Pediatric Trials in Antibacterial Drug Development: Findings from the Clinical Trials Transformation Project

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CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Background

Under the Pediatric Research Equity Act (PREA), companies developing antibacterial drugs (AB) for adults are required to conduct pediatric trials unless a waiver is obtained. Conducting pediatric AB drug trials is more challenging than with adults, making it difficult for some companies to comply with PREA, despite considerable efforts. Our research has demonstrated that far fewer pediatric AB drug trials are conducted relative to studies on other pediatric conditions: only 110 of all intervention-al and observational pediatric studies registered in ClinicalTrials.gov between 2007 and 2015 (n=12,703) examined AB drugs (110/12703, 0.9%; Table 1/Figure 1).

Few studies have been conducted on the challenges of conducting pediatric clinical trials, particularly AB trials in children.

The Clinical Trials Transformation Initiative (CTTI), a public-private partnership between the Food and Drug Administration (FDA) and Duke University, implemented a project to identify the scientific and operational facilitators and challenges in conducting pediatric AB drug trials and to develop recommendations to address the challenges. This project included surveys with investigators of pediatric AB clinical trials and community providers; qualitative interviews with parents and industry representatives; and the review of the clinicaltrials.gov database described above.

Surveys with Investigators of Pediatric Antibacterial (AB) Drug Trials and Community Providers

Purpose

- Identify the severity of barriers to conducting AB drug trials among pediatric populations.

Methods

- We administered an online survey to a convenience sample of investigators and community providers over a 5-week period in August and September 2015.
- We presented investigators with 36 potential barriers to pediatric AB drug trials, arranged in six categories: (1) ethics and regulatory, (2) study protocol, (3) parental concerns, (4) parent and child logistics, (5) colleagues' concerns, and (6) miscellaneous
- We presented community providers with 30 potential barriers to serving as a site for pediatric clinical trials, arranged in four categories: (1) study implementation, (2) ethics and regulatory, (3) parental concerns, and (4) parental and child logistics.

Results

COMMUNITY PROVIDERS

Demographics
Of the 136 providers surveyed, 52/136 (38%) had previously referred a pediatric patient to a clinical trial, and only 17/136 (12%) had ever been an investigator for a pediatric trial (Table 2).

Barriers
- All potential barriers were classified as ("somewhat," "moderate," or "major") by the majority of providers (Tables 3 and 4).
- Providers perceived greater challenges related to parental concerns and parent or child logistical barriers than study implementation and ethics or regulatory barriers.

INVESTIGATORS

Demographics
- Of the 74 investigators surveyed, most were specialists in pediatric infectious diseases (47%, n=35) or were neonatologists (23%, n=17).
- The majority of participants had conducted pediatric AB trials for more than 10 years (53%, n=39) and at academic children's hospitals (87%, n=64) (Table 5).
- Among those who conducted research in a hospital setting (n=71), almost all hospitals had a neonatal intensive care unit (97%, n=69).

Barriers
- Each factor was found to be a barrier ("somewhat," "moderate," or "major") by a considerable percentage of participants (range: 47.9% to 98.6%) (Tables 6 and 7).
- In comparison with the other categories, almost all of the factors presented in the parental concern category were identified as a barrier ("somewhat," "moderate," or "major") by a high percentage of participants (>80%).

Conclusions

- Community providers and investigators perceive many barriers to participating in or conducting pediatric AB drug trials.
- Findings suggest that further engagement with parents is needed (see section on parent interviews).
- The identification of these barriers is key to designing effective interventions.

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Table 1: Number of antibacterial trials by infection type

Infection type	Number of Trials N=110 n (%)
Otitis media	25 (23%)
UTI	6 (5%)
Pneumonia	16 (15%)
Intra-abdominal	9 (8%)
CNS	2 (2%)
Skin	10 (9%)
Bacteremia/CLABSI	1 (1%)
Sepsis	6 (5%)
Other/Not specified	40 (36%)

Figure 1. Flow Diagram (for focused subset)
Population: Study registration data downloaded from ClinicalTrials.gov on 27 September 2015

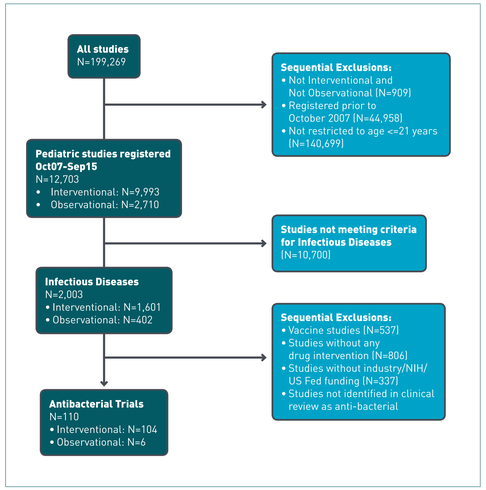


Table 2: Community Provider Characteristics, n (%)

	N=136
Specialty	
Pediatric Infectious Disease	15 (11)
General Pediatrics	45 (33)
Pediatric Hospitalist	21 (15)
Family Medicine	55 (40)
Years practicing medicine	
< 5 years	9 (7)
5-10 years	14 (11)
> 10 years	110 (83)
Approximate distance from practice/institution to the nearest academic medical center or children's hospital	
Practice is located in an academic medical center or children's Hospital	23 (17)
< 30 minutes	70 (52)
30 minutes to 2 hours	39 (29)
> 2 hours	4 (3)

Table 3. Community provider perceptions of potential study implementation and ethics regulatory barriers to pediatric clinical trial implementation, %.

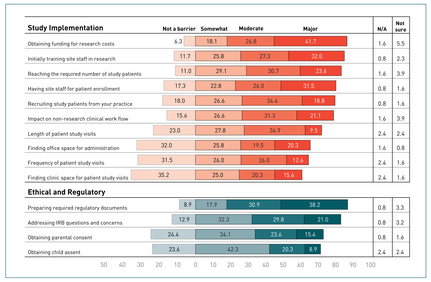


Table 4. Community provider perceptions of potential parental concerns and parent or child logistical barriers to pediatric clinical trial implementation, %.

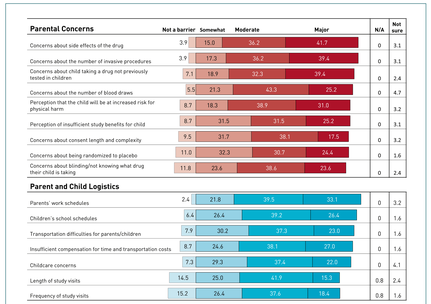


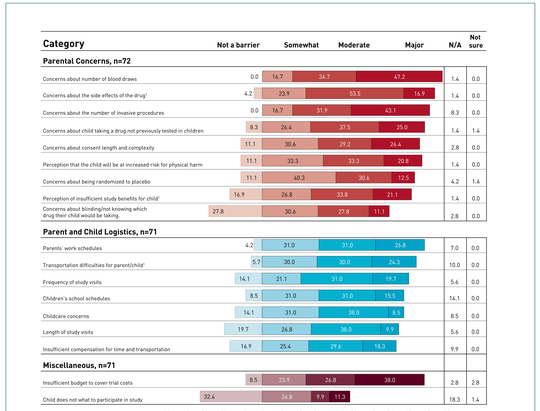
Table 5. Investigator Characteristics, n (%)

Variable	n=74
Specialty[1]	
Pediatric infectious disease	35 (47.3)
Neonatologist	17 (23.0)
Pediatric intensivist	8 (10.8)
Pediatrician (general)	7 (9.5)
Pharmacologist	7 (9.5)
Pediatric hematologist/oncologist	0 (0)
Other[2]	11 (14.9)
Years conducting pediatric antibacterial drug trials	
Less than 5 years	20 (27.0)
5-10 years	15 (20.3)
More than 10 years	39 (52.7)
Type of facility	
Academic children's hospital	64 (86.5)
Large community hospital (e.g. 100 beds)	7 (9.5)
Children's hospital (nonacademic)	4 (5.4)
Private clinic	3 (4.1)
Community clinic	0 (0)
Small community hospital	0 (0)
Other[3]	7 (9.5)

[1]Participant selected all that applied
[2]Pediatric hospital medicine, neonatal study coordinator, pediatric nephrologist, pediatric clinical pharmacology, clinical pharmacologist, pediatric cardiologist, pediatric emergency medicine, pediatric pulmonologist
[3]Pediatric clinical research unit/clinical research unit, academic general hospital/medical center, integrated health system

Table 6. Investigators' perceptions of potential barriers related to pediatric AB study protocols, ethics and regulatory processes, and colleagues' concerns about pediatric AB trials, %.

Table 7. Investigators' perceptions of potential barriers related to parental concerns and parent or child logistics, %.



[1]Data missing from 1 participant

Industry interviews

Purpose

To identify industry perspectives on the slow progression of pediatric AB drug trials

Methods

In-depth interviews were conducted with 12 industry representatives who have experience with pediatric antibacterial drug development.

Main take home points

- Recruitment and enrollment are the main reasons for the slow progression of pediatric antibacterial clinical trials.
- Suggestions for simplifying antibacterial drug trials are to:
  - Use extrapolation
  - Reduce burden of trial participation for parents and children by limiting number of assessments, blood draws, and invasive procedures
  - Reduce burden among trial investigators by altering eligibility criteria to make trials easier to recruit, combining trials, and using pediatric trial sites

Parent interviews

Purpose

- To gain a better understanding of the factors involved in parents' decision-making about whether to enroll their child in a clinical trial, with particular attention to the barriers to enrollment and ways to overcome them when possible.
- To better understand parents' perceptions about the kinds of approaches that are most effective, and the kinds of information and level of detail parents want about the potential risks and benefits of trial participation.

Methods

- In August 2015, 24 in-depth telephone interviews were conducted with parents whose children were offered an opportunity to participate in a clinical trial.
- The children ranged in age from neonates to teenagers, represented a national geographic mix and had a wide variety of conditions and illnesses, including lung infections, asthma, allergies, autoimmune diseases, cystic fibrosis and ADHD.

Based on these interviews, we offer the following 10 strategies will help increase the success rate of clinical trial recruitment.

The Initial Contact

1. The initial contact with parents is best made by the child's own pediatrician or a health care provider who has already been participating in child's medical care, rather than a stranger on the study team. The trust factor in such providers is key.
2. If the initial contact must be made by a "stranger" on the study team, provide them with sensitivity training on best ways to approach parents, e.g., knowing the child's name and understanding their medical situation. Spending the extra time to show empathy and concern for the family's predicament is extremely important.
3. When recruiting premature newborns into clinical trials, do not approach parents in the first few days after the birth of the baby so as not to add additional their stress and anxiety at such a difficult time.
4. Remember that parents would strongly welcome the opportunity to communicate with other parents who have enrolled their child in the trial in question, and facilitate those connections.
5. Flexible scheduling of appointments is necessary. Working parents and older children need to be able to schedule study appointments that allow them to carry out their other responsibilities. Provide weekend and evening appointment hours. Consider letting families who live far from the study site have some of the study monitoring visits completed by their child's own pediatrician. Consider sending a nurse to the child's home for some of the visits.

The Message

6. Tell parents how the clinical trial could directly benefit their particular child, and let them know that their child's safety and wellbeing are of primary importance to those conducting the study.
7. Tell parents about the potential benefits of the study with realistic expectations. Make them aware of all possible risks and side effects their child could experience and whether each is probable, possible or extremely rare. Let them know that, should their child experience a side effect, they will have access to a study team member to help them 24/7.
8. Make the clinical trial kid-friendly:
   a. For young children, friendly people; fun activities; and kid-friendly environment are important. Access to toys, games, and videos at the study site will encourage them to want to go back for future appointments.
   b. For older children, incentivize them with money or money substitute (gift cards; on line credits) that provide them the opportunity to get things they would not otherwise have.

After the Study

9. Tell the parents about the study findings when they become available, either in a letter, or by providing them with a published article.
10. Parents whose children have had positive experiences in clinical trials are more likely to enroll them in subsequent studies, especially with the same study team. Remembering to show special appreciation to the family for their participation in the clinical trial can bring future benefits.