WHITE PAPER

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Effectively Addressing the Challenges of Pediatric Clinical Trials with Patient-Centric Best Practices

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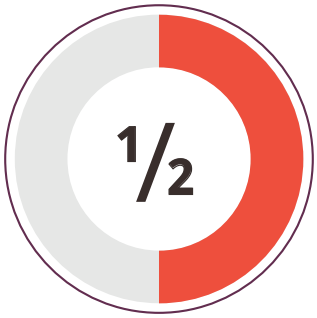
EXECUTIVE SUMMARY

The medical community has an innate responsibility to study the agents marketed for use with children. Additionally, legislative changes in the United States and Europe have made it even more critical that drug developers ensure clinicians have adequate efficacy, safety, and dosing information to effectively prescribe appropriate medications to children.

Pediatric trials, however, are notoriously challenging with unique barriers to successful trial completion such as parental perceptions, motivations, and attitudes in relation to the benefit and burden of trial participation; a higher rate of early patient drop-out; and the inherent characteristics of the pediatric patient population. These barriers all contribute to reduced patient participation or retention and result in far fewer therapeutic advances for the pediatric cohort.



Nearly half of all pediatric clinical trials go unfinished or unpublished

To create a more successful pediatric clinical trial ecosystem, we need to take a look at where along the critical path additional support and operational approaches could mitigate barriers and improve both recruitment and retention.

Enhancing and improving support for pediatric patients and their guardians/caregivers better positions trials for optimal participation and adherence, positively contributing to trial involvement, timelines, and data quality. Improvements in these areas lead to faster time to market for pediatric drugs, ultimately contributing to the improvement of health outcomes in children. To that end, this white paper presents:

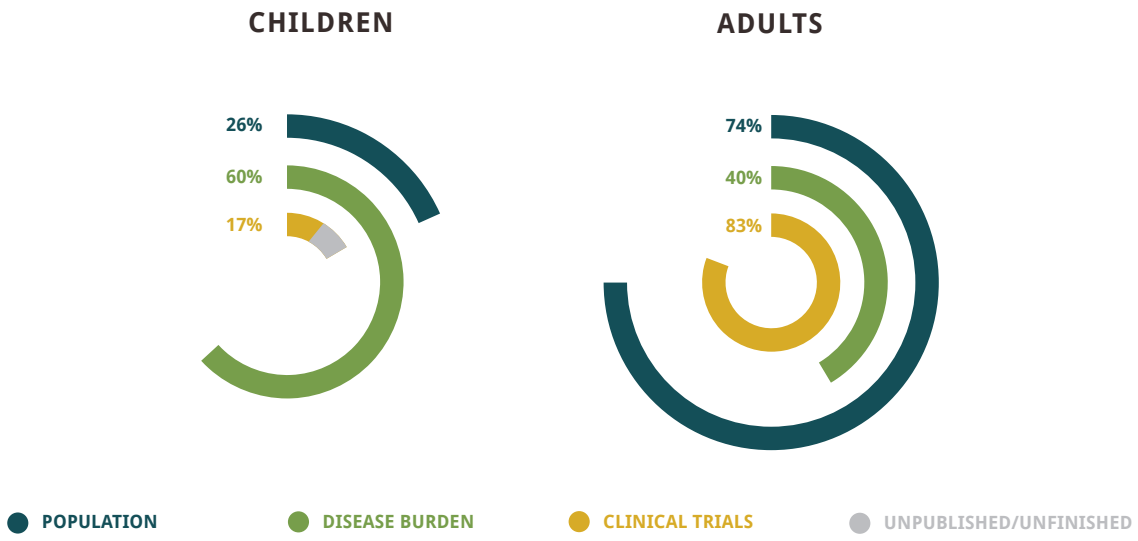
- The pediatric clinical trial landscape
- Challenges conducting pediatric clinical trials
- Seven best practices to meet these challenges

PEDIATRIC CLINICAL TRIAL LANDSCAPE

Medication use in children under 17 years old has historically been extrapolated largely from adult data[1] due primarily to an insufficient number of pediatric studies. Consequently, pediatric prescriptions are often considered off-label. The problem is (as the notable analysis conducted by Duke University investigators determined), if we rely on adult data to guide medication administration for children, we will be wrong half of the time.[2]

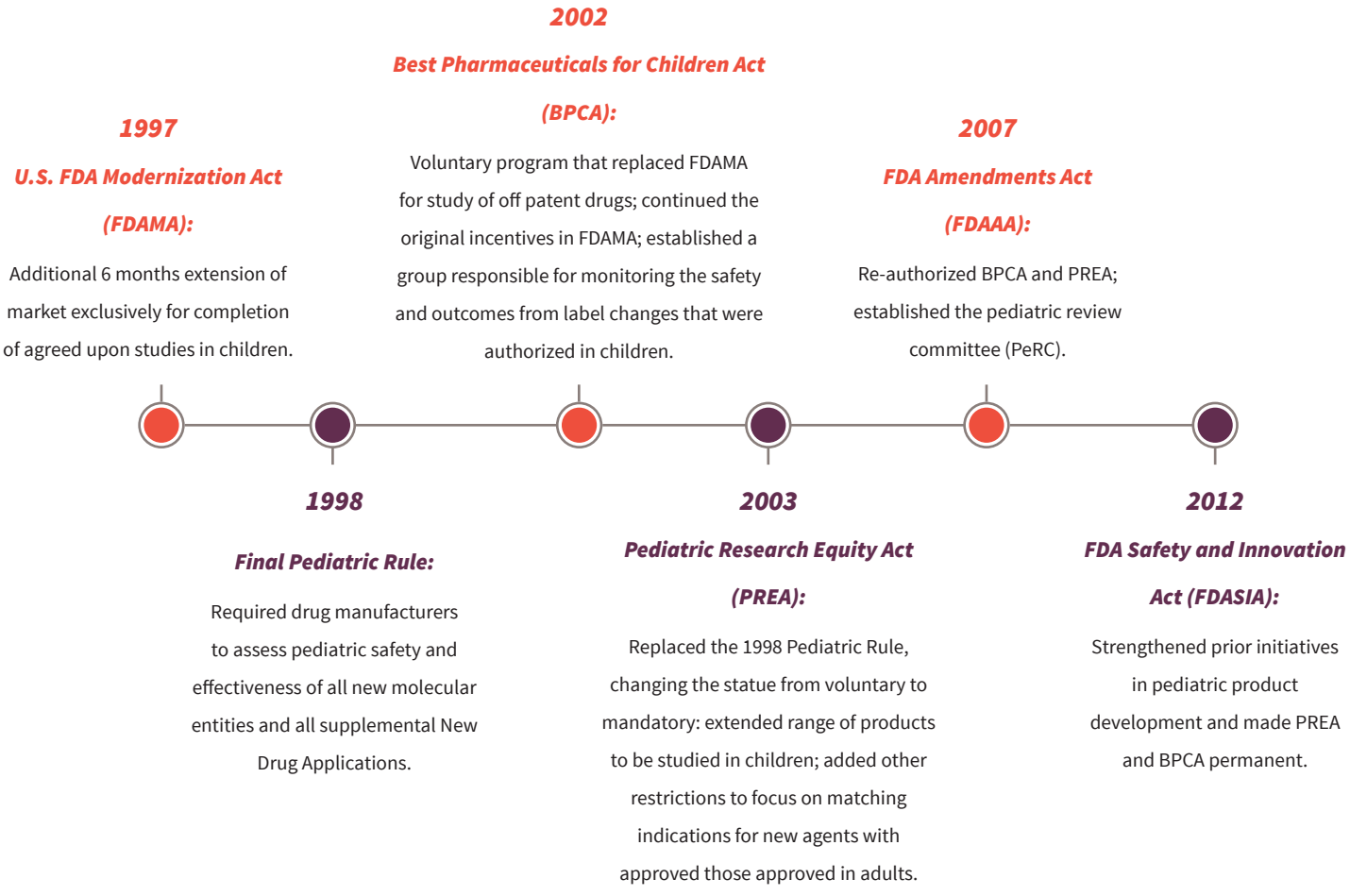
Children under 14 years old comprise 26% of the world's population[3] and bear nearly 60% of the total disease burden[4], but pediatric trials make up only 17% of the total number of registered trials.[5] And nearly half of all pediatric trials go unfinished or unpublished.[6]

The result: 50% of medicines used to treat children do not have adequate randomized controlled trial data to support safe and effective dosing.[7] This number increases dramatically to 90% if we look specifically at newborns.[8]



Consequently, regulatory agencies in the United States and Europe have enacted several regulatory mandates, incentives, and oversight measures over the last 20 years aimed at stimulating pediatric drug development and research. Since 1997, the U.S. Food and Drug Administration (FDA) has instituted a number of initiatives to further pediatric research (see Figure 1), in addition to their typically mandated minimum 2 to 3 trials to satisfy pediatric exclusivity requirements (e.g., a pharmacokinetics trial, short-term efficacy trial, and a long-term safety extension).[9]

Figure 1



In 2007, the European Medicines Agency (EMA) instituted Pediatric-Use Marketing Authorization (PUMA) approvals, allowing 10 years of data production for a new indication of an off-patent drug. The EMA further strengthened their commitment in 2008 by requiring drug developers to submit a pediatric investigation plan (PIP) for all new pharmaceutical products under development and for marketed products for new indications.

While pediatric clinical trial research has been on the rise, growing 47% from 2012 to 2017[10], the number of pediatric trials still pales in comparison to the vast quantity of adult clinical trials. Much work remains to close the gap between the critical need for pediatric research and the pediatric clinical trials performed.

OBSTACLES TO A SUCCESSFUL PEDIATRIC TRIAL

Although these regulatory incentives have spurred drug developers to initiate pediatric clinical trials, often-encountered barriers to successfully completing a pediatric clinical trial (such as patients discontinuing early from the trial; parental perceptions, motivations, and attitudes of the benefit and burden of trial participation; and the inherent unique characteristics of the pediatric patient population) require additional support and operational approaches to mitigate the barriers and enhance trial success.

Dropouts

Patient retention is a key factor to ensuring clinical trial success. Retention of patients throughout the entire cycle of a clinical trial is vital from a scientific, as well as economic, point of view. Poor retention negatively impacts the quality of evaluable data and increases costs by imposing delays for pharmaceutical companies.[11]

Results of a recent study revealed that 19% of pediatric trials were discontinued early, with patient accrual difficulty (37%) as the most common reason for discontinuation.[12] Further, an analysis of 40 randomized studies of cognitive interventions in children found that 20% of participants did not complete the initial follow-up assessments and 32% did not provide follow-up data.[13] The following are the main reasons patients gave for dropping out of the clinical trials:

- Too busy
- Not interested
- Too much hassle
- Intervention was not necessary
- Technical complications with study procedures
- Travel distance was too far
- Too many doctor appointments
- Family concerns

Parents' Perceptions, Motivations, and Attitudes

A parent's comprehension and perception of their child's involvement in a clinical trial may substantially differ from that of the sponsor or investigator.[14]

Some parents may be anxious, concerned about their child being a "guinea pig," and reluctant to have their child participate in a trial. Parents have expressed the following concerns for their children participating in a clinical trial: [15]

- Length and frequency of study visits
- Number of invasive procedures, including blood draws
- Conflicts with schedules or childcare
- Transportation difficulties or insufficient compensation for time and transportation costs
- Insufficient study benefit
- Taking a drug not tested in children or being randomized to placebo drug side effects
- Consent length and complexity

On the other hand, other parents view participation in a trial as an exciting opportunity. Other positive aspects parents have acknowledged include the altruistic desire to help other children, the opportunity to access new therapies, increased access to health care professionals and medical information, better medical care for their child, meeting other parents in a similar situation, and feeling a sense of hope when no other effective therapies are available.[16]

So, parents in general are not averse to their child participating in a clinical trial, they just want the experience to not encumber their busy lifestyles or adversely affect their child.

Unique Characteristics of the Pediatric Population

Pediatric trials have unique challenges because to recruit effectively they have to be tailored to the needs of children and their families. Since families are busier than ever, clinical trials need to adapt.

And, children are not miniature adults. Children may be at different development milestones and have a range of conditions and differing levels of physical, cognitive, and emotional maturity. Their disease presentation may have a different natural history from adults. Not only do children have complex physiologic, developmental, psychologic, and pharmacologic characteristics that differ from adults, these characteristics differ across the pediatric spectrum (preterm newborns to post-puberty adolescents). Children may metabolize and respond to medicines differently from adults, resulting in suboptimal therapy, unexpected responses, adverse drug reactions, and toxicity.[17]

7 BEST PRACTICES TO SUPPORT PEDIATRIC CLINICAL TRIALS

Inconvenient site locations, schedule conflicts, logistical concerns, financial constraints, and missed visits are often cited as reasons patient dropouts occur and noncompliance rates increase. Incorporating a more patient-centered approach that minimizes patient burden can improve those rates.

Home health visits, specifically, is a valuable strategy that helps minimize the burden of site visits and may also improve patient retention. Instead of requiring patients to visit a designated investigative site multiple times over the course of a study, patients can choose to complete study visits at locations and times convenient and comfortable for them.

Additionally, the use of home health visits often allows sites to increase their time and focus to further patient recruitment efforts, which benefits the patient, site, and, ultimately, the trial research.

Following are Firma's 7 best practices to support pediatric clinical trials and participating families while also conferring a strong operational and financial benefit to pediatric drug development.

1 Using Qualified Personnel Increases Retention and Adherence

In the typical pharmaceutical model, it may not be possible to have staff with pediatric experience, whereas a patient-centric home health visit model uses child-friendly nurses, phlebotomists, and other health care personnel who are used to working with children.

In our experience, qualified personnel with pediatric experience have these attributes:

- Extensive knowledge of study execution in this specialty population
- Familiarity with the nuances and special requirements of the pediatric population
- Commitment to and champions for children
- Personal connection to the patients and their parents or caregiver
- Environmental awareness of issues in the home (e.g., overly anxious parent)

Well-trained pediatric nurses can quell any sponsors' and parents' concerns of study procedures based on their direct experience supporting pediatric patients. They can also skillfully undertake protocol procedures, as well as provide instruction to the caregiver on how to administer any required procedures to the pediatric patient for the trial period. Nurses experienced in supporting pediatric patients provide a skilled and friendly face for trial support, enhancing patient retention, and protocol adherence.

2 Widening Location Increases Enrollment

For 55% of caregivers, the physical location of the research center (distance from home or work) was the most important factor to participating in a clinical trial.[18]

With a home health visit model, parents don't have to undertake frequent travel, and their child can be seen in a known comfortable environment, such as their home or childcare center. This treatment at home approach ensures a greater sense of patient comfort during the trial and the widening geography allows for a larger population to be supported as part of the trial, increasing patient enrollment possibilities for the site and the trial.

3 Mitigating Clinical Trial Concerns Increases Interest

The number of study visits and types of medical procedures required and the time commitment were listed by 53% and 49% of parents, respectively, as the most important factor influencing participation in a clinical study.[19]

The most common reason for children to reject participation was the need to undergo procedures that were scary or painful, such as injections or blood draws. In other cases, the required time commitment for traveling to the study site for evaluations interfered with other activities the children preferred. The less "medical" their experience, the more likely they are to enjoy their participation in the study.[20]

Home health visit personnel employ a number of techniques to mitigate children's fears and engage them as partners in the process:

- Age-appropriate tools
- Smallest needle gauge possible for a particular patient (one size doesn't fit all)
- Sensory devices (e.g., Buzzy® shotblocker)
- Alternative sampling techniques (e.g., finger or heel pricks, salivary samples)

4 Managing Expectations Prevents Early Discontinuation

Firma's experienced healthcare personnel realize the importance of clear and upfront detailing of responsibilities when discussing protocol procedures and commitments with trial patients. Applying clear and transparent discussions will help prevent early trial discontinuation by patients, including through some of the following ways:

- Set early expectations
- Allow ample opportunity for questions and clarifications of responsibilities
- Explain importance of participation
- Show appreciation and recognition for their time and efforts

5 Effective Communication Ensures Protocol Compliance

As pediatric drug development is advanced in close partnership/collaboration with industry, regulators, and investigators, it's important to maintain effective communication between the multiple stakeholders in the clinical trial (e.g., site, laboratory, patient, and parents or caregiver).

A well-trained team actively reviews all protocol procedures and examines the communication pathways between all groups involved to ensure proper communication between site, patient, caregiver, and central laboratories (as applicable). This overview and management ensure proper coordination and planning of visit procedures and shipment of visit samples to maintain protocol compliance.

6 Benefits of Preparation to Enhance the Patient Trial Experience

Patient-centric home health visit teams advance preparation prior to scheduled trial procedures and visits facilitates smooth and successful interactions by:

- Clearly defining and communicating to parents when and how their assistance is needed
- Explaining the details and actions associated with each visit
- Emotionally preparing the parent and child
- Physically preparing the child (e.g., adequate hydration)

7 Flexibility Encourages Recruitment and Trial Participation

Integrating the option of home health visits provides increased flexibility to trial patients, encouraging them to consider participation in clinical trials when they may not have previously. Applying home health visits to clinical trials allows patients and caregivers to benefit through:

- Accommodating busy schedules, as visits can be scheduled outside of the clinical trial site
- Home visits that allow adequate time for blood draws, vital signs, questions, observations, and drug administration
- Use of nontraditional locations (e.g., schools, places of employment) to meet patient needs
- Accommodating family vacations by arranging visits out of city or state

CONCLUSION

The advancement of pediatric regulations and an expanding commitment to pediatric studies by sponsors have greatly increased the demand for timely, high-quality, cost-effective pediatric clinical trials. Unlike clinical trials in adult populations, pediatric patients and the involvement of their caregivers present unique challenges within drug development and trial operations. Integrating a patient-centric home health visit offering into clinical trials enables sponsors to overcome and mitigate some of the challenges inherent in trial conduct and enhances recruitment, while fostering increased patient retention and compliance. Given these potential benefits, sponsors should consider the application of this supportive service to increase the value to patients, caregivers, and the pediatric drug development process.

End Notes

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About Firma Clinical Research

Firma is a boutique contract research organization (CRO) that believes a patient-centric approach is the key to unlocking positive outcomes in the drug and medical device development process. Using an integrated suite of specialized solutions, Firma makes the clinical trials process easier and more valuable for patients and produces higher-quality data for sites and sponsors.