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EDITORIAL

Accelerating Pediatric Drug Development: A 2022 Special Issue of *Therapeutic Innovation & Regulatory Science*

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Introduction

In 2015, Spielberg and Portman introduced a special section in *Therapeutic Innovation & Regulatory Science* (*TIRS*) on "New Horizons in Pediatric Drug Development" [1]. This special section highlighted the challenges and opportunities in pediatric research and therapeutic development following the early legislative efforts to provide safe and effective medicines to children. In 2019, we updated the New Horizons special section with articles on "Innovation and Opportunities in Pediatric Therapeutic Development" [2]. As the pediatric community has gained experience in regulatory level clinical trials over the past 15 years, new strategies to enhance the chance for trial success through better dose selection, increased patient enrichment, leveraging all available data and identification of more suitable clinically relevant endpoints have been implemented. The next phase of augmented pediatric trial implementation involves the use of more complex trial designs, the implementation of targeted approaches in specific patient populations, and the use of new technologies with unique applications in pediatric trials. Once again, we are updating the importance of collaboration through global networks and stakeholder engagement, including health equity and the voice of children and their families.

Pediatric legislation underpinning the development of pediatric therapeutics was required to overcome the hesitancy to include children in clinical trials. In the U.S., the Best Pharmaceuticals for Children Act (BPCA) of 2002 and the Pediatric Research Equity Act (PREA) of 2003 provided an incentive and a requirement for pediatric drug development, respectively. These programs were made permanent in 2012 under the Food and Drug Administration Safety and Innovation Act (FDASIA). Since 2007, the FDA has issued priority review vouchers for tropical diseases, medical countermeasures, and rare pediatric diseases. In 2016, the Advancing Hope Act updated the definition of "rare pediatric disease" and created a requirement for sponsors seeking a rare pediatric disease priority review voucher to request the voucher on submission of the rare pediatric disease product application [3]. In 2020, the Rare Pediatric Disease Priority Review Voucher Program was extended for rare disease product applications that have rare pediatric disease designation granted by September 30, 2024 [4]. In 2018, the Research to Accelerate Cures and Equity (RACE) for Children Act was signed into law as part of the 2017 FDA Reauthorization Act which amended PREA. The RACE for Children Act promotes the development of new cancer treatments for children by requiring pediatric investigation of drugs or biologics that are directed at molecular targets relevant to pediatric cancers and it eliminates the orphan exemption for these oncology products [5]. In addition, the 21st Century Cures Act established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to advise the Secretary of Health and Human Services on the gaps in knowledge and research on safe and effective therapies for pregnant and lactating individuals [6]. In the EU, Pediatric Regulation was introduced in 2007 with the requirement for Pediatric Investigation Plans (PIPs) to be submitted to the EMA for evaluation and approval by the Pediatric Committee (PDCO). A PIP or waiver must be submitted for new active substances and for already authorized products under patent whenever a new indication, pharmaceutical form or route of administration is being developed. The articles in this issue touch on a number of the new initiatives that have been instituted to continue to encourage the development of pediatric therapeutics, recognizing that

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successful approaches will require innovative strategies and global stakeholder involvement.

In this pediatric special issue of *TIRS*, a series of articles propel us into the next phase of pediatric drug development. These efforts are focused on innovative trial designs, issues related to rare diseases and pregnant individuals, advances in pediatric formulation development, development of digital technologies in pediatric trials, an update on pediatric global networks, and a discussion of stakeholder engagement with a focus on health equity and the voices of the children and their families.

In the 2019 *TIRS* pediatric special section, the importance of leveraging data from all studies, utilizing extrapolation whenever possible, and developing creative analytic strategies including modeling and simulation were discussed. In the current special issue, extrapolation is updated from a few slightly different perspectives, including a discussion of the optimization of extrapolation, and extrapolation as a default strategy. The use of novel trial designs, including the development and refinement of platform designs and master protocols specifically for use with pediatric patients, is presented. As a substantial number of rare diseases occur primarily in pediatric patients, global initiatives in rare diseases are examined. The PRGLAC initiative provides a spotlight on pregnant individuals and the fetus, a new area for consideration for therapeutic studies, and one that can benefit from the work done in the pediatric space. Companies have continued to struggle with the development of pediatric specific formulations, so it is particularly exciting to learn about innovative approaches to studying the acceptability of pediatric formulations as well as the development of 3D printing approaches to the individualization of pediatric medicines. Digital approaches have been integrated into our lifestyles and are becoming an important component of pediatric trials. Finally, we have highlighted the importance of stakeholder engagement in each of the prior TIRS pediatric special sections, and we continue here by updating the tailored approach to children and families in trials and highlighting heath equity in pediatric drug development.

It is only fitting that in 2022, we review the progress in pediatrics over the last 10 years since the first passage of BPCA. As Dunn et al. discuss the ability to accelerate the availability of medicines for children, they present a historical framework starting with a period of acknowledgement, followed by a period of suggested action and a period of required action, leading to the current period of refinement [7]. Extrapolation is a concept that was highlighted in the 2014 FDA guidance on "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products [8]." Dunn et al. examined the new molecular entities approved between 2002 and 2020 and documented the extrapolation method (none, partial, full extrapolation of efficacy). They provided examples from infectious diseases, cardiac arrhythmias, pulmonary arterial hypertension, schizophrenia, partial onset seizures, cystic fibrosis, and relapsing remitting multiple sclerosis. Each of the examples highlights the degree of disease similarity with respect to disease progression and response to therapeutic intervention between pediatric and adult patients. These approaches continue to be refined as pharmaceutical companies, academia, and patient advocacy groups collaborate with the regulatory agencies to incorporate the latest scientific knowledge into the extrapolation assessment [7].

As the science advances and helps to support additional opportunities for extrapolation, Gamalo et al. propose that all pediatric drug development programs for products developed initially for adults or different pediatric age groups should "initially assume some degree of extrapolation" with a justification for utilizing extrapolation as the default position. They present a framework for extrapolation within the context of three archetypes: (1) first in class or first indication in adults, (2) established class where adult trials have confirmed safety and efficacy achieving registration, and (3) established class where adult and pediatric trials have been conducted achieving registration. A more refined and expanded use of extrapolation for both efficacy and safety through the appropriate use of both non-clinical and clinical data should help to decrease the time to approval for pediatric drugs. The expanded efforts in extrapolation may be augmented by the use of master protocols in basket, umbrella, and/or platform trials [9].

Master protocols can be particularly useful in the setting of multiple companies enrolling patients into trials of drugs to treat the same disease, as they may be able to streamline operations, improve enrollment, and potentially share a control group. Nelson et al. discuss the intricacies of the implementation of master protocols and the expanded use from oncology trials to other pediatric therapeutic areas. Further, as new drugs with mechanisms of action that can be effective for multiple indications are developed, commonalities such as formulation development, toxicity in juvenile animals, and pharmacokinetic/pharmacodynamic studies in the resulting pediatric indications should be sought to make pediatric studies more efficient [10].

In addition to advances in trial execution, progress has been made in the development of pediatric formulations and the use of digital technologies. A major issue in the development of pediatric friendly formulations is the acceptability of the product and its impact on compliance. However, there is no universal definition of acceptability that takes both palatability and deglutition into consideration. Wargenau et al. present the development and validation of a composite acceptability endpoint for deglutition and palatability in children of different ages (newborn to 18 years) with different galenic placebo formulations (mini-tablets, oblong tablets, orodispersible films, and syrup). This highly sensitive

composite endpoint will facilitate the ability to assess and compare the acceptability of pediatric formulations that are developed as part of drug programs for children [11]. Quodback et al. present the unique considerations of fused deposition modeling (FDM) 3d printing of drug doses to provide individualized small dosage forms. For rare diseases, small batches of individualized medicines with varying dosages, sizes, release profiles, and drug combinations can be designed. The article presents the work of the PolyPrint consortium with respect to the quality aspects, engineering considerations, and measures for 3d printing of medicines for children [12].

While highly innovative approaches are being designed to create individualized medicines, the miniaturization of sensors and other technologies support the acquisition of physiological and/or functional data from patients who are participating in clinical trials. Sacks et al. discuss the use of these technologies for a number of pediatric diseases including seizures and neuromuscular disorders, cardiorespiratory diseases, and metabolic diseases. Wearable devices may allow an increase in decentralized trial activities, thus limiting the site-based visits which may reduce the disruptive burden of the trial. Home-based activities may be more reflective of the capabilities of the child than would be captured in a site visit. Measurement of activity and sleep may provide important information about the well-being of children, particularly infants. In addition, digital health technology (DHT) has also been able to be used for biochemical measures such as monitoring blood glucose in patients with diabetes. Design considerations have limited some use of DHTs but this is promising technology to obtain clinical data in pediatric patients [13].

Clinical trials are undertaken to provide safe and effective therapies to patients. It is important that all stakeholders are included in the development process, especially children and their parents. In this issue, we update the status of pediatric global networks. Greenberg et al. update the pediatric clinical research networks in the US, Europe, Japan, and Canada. Now that these networks have been developed, it is important that they focus on collaboration and not competition while establishing standardized approaches. Each site needs to understand their therapeutic areas of excellence and their operational feasibility as we expect a significant number of pediatric trial opportunities in the next five years. Patient and parent advocacy groups are actively engaged in the network activities [14]. In previous issues, we have written of the importance of including the patient/pediatric voice but it has not routinely been accomplished. Preston et al. share lessons learned and practical information to ensure Patient and Public Involvement in all stages of research. Their community working with the International Children's Advisory Network (iCAN) and the European Young Person's Advisory Group Network (eYPAGnet) utilized the Patient Engagement Quality Guidance (PEQG) tool to assess lessons learned with respect to shared purpose, respect and accessibility, representativeness of stakeholders, roles and responsibilities, capacity and capability for engagement, transparency, communications and documentation, and continuity and sustainability [15].

Two groups that need special consideration are patients with rare diseases and pregnant individuals. Epps et al. describe the recent regulatory approaches and public health policies to foster the development of rare pediatric therapies as well as emerging trends in product development, innovations in trial endpoints and data collection, and efforts to promote equity and encourage patient engagement in clinical trials [16]. David et al. review the regulatory requirements for the study of drugs in pregnancy and highlight the need for developing therapies for the pregnant individual and the fetus, including the development of drugs to treat rare fetal conditions. New guidance is available on scientific and ethical considerations for including pregnant and lactating individuals in clinical trials as well as new safety terminology to define and grade adverse events that are specific to the mother, fetus, and neonate [17].

Health equity is a concept that overarches all of the articles in this issue. Folayan et al. present case studies of stakeholder and community engagement in clinical research with strategies for actively involving under-represented communities where there have previously been geographic, economic, racial/ethnic, legal, cultural, and linguistic barriers to trial participation. The three case studies include St. Jude's Hospital affiliate program in pediatric oncology research overcoming geographical inequity, the development of inclusive ethics guideline in West Africa overcoming legally-based lack of equity in access to research, and the efforts to change the culture of clinical trials overcoming the lack of equitable influence on research. While acknowledging that it is important to provide equitable access to all patients in clinical trials, accomplishing this is more complicated and requires sustained resources, time, a focus on outcomes that are meaningful to all stakeholders, and strong communication [18].

The pediatric drug development community has been working to accelerate access to safe and effective therapies. Nine years between adult approval and pediatric labeling is too long. In this issue, approaches to trial implementation are all focused on decreasing that development timeline through innovative trial designs (extrapolation and master protocols), improved formulation development with respect to palatability and manufacturing, and the use of DHTs to supplement clinical trial endpoints. The most important person is the patient whose condition impacts both them and the family. We must always focus on their needs, their concerns, and their burden. Pediatric trials designed with the individual patient in mind need to offer the potential for

timely access to therapies while optimizing trial strategies, utilizing novel decentralized approaches to data acquisition, and enhancing formulation development for acceptability, all in an effort to streamline trial implementation to minimize any delay in access to therapies for pediatric patients.

Disclaimer

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