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Review Article

Advancing Pediatric Healthcare: Legislation, Clinical Trials, and Technological Innovations in Drug Development

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ABSTRACT

Historically, there have been constraints on pediatric drug trials, resulting in an absence of authorized medicines for children and a significant reliance on off-label use. Pediatric drug development is critical to addressing the special issues of treating children and adolescents. The lack of authorized pediatric treatments has led to efforts to incentivize and compel pediatric medical research in the United States and Europe. The data collected from the FDA and the EMA databases from 2013 to 2023 were analyzed. Statistical analyses revealed trends and changes in exclusive interventions, and qualitative analyses examined research methodologies specific to pediatrics. Clinical trials play a vital role in closing the knowledge gap and improving pediatric treatment. Recent advancements in technology and research methodologies have helped improve pediatric healthcare and treatment.

Keywords: Clinical Trials, Pediatric Drug Development, Pediatric Exclusivity, Pediatric Regulations, Healthcare.

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INTRODUCTION

Pediatric medication studies have historically been restricted, resulting in a shortage of authorized treatments for children and substantial off-label usage.[1] Before the 20th century, there were no explicit ethical standards or laws controlling research with minors, which led to certain unethical acts (Table 1).[2] Recognizing this gap, legislative actions in the United States were implemented in 1997 to reward and compel pediatric medical research, addressing the long-standing need for greater information on safety and efficacy in this group.[3] Pediatric drug development is critical to addressing the special issues of treating children and adolescents.[4] Many drugs are designed for adults, resulting in extensive off-label usage and a scarcity of children's versions.[5] It is critical to develop novel formulations and dosage techniques that are especially customized for pediatric usage. Access to essential medications for children is a critical component of their right to health, yet securing this access remains difficult.[6] Efforts have been made to include new chemotherapeutic drugs used in juvenile cancer therapy on the Model List of Essential Medicines for Children (EMLc), although there are concerns regarding the impact on outcomes for children in Low- and Middle-Income Countries (LMICs).[7] In Europe, pediatric regulation directives were adopted in 2006,[8] which came into force in 2007.[3] As for Japan no laws or regulations mandating pediatric drug development have been established.[9] Canada lags in ensuring access to pediatric medicine but in 2020 Health Canada Pediatric Drug Action Plan was developed.[10]

Pediatric clinical trials aim to assess safety and efficacy in pediatric populations, address the specific needs and responses of children, as they have different pharmacokinetic and pharmacodynamic profiles compared to adults, determine appropriate dosages and formulations and the time frame of clinical trials in pediatrics is a significant concern, particularly for medications used in long-term therapy.[14] Clinical trials in children are required to enhance their health and guarantee that they receive therapy based on the same level of information as adults (Figure 1).[15] Children have distinct pharmacokinetic and pharmacodynamic reactions than adults, thus extrapolating adult data for pediatric medication can be devastating.[16] There is a knowledge vacuum about the efficacy and safety of medications in children, and they are frequently administered off-label.[17] Pediatric neurological illnesses need specialized studies since

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their clinical symptoms and results differ from those of adults.[18] The number of pediatric clinical trials approved in the United States has grown over time.[19] ClinicalTrials.gov registered 36,136 clinical trials and 16,692 observational studies from January 2008 to December 2019.[19] FDA and EMA have provided incentives in the form of pediatric exclusivity (Table 2). Pediatric exclusivity, which allows manufacturers an additional 6 months of market exclusivity after completing pediatric clinical trials, has had a substantial influence on the development of novel pediatric drugs.[20] Pediatric exclusivity has been critical in motivating pharmaceutical research and boosting pediatric medicine supply, although its efficacy and influence may vary based on unique circumstances and legal issues.[21]

Pediatric Regulations

WHO (World Health Organization)

The World Health Organization (WHO) standards for pediatric medication development are critical in fostering ethical and effective procedures around the world.[24] They give advice and best practices through papers such as the WHO Good Clinical Practice guidelines, they promote research and capacity building in poor countries, and they advocate for children's health and ethical research conduct.[25] While national laws such as those issued by the US FDA have legal power, WHO's efforts have a substantial effect on these regulations and contribute to the establishment of a worldwide framework for responsible pediatric drug development.[26] Specific incentives contributions for pediatric drug development include the Pediatric Tuberculosis Development Initiative (TB-PDT), the Pediatric HIV/AIDS Treatment Optimization Project (TOPE), Data collection and sharing and Ethical considerations in pediatric research.[27]

India

The Drugs and Cosmetics Act and Rules regulate paediatric medication development and clinical trials in India. Schedule Y of the Act details the standards for study protocols, informed consent forms, documentation, and the makeup and duties of ethics committees, with a specific focus on child patients as a vulnerable population.[28] However, there is presently no laws in India that specifically addresses pediatrics clinical trials.[29] In 2019, the New Drugs and Clinical Trials Rules were enacted to improve India's clinical trial regulatory system, including bioequivalence and bioavailability studies, ethics committees, and experimental novel pharmaceuticals.[30] There is a growing recognition of the need for more robust regulations devoted specifically to paediatric drug development.

United States

FDA Modernization Act (1997)

A legislation in the U.S. which encourages pediatric drug development and provides market exclusivity to manufacturers leads them to produce safe and effective drugs for children.[31]

Pediatric Rule (1998)

The goal of this guideline was to guarantee that drugs intended for use in children were sufficiently researched, even if the initial prescription was for adults.[32]

Best Pharmaceuticals for Children Act (BPCA) 2002

The BPCA increased and broadened incentives for pediatric medication development. It gave pharma companies more exclusivity when undertaking pediatric trials, promoting more detailed research on medications used in children.[33]

Table 1: Milestones in development of Pediatric regulations[11-13]

Era	Milestone	Year	Significance
Pre-20th Century	Limited ethical considerations.	N/A	Unethical practices due to lack of regulations.
20th Century	Kefauver-Harris Amendment.	1962	Shift towards requiring pediatric data for drug approval.
20th Century	First FDA requirement for pediatric labelling.	1979	Voluntary participation limited data availability.
20th Century	Formation of the Pediatric Research Committee (PRC).	1983	Provided guidance for pediatric drug development.
21st Century	ICH Guideline E11.	2000	Established international standards for pediatric trials.
21st Century	Best Pharmaceuticals for Children Act (BPCA).	2002	Streamlined processes, funded research, and mandated PRMPs.
21st Century	Pediatric Research Equity Act (PREA).	2003	Significantly increased number of drugs investigated in children.
21st Century	Food and Drug Administration Amendments Act (FDAAA).	2007	Strengthened PREA and allowed conditional approvals.
21st Century	Continued efforts (2012 onwards).	2012+	Improved efficiency, addressed complexities, and secured funding.

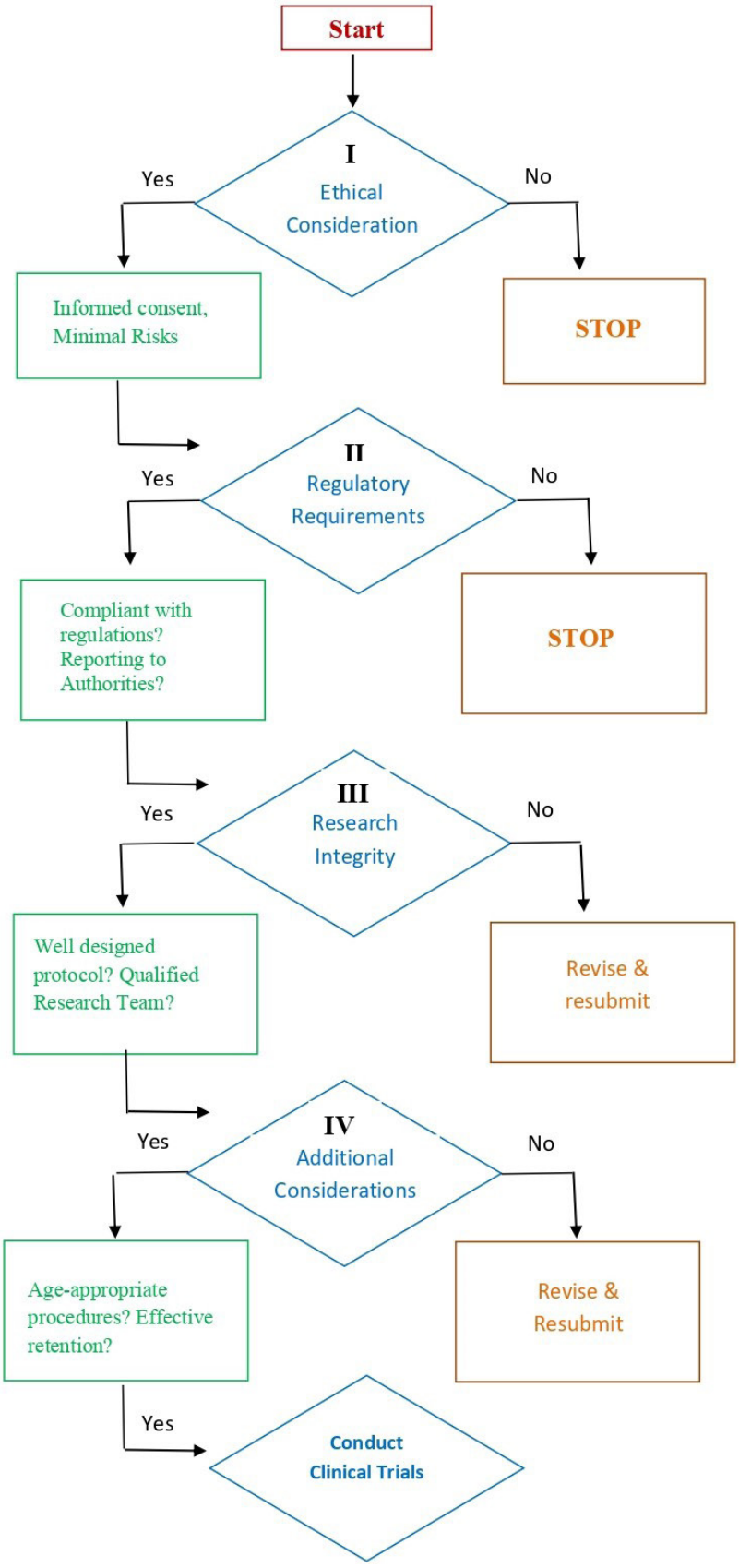

Figure 1: Requirements for Conducting Pediatric Clinical Trials.

Table 2: Comparative Analysis of Drugs Granted Exclusive in the U.S. and Europe.[22,23]

Drug Name	Country	Date of Exclusivity	Length of Exclusivity/ Market Exclusivity	Indication
Vraylar (cariprazine).	U.S.	February 14, 2019	6 months.	Schizophrenia and bipolar disorder in adults and adolescents aged 13-17 years.
Ontruzant (narabeglumab).	U.S.	May 23, 2019	6 months.	Hypersensitivity pneumonitis (an inflammatory lung disease).
Rezolve (canagliflozin).	U.S.	May 28, 2019	6 months.	Type 2 diabetes mellitus in adults and adolescents aged 10 years and older.
Uplizna (necitumumab-tmcd).	U.S.	August 15, 2019	6 months.	Metastatic squamous non-small cell lung cancer.
Oxervate (glucagon).	U.S.	January 10, 2020	6 months.	Severe hypoglycemia (low blood sugar) in children aged 2 years and older and adults.
Daurismo (diflunisal).	U.S.	August 21, 2020	6 months.	Familial adenomatous polyposis (a hereditary condition that increases the risk of colon cancer).
Vyndaqel (taflupromil).	U.S.	June 11, 2021	6 months.	Narcolepsy type 1 in children aged 7-17 years.
Axumin (fluciclovine F 18).	U.S.	March 7, 2023	6 months.	Imaging agent for the detection of recurrent prostate cancer after primary definitive therapy.
Tecentriq (atezolizumab).	U.S.	July 26, 2023	6 months.	Treatment of locally advanced or metastatic urothelial carcinoma (a type of bladder cancer) in pediatric patients aged 12 years and older.
Vyondys 51 (dextrorphan tartrate).	U.S.	September 26, 2023	6 months.	Treatment of pseudo-obstruction or constipation associated with Hirschsprung's disease in pediatric patients aged 2 weeks and older who have not responded to laxatives.
Zynquel	Europe	March 2022	10 years PUMA.	Spinal muscular atrophy (SMA).
Evrysdi	Europe	July 2020	10 years PUMA.	Spinal muscular atrophy (SMA).
Hemlibra	Europe	September 2019	10 years PUMA.	Hemophilia A.
Uplizna	Europe	May 2023	10 years PUMA.	Chronic inflammatory demyelinating polyneuropathy (CIDP).
Nivolumab	Europe	June 2020	10 years PUMA.	Metastatic neuroblastoma.
Kisqali	Europe	May 2023	8 years PUMA.	Hormone-receptor positive, HER2-negative advanced breast cancer.
Tezspire	Europe	November 2022	8 years PUMA.	Severe asthma.

Pediatric Research Equity Act (PREA) 2003

To ensure that manufacturers perform research in pediatric populations to examine the safety and effectiveness of certain medications. The primary objective is to better understanding of how pharmaceuticals impact children, stimulate the development of pediatric-specific doses and formulations, and eventually improve the safety and efficacy of pediatric medications.[34]

Europe

Regulation (EC) No 1901/2006 on Paediatric Medicinal Products: On January 26, 2007, this regulation went into force. The Paediatric Regulation, as it is commonly known, was implemented by the European Commission to enhance children's health by easing the development and availability of pharmaceutical goods particularly tailored for them.[35]

Table 3: Key differences in pediatric clinical trials before and after regulations came into force.

Feature	Before Regulations	After Regulations
Ethical considerations	Limited or non-existent formal ethical frameworks and regulations, lead to potential exploitation of children in research.	Emphasis on ethical considerations, informed consent, and protection of children's rights and well-being through regulations and guidelines.
Data availability	Scarce data due to voluntary participation and lack of requirements for pediatric trials.	Increased availability of pediatric data due to mandatory or encouraged trials, leading to a better understanding of drug effects in children.
Standardization	Inconsistent practices and methodologies, making it difficult to compare results across studies.	Standardized protocols and guidelines (e.g., ICH E11) promoting consistency and ensuring data quality.
Trial design	Often designed based on adult data with limited adaptations for children, potentially leading to inaccurate or misleading results.	Trials designed specifically for children, considering their unique physiological and developmental characteristics.
Oversight and monitoring	Limited oversight and monitoring, increasing the risk of unethical practices and inadequate data collection.	Rigorous oversight and monitoring by regulatory bodies (e.g., FDA) to ensure safety, ethical conduct, and data integrity.
Funding and incentives	Limited funding and lack of incentive for conducting pediatric trials, hindering research efforts.	Increased funding opportunities and incentives (e.g., extended marketing exclusivity) to encourage pharmaceutical companies to invest in pediatric research.
Participation rates	Low participation rates due to logistical challenges and ethical concerns.	Improved recruitment and retention strategies, leading to more efficient and representative trials.

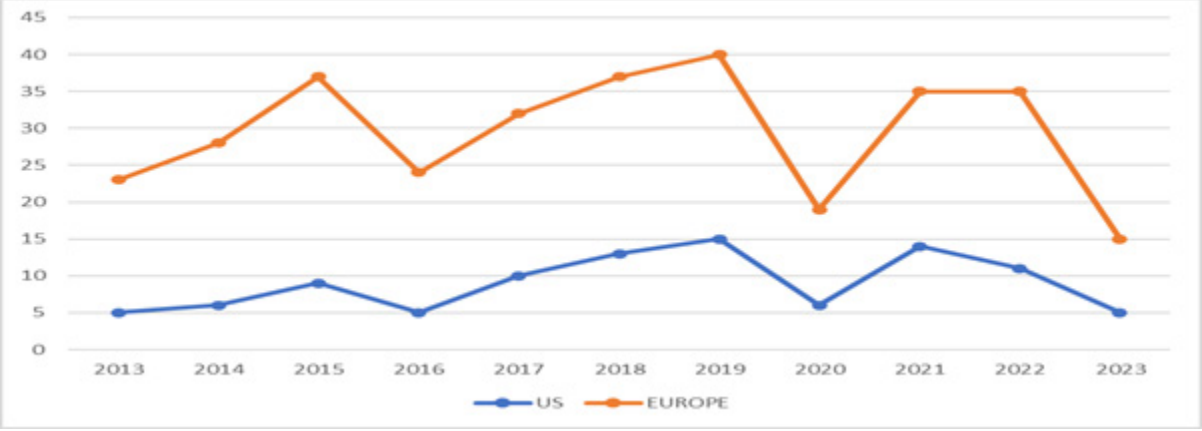

Figure 2: Total Number of Pediatric Exclusivity Granted.

Pediatric Investigation Plans (PIP)

It requires manufacturers to submit PIP when applying for marketing authorization of new drugs unless waivers and deferrals are granted.[36]

Rewards and Incentives

Include a six-month extension of the Supplemental Protection Certificate (SPC) and, in some circumstances, a monetary prize if the pediatric studies are completed in accordance with the PIP.[37]

Pediatric Committee (PDCO)

The PDCO is in charge of evaluating PIPs, issuing waivers or deferrals, and offering scientific advice on paediatric development.[38]

Pediatric-Use Marketing Authorization (PUMA)

Granted to medications that are specially developed for children and are previously approved but lack patent or additional protection coverage. PUMA certification provides 10 years of market protection.[39]

Analysis of pediatric exclusivity granted in the U.S. and Europe

The information was collected on granted pediatric drugs for exclusivity from 2013 to 2023 from FDA[22] and EMA[23] databases (Figure 2). Statistical analyses revealed trends and changes in exclusive interventions, and qualitative analyses examined research methodologies specific to pediatrics. Data were analyzed for selected compounds. Objectives and factors influencing exclusivity were considered in the data interpretation. Limitations of the study were acknowledged, and future research directions were suggested. This comprehensive approach allowed us to examine the distribution and impact of pediatric stimulation alone, contributing to insights into pediatric treatment over five years.

A total number of exclusivity grants in Europe and the United States were identified, which included an active ingredient that was already approved for pediatric indication in younger children. Among these drugs, generic drugs, biosimilar products, vaccines, and combined hormone products were excluded.

Clinical Trials

Clinical trials play a crucial role in advancing medical knowledge and improving patient care across various fields of medicine.[40] However, when it comes to pediatric medicine, clinical trials hold even greater significance due to the unique challenges and considerations associated with treating children.[41] These trials are critical because children respond differently to drugs than adults and extrapolating findings from adult trials can have negative consequences.[42] Conducting clinical trials in children contributes to closing the knowledge gap in pediatric treatment about the effectiveness and safety of medications.[43] It also guarantees that children receive therapy based on evidence-based information rather than off-label usage of adult-only medications.[44] Without pediatric clinical trials, healthcare providers would have limited evidence-based information on how to safely and effectively treat children with various diseases and conditions.[45] The importance of pediatric clinical trials is underscored by the fact that children have been identified as uniquely vulnerable clinical research subjects since the early 1970s (Table 3).[46] Informed consent is a critical aspect of pediatric clinical trials, and it has been highlighted that parental permission holds considerable weight when it comes to participation in these trials.[47] Moreover, ethical issues in neonatal and pediatric clinical trials have been discussed, emphasizing the importance of addressing the unique ethical considerations involved in conducting clinical trials in children.[48]

Several illnesses and disorders require pediatric clinical trials. Inflammatory Bowel Disease (IBD) is one such disorder that necessitates pediatric clinical trials to bridge the gap between adult and pediatric therapy.[49] Childhood Interstitial Lung Disease (chILD) is another area where clinical trials are desperately needed, as therapeutic choices for pediatric patients are limited.[50] The continuing COVID-19 pandemic has also emphasized the need for pediatric clinical studies to demonstrate the effectiveness, safety, and pharmacokinetics of antiviral treatments for children infected with SARS-CoV-2.[51] There is a difference in the number of medications licensed for pediatric cancer patients compared to adults in the area of oncology, making pediatric clinical trials critical for the development of effective therapies.[52] Finally, pediatric clinical trials are needed to find early therapies that might reduce long-term consequences in afflicted children and young people with Autosomal Dominant Polycystic Kidney Disease (ADPKD).[53]

The Thalidomide Tragedy, Sulfanilamide Disaster, and Clioquinolol Tragedy were all tragic incidents in pediatric clinical trials that resulted in significant morbidity and mortality.[54] Suicidal ideation and behavior have also been seen in pediatric antidepressant medication clinical studies, raising concerns about their safety.[55] Despite previous tragedies, a continuing commitment to pediatric clinical research is critical for solving unmet medical needs, guaranteeing pediatric patient safety, and improving long-term health outcomes in children and young people.[56]

DISCUSSION

Recent studies in pediatric development

Recent pediatric development research and technologies in 2023 have focused on the utilization of Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) in clinical pediatric medical settings and pediatric medical training.[57] Randomized Controlled Trials (RCTs) have proven that these technologies have made considerable gains in clinical application and medical training.[58] There has been a change in cancer treatment towards targeted therapy and biomarker-selected phase 2 studies, with the goal of identifying innovative medicines and combinations to enhance the care of children with cancer. New technologies, such as nose-to-lung administration, active positive-pressure devices, and highly dispersible excipient-enhanced growth particle formulations, have been developed in the field of dry powder aerosol formulations to improve lung delivery efficiency and consistency in children.[59] With applications such as telemedicine, precision medicine, automated decision support systems, electronic health records, patient portals, Artificial Intelligence (AI), and mobile and wearable technologies, Information and Communication Technology (ICT) has also revolutionized pediatric healthcare.[60] Nanotechnology has been presented as a valuable technique for pediatric formulation development, with benefits such as greater treatment efficiency, better medicine taste, and focused therapy.[61]

Advancement in pediatric clinical trials

The TEENS Study

The goal of this large-scale research is to avoid chronic illnesses like as obesity and diabetes by employing wearable devices and smartphone apps to monitor health data and physical activity in adolescents.[62] The objective of this study was to investigate the effectiveness of a technology-assisted intervention in promoting weight loss and healthy lifestyle changes in adolescents with overweight or obesity. The study highlights the potential benefits of such approaches and encourages further research and development in this area.[63]

The ACTT trial

This virtual trial used telehealth platforms to investigate the efficacy of a repurposed medicine in treating critically sick children with COVID-19, proving the value of virtual platforms in time of need.[64] The ACT trials are international trials evaluating the efficacy of anti-inflammatory therapy with colchicine and antithrombotic therapy with aspirin in patients with symptomatic COVID-19. The outpatient trial aims to enroll 3500 patients and is evaluating colchicine vs usual care and aspirin vs usual care. The trials will provide valuable insights into the efficacy of these therapies in patients with mild, moderate, and severe COVID-19.[65]

The CHOP-TCGA initiative

The CHOP-TCGA (The Cancer Genome Atlas Pilot Project) effort in children aims to enhance surgical treatment for children, particularly those in low-resource settings. A group of paediatric surgical care professionals known as the Global Programme for Children's Surgery (GICS) established the programme. GICS intends to bring together a diverse team of doctors and activists to address the disparities in access to safe and inexpensive surgical and anaesthesia treatment for children in Low- and Middle-Income Countries (LMIC).[66] The programme aims to improve surgical treatment for children by providing training, resources, and support to healthcare practitioners in low- and middle-income countries, with the ultimate objective of closing the global gap in access to surgical care for children. GICS's expertise in improving surgical treatment for children might serve as a model for international collaboration in other areas of public and global health.[67]

CONCLUSION

The lack of authorized pediatric treatments and extensive off-label usage has led to efforts to incentivize and compel pediatric medical research in the United States and Europe. Legislative actions and regulations in the United States and Europe have been implemented to incentivize pediatric drug development. Clinical trials play a vital role in closing the knowledge gap and improving pediatric treatment. Recent advancements in technology and research methodologies have helped improve pediatric healthcare and treatment.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

EMLc: Model List of Essential Medicines for Children; **TB-PDT:** Pediatric Tuberculosis Development Initiative; **PUMA:** Pediatric-use Marketing Authorization; **BPCA:** Best Pharmaceuticals for Children Act; **PREA:** Pediatric Research Equity Act; **chILD:** Childhood interstitial lung disease; **ADPKD:** Autosomal Dominant Polycystic Kidney Disease.

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