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Perceived barriers to pediatrician and family practitioner participation in pediatric clinical trials: Findings from the Clinical Trials Transformation Initiative

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ABSTRACT

Despite legislation to stimulate pediatric drug development through clinical trials, enrolling children in trials continues to be challenging. Non-investigator (those who have never served as a clinical trial investigator) providers are essential to recruitment of pediatric patients, but little is known regarding the specific barriers that limit pediatric providers from participating in and referring their patients to clinical trials. We conducted an online survey of pediatric providers from a wide variety of practice types across the United States to evaluate their attitudes and awareness of pediatric clinical trials. Using a 4-point Likert scale, providers described their perception of potential barriers to their practice serving as a site for pediatric clinical trials.

Of the 136 providers surveyed, 52/136 (38%) had previously referred a pediatric patient to a trial, and only 17/136 (12%) had ever been an investigator for a pediatric trial. Lack of awareness of existing pediatric trials was a major barrier to patient referral by providers, in addition to consideration of trial risks, distance to the site, and time needed to discuss trial participation with parents. Overall, providers perceived greater challenges related to parental concerns and parent or child logistical barriers than study implementation and ethics or regulatory barriers as barriers to their practice serving as a trial site. Providers who had previously been an investigator for a pediatric trial were less likely to be concerned with potential barriers than non-investigators. Understanding the barriers that limit pediatric providers from collaboration or inhibit their participation is key to designing effective interventions to optimize pediatric trial participation.

1. Introduction

In the United States, the number of registered clinical trials for adults exceeds the number for children by a factor of 10 [1]. While clinical trials have long been recognized as the gold standard source of evidence for medical decision-making, a number of factors have contributed to difficulty in performing clinical trials in children, including: 1) a relatively small population of available participants; 2) the high cost and lack of incentives for pharmaceutical companies to perform drug trials; 3) potential legal risk to the pharmaceutical sponsor; 4) ethical concerns regarding participation of children in trials; and 5) a lack of adequately trained pediatric investigators [2–4]. Since 1997, multiple federal policies have attempted to stimulate pediatric drug development through encouragement of pediatric-specific studies [5–9]. Despite these incentives, relatively few pediatric trials have been performed, and many trials have enrolled < 100 participants [1].

Abbreviations: AAP, American Academy of Pediatrics; ABDD, antibacterial drug development; CTTI, Clinical Trials Transformation Initiative; FDA, Food and Drug Administration; NIH, National Institutes of Health; Peds ABDD, Clinical Trials Transformation Initiative Pediatric Trials in Antibacterial Drug Development; US, United States

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Even if sponsors and investigators can overcome the above factors to launch a pediatric clinical trial, low enrollment can cause even the best-designed trial to be unable to meet its stated objectives [10]. The obstacles that prevent recruitment and enrollment of children into clinical trials are complex and can include a combination of factors related to the participants, their parents, and their doctors [11,12]. The role of the non-investigator primary pediatrician or pediatric specialist is substantial. Families are more likely to participate in trials if approached by the child's primary physician [13,14]. However, primary providers may be reluctant to enroll or refer children to trials, which leads to poor recruitment rates and decreases trial success [15]. Therefore, the design and execution of future pediatric clinical trials relies heavily on understanding the attitudes of non-investigator primary providers toward trials. However, little is known regarding the specific barriers that limit non-investigator pediatric and family practice providers from participating in and referring their patients to clinical trials. The purpose of this study was to describe factors influencing providers' awareness and willingness to refer their patients for pediatric clinical trials and the perceived barriers to their practice serving as a pediatric clinical trial site.

2. Methods

2.1. Participants

We administered a voluntary online survey in August and September of 2015 to a convenience sample of medical providers who provide care and treatment to children. We identified potential participants through 2 mechanisms: 1) we partnered with a recruitment firm to identify family practice physicians and general pediatricians from their database of United States (US)-based physicians who are interested and willing to participate in surveys; and 2) we identified physicians of 6 sections of the American Academy of Pediatrics (AAP), including Section on Clinical Pharmacology & Therapeutics, Section on Infectious Diseases, Section on Critical Care, Section on Hospital Medicine, Section on Advances in Therapeutics and Technology, and Section on Neonatal-Perinatal Medicine. These sections included providers who are primarily US-based, although some sections included a small number of international members. An emailed invitation to participate in the survey was sent to potential participants identified by these 2 mechanisms. Participants were also asked to forward the invitation email and survey link to either other pediatric practitioners. Any surveys received from providers who did not provide care for children were excluded. This study received a determination of exempt status by the Duke University Health System Institutional Review Board. Participants provided their agreement to participate in the survey by activating the survey link sent in the invitation email and initiating the online survey.

2.2. Data collection

When completing the survey, providers were asked to share their experiences with and perspectives in referring pediatric patients to clinical trials. Providers were asked to rate the importance of multiple factors to consider when referring pediatric patients to clinical trials using a 4-point Likert scale (very important, somewhat important, somewhat unimportant, unimportant). Participants could also choose "unsure" if they were not certain of the importance of a factor. Providers reported whether they had previously served as an investigator for a pediatric clinical trial. Providers were then asked to reflect upon the severity of 30 potential barriers to pediatric trial implementation, considering what they anticipated would be barriers at their site. The specific barriers were identified by the Clinical Trials Transformation Initiative (CTTI) Antibacterial Drug Development (ABDD) team members, who include experts in pediatric clinical trials from the pharmaceutical industry, academia, and the Food and Drug Administration (FDA). Identified barriers were classified into 4 categories: study implementation, ethics and regulatory, parental concerns, and parental and child logistics. Providers used a 4-point Likert scale (major barrier, moderate barrier, somewhat of a barrier, not a barrier) to indicate the severity of each barrier. Participants could also choose "not applicable" if they believed the barrier would not apply to their site, or "unsure" if they were uncertain of severity of the barrier.

2.3. Data analysis

Descriptive statistics were used to describe the quantitative data and thematic analysis was used to analyze the open-ended responses. The providers were divided into 2 groups: those with previous experience as an investigator for a pediatric clinical trial and those without this experience. We compared the probability of providers answering "not a barrier" among these 2 groups using Fisher's exact test. P values < 0.05 were considered to be significant. Analyses were conducted using SAS 9.4 (SAS Institute Inc. Cary, NC).

3. Results

3.1. Study population

A total of 168 providers participated in the survey. Of these, 32 were excluded because they were not pediatric providers. Therefore, the final sample size was 136. Most of the providers practiced either family medicine (55/136; 40%) or general pediatrics (45/136; 33%). The majority (110/136; 83%) had practiced medicine for more than 10 years (Table 1).

3.1.1. Experience with referring pediatric patients to clinical trials

Thirty-eight percent (52/136) of providers had previously referred a pediatric patient to a clinical trial. Of those who had not previously referred a patient, almost all (76/84; 92%) were not aware of any drug trials to which they could refer their patients. However, most (65/84; 77%) were interested in learning more about referral to drug trials. When asked to consider the importance of different factors when referring their pediatric patients to a clinical trial, providers were in agreement that it is very important to consider the potential benefits (120/136; 88%) and potential risks (127/136; 93%). Most providers also reported that it was either very important (29/136; 21%) or somewhat important (89/136; 65%) to consider the distance to the study site, and most believed it was very important (49/136; 36%) or somewhat important (72/136; 53%) to consider the time needed to discuss the clinical trials with the parents of their pediatric patients.

Table 1
Pediatric provider characteristics.

Pediatric Provider Characteristics (N = 136)	No. (%)
Specialty	
Family Medicine	55 (40)
General Pediatrics	45 (33)
Pediatric Hospitalist	21 (15)
Pediatric Infectious Disease	15 (11)
Years practicing medicine[a]	
< 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 min	70 (52)
30 min to 2 h	39 (29)
> 2 h	4 (3)
Previous investigator for a pediatric clinical trial[a]	17 (12)

[a] 3 participants did not answer these questions.

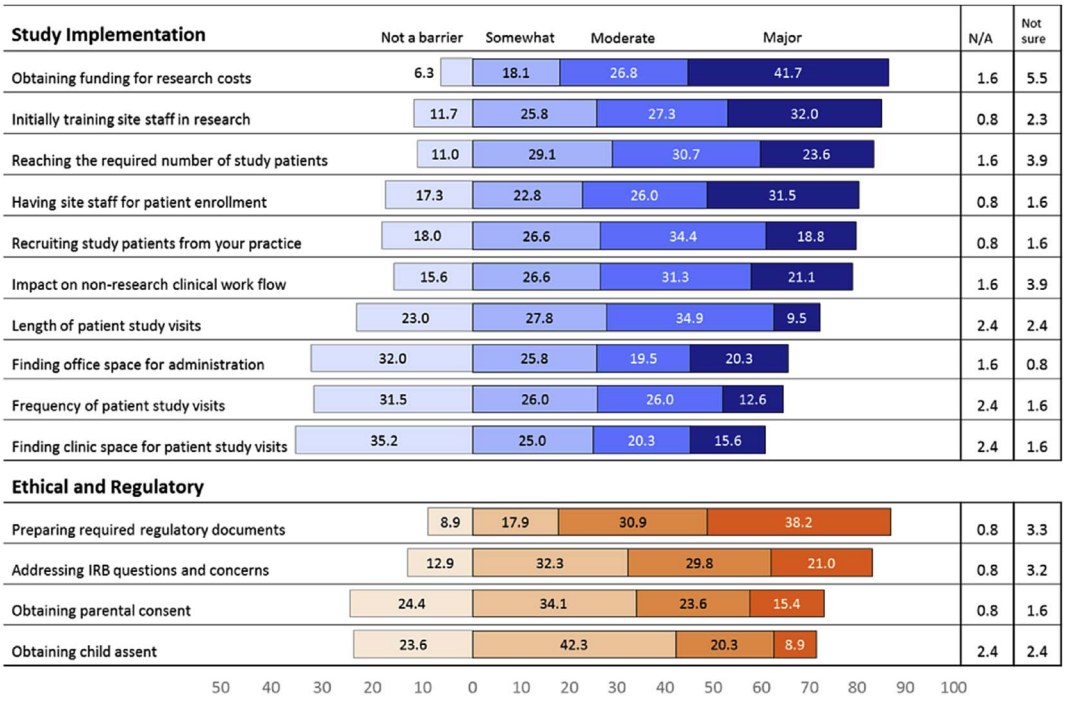

Fig. 1. Provider perceptions of potential study implementation and ethics regulatory barriers to pediatric clinical trial implementation.

Responses varied, however, on the importance of the potential to lose control of the pediatric patients' care. When evaluating the significance of this factor when considering whether to refer patients, almost equal numbers of providers reported that this factor was very important (26/136; 19%), somewhat important (35/136; 26%), somewhat unimportant (36/136; 27%), and unimportant (34/136; 25%). Other barriers that were elicited from multiple providers in free-response answers included the level of trust or existing relationship between the provider and investigator, potential cost and compensation to the patient, and time spent by the patient and family. Several responders indicated that referring patients to a study depended on "clinical importance" of the study and that "the gravity of the condition being treated" must be weighed against "the time and effort to get the patient into the study."

3.1.2. Perceived barriers to serving as a clinical trial site

When asked to consider the barriers they may experience if their practice became a pediatric clinical trial site, providers reported major barriers in every category investigated (Fig. 1, Fig. 2). All potential barriers explored in the survey were classified as at least "somewhat of a barrier" by the majority of participants. Overall, providers perceived greater challenges related to parental concerns and parent or child logistical barriers than study implementation and ethics or regulatory barriers. When asked to describe other potential barriers not mentioned in the survey, providers responded that several issues would represent challenges, including concerns regarding the "effect on my own productivity and hence pay," "divergent parent viewpoints," and having to manage and explain "the consequences of a negative outcome [for the child] despite [the parents] having consented."

The Effect of Experience as an Investigator on Perceived Barriers.

The majority of providers (119/136; 88%) had never been an investigator for a pediatric trial, although 49/119 (41%) of these non-investigator providers reported having considered being an investigator or having their institution or practice be a clinical trial site. Overall, providers who had previously been an investigator for a pediatric trial (17/136, 12%) had a trend toward less concern with potential barriers than providers who had never been an investigator for a pediatric trial (Fig. 3). Compared to providers without experience as an investigator, providers with investigator experience were significantly more likely to consider the following 2 issues to be "not a barrier": 1) obtaining adequate funding to cover research costs (investigators: 3/14 (21%); non-investigators: 5/113 (4%); $P = 0.04$), and 2) perception of insufficient study benefits for the child (investigators: 4/15 (27%); non-investigators: 7/112 (6%); $P = 0.03$).

4. Discussion

A survey of 136 pediatric providers confirmed the significance of 30 potential barriers to clinical trial implementation identified by a team of pediatric clinical trial experts. For all 30 of the potential barriers, a majority of participants indicated that they indeed represented barriers if they were to get involved in a clinical trial. Providers also reported additional perceived barriers that were not included in the survey. Although providers' responses demonstrated the presence of challenges regarding study implementation and ethics/regulatory issues, providers reported a higher level of concern regarding parental concerns and parental/child logistics. These findings are in agreement with previous studies that have highlighted the importance of the parent's perception of safety as well as the practical convenience of the trial as major potential barriers [11,16].

To our knowledge, this study is the first to compare perceptions of barriers to implementation of pediatric clinical trials between pediatric providers with and without experience as pediatric clinical trial investigators. Study results showed that providers with experience as pediatric clinical trial investigators were likely to affirm the presence of the suggested potential barriers to pediatric clinical trials. These responses may reflect that these investigators have previously encountered these issues during their prior participation in clinical trials. However, having had experience as an investigator was associated with higher likelihood of classification of several potential issues as "not a barrier." It is possible that participants with previous experience as an investigator are simply more likely to work in a favorable clinical or institutional environment. Thus, it is understandable that providers with investigator experience might report fewer concerns, particularly related to study implementation and ethics/regulatory barriers. On the other hand, providers with experience as clinical trial investigators also

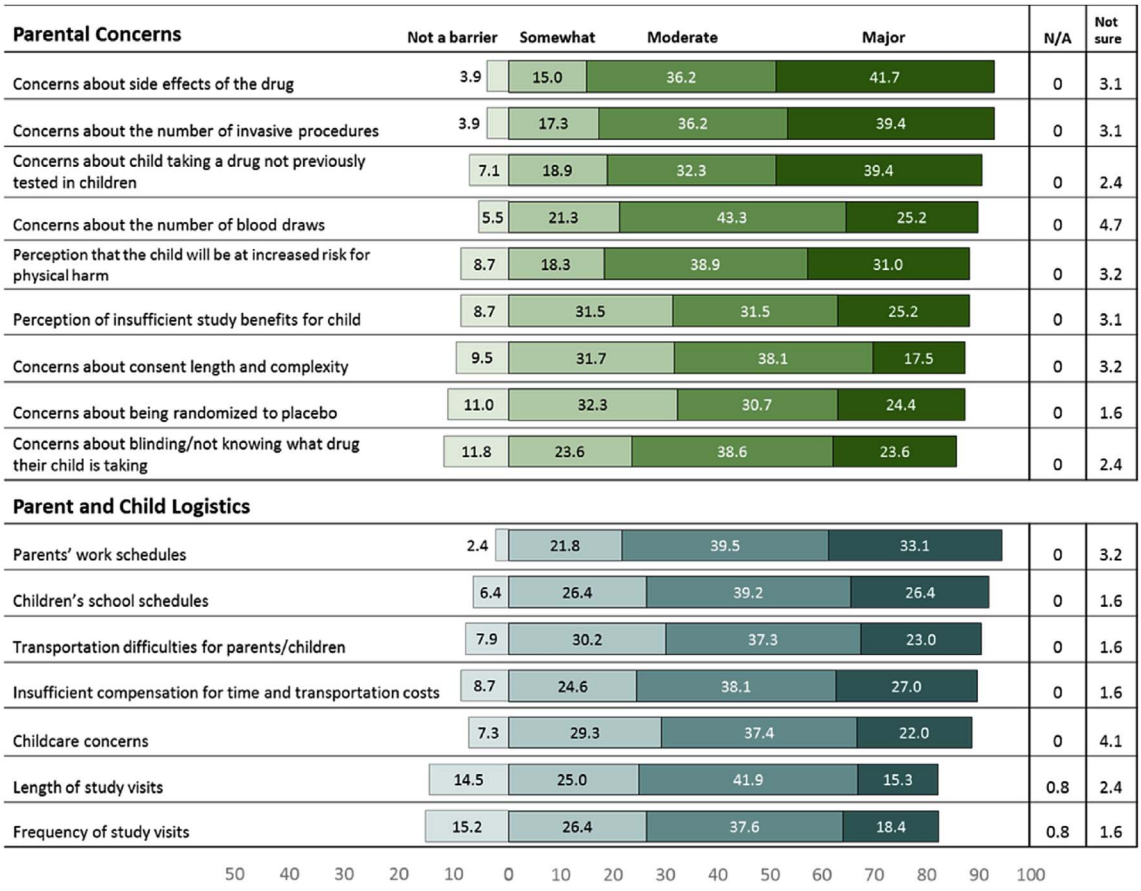

Fig. 2. Provider perceptions of potential parental concerns and parent or child logistical barriers to pediatric clinical trial implementation.

Fig. 3. Effect of investigator experience on perceived barriers. *$P < 0.05$ between groups (previous investigator vs. not a previous investigator).

trended toward being more likely to report parental concerns and parent/child logistical issues as “not a barrier.” This finding may reflect some degree of overestimation of these barriers by providers who do not have previous experience as investigators. However, 83% of the survey participants had been in practice for more than 10 years with only 12% having participated in studies, suggesting that many practices may not show interest or have been given adequate opportunities in clinical research.

Previous work has shown that involvement of community-based sites is critical to the success of clinical trials. The majority (83%) of the participants in our study were community-based providers (not located in an academic center or children's hospital). In one study that surveyed parents of children who were being asked to participate in a clinical trial at the time of cardiac surgery, 56% of parents preferred that their child's own cardiologist or cardiothoracic surgeon explain the details of the study, compared to 23% preferring the principal investigator and 3% preferring the research coordinator [13]. Another survey of a socioeconomically diverse population showed that parents reported being most likely to allow their child to participate in research if approached by their child's own doctor [14]. Involvement of community sites in recruitment has also been shown to increase trial recruitment rates, particularly in minority/underserved populations. In one study, the authors employed new strategies that focused on location, cultural competency, and community-based research methodologies [17]. Following this intervention, the authors reported a 62% increase in the enrollment of black participants in clinical research. Studies in both adults and children have shown that referral by primary pediatric providers to clinical trial centers is vital to ensuring clinical trial recruitment [18,19]. From these previous studies, the importance of primary pediatric provider involvement in clinical research is clear.

Knowledge of which barriers are most important to pediatric providers, including those identified in our study, is key to the design of interventions that can reduce the impact of these barriers, leading to more successful clinical trials. The best method for addressing these barriers likely lies in a multi-targeted approach. A first step in any clinical research endeavor involves establishing a trusting relationship between the principal investigator and the clinical providers. Multiple participants in our survey highlighted the importance of this relationship, especially since it was so imperative to the providers to have understanding of the importance of the trial before investing the time and effort into recruiting their own patients.

Other approaches to reduce these barriers include improvements in the compensation of sites so that logistical challenges (facilities, appropriate staff training, clinical time for study visits) can be overcome. Interestingly, the providers surveyed in our study were interested in compensation not only for themselves and their staff but also the participants' families. The question of incentives for pediatric research participation is complex; incentive and payment practices are widely inconsistent, and AAP and federal guidelines take different approaches regarding how and when to approach this subject with families [20–24]. If more overarching, standard guidelines for family incentives and payment could be developed, this could result in improved perceptions of this issue among providers and potentially lead to their increased involvement in clinical trials.

Perhaps the most important strategy for reducing perceived barriers is education for providers at potential clinical trial sites. Most providers were unaware of community-based pediatric drug trials in progress in which their pediatric patients could potentially participate, so dissemination of information to these providers is an essential step. It is encouraging that the majority of providers who had not referred patients to clinical trials were willing to consider participation in the future. With visits to potential sites and other methods of communication between study personnel and the sites, study coordinating centers could facilitate development of methods that sites can use to overcome potential logistical problems. Site visits and other methods of site education have been shown previously to increase patient recruitment rates in both adult and pediatric multi-center randomized trials [25,26]. In addition, coordinating centers may be able to develop and teach new approaches to improve feasibility of trials, such as the use of mobile and web-based technology to conduct study visits and procedures remotely [27–29]. If coordinating centers were able to take full advantage of these educational strategies, the gap in perceptions between providers with and without previous investigator experience could be minimized.

The strengths of our study include the large number of pediatric providers that participated in the survey and the detail with which we were able to evaluate multiple categories of barriers. We were able to examine the impact of previous investigator experience on perceived barriers to pediatric clinical trial implementation. Our study was limited by several factors. The nature of our survey is descriptive and dependent on voluntary responses rather than completely representative of the entire possible group of pediatric providers. Because the survey email was disseminated in part by asking participants to forward it to other pediatric practitioners, it was not possible to calculate the survey response rate. The number of participants with previous experience as pediatric clinical trial investigators was relatively small, which limited our ability to detect statistically significant differences between groups and thus we could only report trends for some cases. We were also unable to perform multivariable modeling to examine the effect of investigator experience. Since our data was obtained through a voluntary survey, we cannot determine if the opinions of individuals who chose not to participate in the survey would have been different from those who did participate.

5. Conclusions

Design and implementation of pediatric clinical trials remains difficult despite new incentivizing legislation for pharmaceutical sponsors. As a result, children are still relative therapeutic orphans. Involvement of clinical pediatric providers is crucial to the success of pediatric clinical trials, but we found that these providers perceive massive barriers to participating in and referring patients to clinical trials. Understanding these barriers that prevent providers from collaboration or inhibit their successful participation is key to designing effective interventions. Further studies are needed to determine what strategies can best reduce these barriers or perceptions of these barriers.

Conflicts of interest

Dr. Greenberg receives salary support for research from the National Institutes of Health [grant numbers 5T32HD043029-13, HHSN 275201000003I, HHSN 272201300017I] and from the FDA [grant number HHSF223201610082C]. Dr. Smith receives salary support for research from the NIH [grant number NIH-1R21HD080606-01A1] and the National Institute for Child Health and Human Development (NICHD) [grant number HHSN275201000003I]. Dr. Benjamin receives support from the NIH [grant number 2K24HD058735-06], the NICHD [grant number HHSN275201000003I], the National Institute of Allergy and Infectious Diseases [grant number HHSN272201500006I], the Extended Care Health Option Program [grant number 1U2COD023375-01], and the National Center for Advancing Translational Sciences [grant number 1U24TR001608-01]; he also receives research support from Cempra Pharmaceuticals [subaward to grant number HHSO100201300009C] and industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp).

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Disclaimer

The views expressed in this publication are solely the responsibility of the authors and do not necessarily reflect the official policies of the US Department of Health and Human Services.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.conctc.2017.11.006.

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