: Presentation of Considerations and Breakouts

Facilitator: Chris Wheeler, Food and Drug Administration

Objectives:

- ▶ Present and discuss considerations for communicating with parents
- ▶ Present considerations for conducting studies for neonatal infections
- ▶ Present and discuss considerations for improving trial design and development

1:45 Communicating with Parents: Approaches to Informed Consent
Breck Gamel, Patient Representative

2:00 Considerations for Conducting Studies in Neonates
P. Brian Smith, DCRI

2:15 Improving Trial Design: Meeting the Needs of Investigators
John Bradley, Rady Children's Hospital, UCSD

2:30 Discussion

2:45 Intro and Move to Breakout Sessions

3:00PM Breakout Sessions

Breakout 1: Addressing challenges in neonatal infection studies

Facilitator: P. Brian Smith, DCRI

Breakout 2: Addressing challenges in informed consent for children

Facilitator: Rosemary Tiernan, Food and Drug Administration

Breakout 3: Making pediatric antibacterial drug trials more feasible and efficient

Facilitator: Pamela Tenaerts, CTTI

4:15 Breakout Report Outs

4:45 Highlights, Next Steps, Adjourn

Jamie Roberts, CTTI

Appendix B. Meeting Participants

Our meeting participants include representatives from a broad cross-section of the clinical trial enterprise including regulators, government sponsors of clinical research, academia, industry, patient advocates, clinical investigators, and other interested parties. Participants are expected to be actively engaged in dialogue both days.

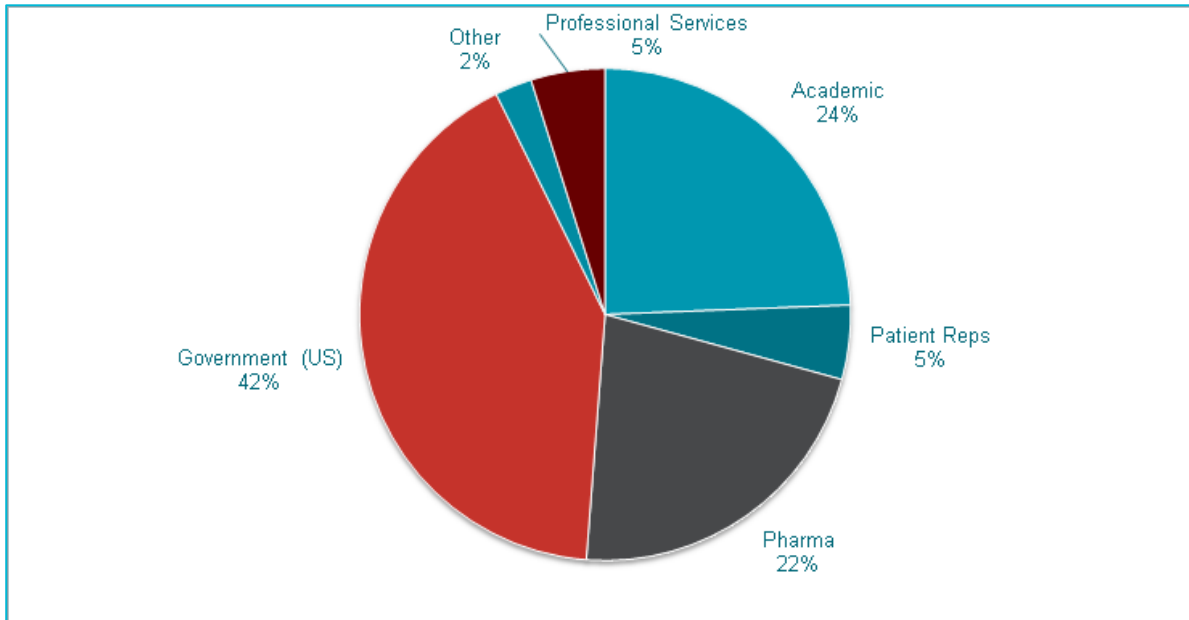


Figure 3. Pediatric ABD Meeting - Stakeholder Representation

APRIL 5, 2016 MULTI-STAKEHOLDER EXPERT MEETING PARTICIPANTS

John Alexander, FDA, CDER	Leonard Krilov, Winthrop University Hospital
Diane Bloom, InFocus Research	Jonathan McCall, DCRI
Jeffrey Blumer, University of Toledo	Erin Moore, Cincinnati Children's Hospital
John Bradley, Rady Children's Hospital, UCSD	Sumathi Nambiar; FDA, CDER
Michael Cinoman, Cempra	Robert "Skip" Nelson; FDA, CDER
Ed Connor, Critical Path Institute	Gary Noel, Johnson & Johnson
Amy Corneli; CTTI	Amanda Paschke, Merck
Edward Cox; FDA, CDER	Brian Perry; Duke University, CTTI
Roger Echols, ID Drug Development Consulting	Jamie Roberts, CTTI
John Farley; FDA, CDER	Jonas Santiago; FDA, CDER
Prabhavathi Fernandes, Cempra	Mike Sharland, St George's University
Maria Fernandez Cortizo, EMA	Sunita Shukla; FDA, CDER
David Friedland, Wockhardt	P. Brian Smith, DCRI
Ian Friedland, Achaogen	Thomas Smith; FDA, CDER
Breck Gamel, Patient Representative	Pamela Tenaerts, CTTI
Dionna Green; FDA, CDER	Joshua Thaden, Duke University
Rachel Greenberg, Duke University	Charles Thompson, Pfizer, Inc.
Tonoah Hampton; FDA, Student Intern	Rosemary Tiernan; FDA, CDER
Ethan Hausman; FDA, CDER	Chris Wheeler; FDA, CDER
Robert Hernandez, Cempra	Bernhard Wiedermann, Children's National Health System
Hasan Jafri, MedImmune	Kunyi Wu; FDA, CDER
Paul R. Jones; FDA, CDER	Lynne Yao; FDA, CDER
	Yuliya Yasinskaya; FDA, CDER