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Facilitators and barriers to the successful implementation of pediatric antibacterial drug trials: Findings from CTTI's survey of investigators

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ABSTRACT

An urgent need exists to develop new antibacterial drugs for children. We conducted research with investigators of pediatric antibacterial drug trials to identify facilitators and barriers in the conduct of these trials. Seventy-three investigators completed an online survey assessing the importance of 15 facilitators (grouped in 5 topical categories) and the severity of 36 barriers (grouped in 6 topical categories) to implementing pediatric antibacterial drug trials. Analysis focused on the identification of key factors that facilitate the successful implementation of pediatric antibacterial drug trials and the key barriers to implementation. Almost all investigators identified two factors as very important facilitators: having site personnel for enrollment and having adequate funding. Other top factors were related to staffing. Among the barriers, factors related to parent concerns and consent were prominent, particularly obtaining parental consent when there was disagreement between parents, concerns about the number of blood draws, and concerns about the number of invasive procedures. Having overly narrow eligibility criteria was also identified as a major barrier. The survey findings suggest three areas in which to focus efforts to help facilitate ongoing drug development: (1) improving engagement with parents of children who may be eligible to enroll in a pediatric antibacterial drug trial, (2) broadening inclusion criteria to allow more participants to enroll, and (3) ensuring adequate staffing and establishing sustainable financial strategies, such as funding pediatric trial networks. The pediatric antibacterial drug trials enterprise is likely to benefit from focused efforts by all stakeholders to remove barriers and enhance facilitation.

1. Introduction

Before the late 1990s, therapeutic drugs were not regularly evaluated for their safety and efficacy in children, leaving pediatricians to rely largely on data from adult studies, as well as on trial and error, to inform their treatment decisions [1]. In 1997, the U.S. Congress enacted the Food and Drug Administration Modernization Act [2], which encouraged the voluntary conduct of pediatric drug trials and also mandated that pharmaceutical companies conduct pediatric studies in certain situations. In 2002, an amendment called the Best Pharmaceuticals for Children Act (BPCA) [3,4] provided companies with a financial incentive of market and patent exclusivity if they conduct a pediatric trial at the request of the FDA. In other legislation, the Pediatric Research Equity Act (PREA) of 2003 [3] required that companies developing drugs for adults conduct pediatric trials unless a waiver is obtained.

Since the initiation of BPCA, PREA, and the regulatory requirement to register pediatric drug trials, many such trials have been conducted and drug label updates approved. Between September 27, 2007, and September 10, 2013, 469 pediatric studies were conducted, including

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studies on efficacy and safety, pharmacokinetics and safety, safety exclusively, and studies of other clinical importance to pediatric populations [5]. Additionally, 535 pediatric label changes have been approved as of July 31, 2015 [6]. Yet, an FDA-commissioned review by the National Academy of Medicine (formerly the Institute of Medicine) concluded that challenges remain in the conduct of pediatric drug trials, including the reluctance among parents and physicians to enroll children in trials [7,8].

In the field of antibacterial drug development, the number of new drugs developed has steadily declined over the past several decades [9], and the current pipeline is "alarmingly thin." [10] There also remains an urgent need for the study of new antibacterial drugs for the pediatric population, especially those that are effective for multidrug-resistant gram negative infections [11]. Conducting antibacterial drug trials with children is more challenging than with adults, making it difficult to comply with PREA, despite considerable efforts [7]. Recent research has demonstrated that far fewer pediatric antibacterial drug trials are conducted relative to studies for other pediatric conditions: less than 1% (n = 82/12,703) of all interventional and observational pediatric studies registered in ClinicalTrials.gov between October 2007 and September 2015 examined antibacterial drugs.[Dr. Joshua Thaden, personal communication, December 21, 2017] Limited information exists on the challenges of conducting pediatric clinical trials from the investigators' perspectives, particularly antibacterial drug trials.

The Clinical Trials Transformation Initiative (CTTI), a public–private partnership between the FDA and Duke University, implemented a multifaceted project to address this concern. The project team—comprised of experts from industry, academia, patient groups, and the FDA—conducted several studies to identify the scientific and operational factors involved in conducting pediatric antibacterial drug trials [12]. In this article, we describe the findings from one of those studies: a survey of investigator perceptions of the barriers to and the important facilitators of successful implementation of pediatric antibacterial drug trials.

2. Methods

We conducted an online survey (Qualtrics software, Provo, UT) with a convenience sample of investigators of pediatric antibacterial drug trials. Because a record or list of all investigators of pediatric drug trials did not exist, we recruited investigators through professional networking and pediatric member organizations. Members of the CTTI Steering Committee and the project team identified potential survey respondents based on their knowledge of U.S.-based investigators of pediatric antibacterial drug trials. Those investigators, together with members of six sections of the American Academy of Pediatrics (AAP) (Clinical Pharmacology & Therapeutics, Infectious Diseases, Critical Care, Hospital Medicine, Advances in Therapeutics and Technology, and Neonatal-Perinatal Medicine), were sent an email invitation describing the purpose of the online survey and requesting their participation; members of AAP were asked to respond if they had ever conducted a pediatric antibacterial drug trial. Investigators were also asked to forward the survey invitation to other investigators they knew who conduct pediatric antibacterial drug trials. The survey was administered over a 5-week period in August and September 2015.

After asking limited demographic questions, we presented respondents with 15 potential facilitators of successful pediatric antibacterial drug trials, arranged in 5 categories: (1) access to potential study participants, (2) staff support, (3) clinic space, (4) finance, and (5) miscellaneous. Respondents were asked to use a four-point Likert scale to rate the degree of importance of each facilitator: very important, somewhat important, somewhat unimportant, or unimportant. Next, we presented respondents with 36 potential barriers to pediatric antibacterial drug trials, arranged in 6 categories: (1) study protocol, (2) ethics and regulatory, (3) parental concerns, (4) parent and child logistics, (5) concerns of colleagues (i.e., fellow physicians), and (6) miscellaneous. Respondents were again asked to use a four-point Likert scale to rate the severity of each barrier: major, moderate, somewhat, or not a barrier. All items were identified by the project team members based on their experience with pediatric antibacterial drug trials. By assessing the importance and severity of these potential facilitators and barriers, we aimed to identify which items were perceived by investigators to be the key factors in supporting and impeding the successful conduct of pediatric antibacterial drug trials. Last, we asked respondents to describe the three most significant challenges they have faced in the conduct of pediatric antibacterial drug trials. For all closed-ended questions, respondents could choose "not applicable" if they had not encountered the issue or "not sure" if they were uncertain about the answer. Open-ended questions were also asked throughout, allowing respondents to list other factors encountered when conducting pediatric antibacterial drug trials. No distinction was made between inpatient and outpatient sites for study conduct.

Descriptive statistics were used to summarize the closed-ended questions. For the open-ended questions, we grouped responses by overall themes and then documented the frequency of each theme. We received a determination of exempt status by the Duke University Health System Institutional Review Board. Respondents agreed to participate in the survey by activating the link and initiating the online survey.

3. Results

3.1. Study population

Of the 101 participants who responded to the survey invitation, 28 were excluded from participating, either because they had not previously conducted a pediatric antibacterial drug trial (n = 21) or because they did not answer any question after the demographic section of the survey (n = 7). The final sample size was 73.

Many respondents were specialists in pediatric infectious diseases (48%) or neonatologists (23%). The majority had conducted pediatric antibacterial drug trials for more than 10 years (53%) and at academic children's hospitals (88%) (Table 1). Almost all associated hospitals had a neonatal intensive care unit (99%).

Table 1
Respondent characteristics, n (%).

Variable	n = 73
Specialty[a]	
Pediatric infectious disease	35 (47.9)
Neonatologist	17 (23.3)
Pediatric intensivist	8 (11.0)
Pediatrician (general)	7 (9.6)
Pharmacologist	7 (9.6)
Pediatric hematologist/oncologist	0 (0)
Other[b]	10 (13.7)
Years conducting pediatric antibacterial drug trials	
Less than 5 years	20 (27.4)
5–10 years	14 (19.2)
More than 10 years	39 (53.4)
Type of facility[a]	
Academic children's hospital	64 (87.7)
Large community hospital (e.g. 100 beds)	6 (8.2)
Children's hospital (nonacademic)	4 (5.5)
Private clinic	3 (4.1)
Community clinic	0 (0)
Small community hospital	0 (0)
Other[c]	7 (9.6)

[a] Respondent selected all that applied.
[b] Pediatric hospital medicine, pediatric nephrologist, pediatric clinical pharmacology, clinical pharmacologist, pediatric cardiologist, pediatric emergency medicine, pediatric pulmonologist.
[c] Pediatric clinical research unit/clinical research unit, academic general hospital/medical center, integrated health system.