

# The Complex Landscape of Drug Development for Children with Chronic Kidney Disease

By Debbie S. Gipson and Howard Trachtman

**C**hronic kidney disease (CKD) in children involves a host of rare diseases affecting children of all ages. The therapeutic needs of these children are largely unmet because of limited disease- and age-specific drug development. The absence of pediatric testing to document appropriate pediatric dosing, safety, and efficacy has many consequences:

- Few drugs are labeled for use in children with CKD.
- Off-label prescribing is often extrapolated from product labels written for adult patients with kidney disease or other non-kidney-related conditions.
- Little progress has been made to fill the information gaps required to guide the pharmacologic treatment of children with kidney diseases.

Drug development for children with kidney diseases must consider issues unique to this vulnerable population. Legislation by the United States and the European Union mandates plans for pediatric development as part of an overall product development strategy. This highlights the need to prioritize those programs that may be deemed most necessary and impactful and to optimize designs to facilitate their successful completion.

The Kidney Health Initiative (KHI) is engaging with relevant stakeholders, including patients, healthcare providers, researchers, professional organizations, industry partners, and regulators, to address these issues by developing recommendations to foster drug development for children with kidney diseases.

## Ethics of pediatric drug development

The ethics of clinical research inclusive of children has evolved “from a culture of protecting children from research to protecting children through research” (1). This perspective incorporates the understanding that access to safe and effective therapies requires testing of these same therapies in children. Failure to control pediatric kidney diseases has a documented adverse impact on the incidence and prevalence of pediatric kidney failure, the reduction in life expectancy after the onset of kidney failure, and the everyday lives of affected children (2).

Studies inclusive of children must pay particular attention to considerations for direct benefit, risk minimization, and study designs that are well suited for the adolescent, child, or infant age groups, or a combination of these, depending on the intended treatment population. The ethical inclusion of children in well-designed clinical trials is a key consideration.

Depending on the specific condition under investigation, pediatric inclusion in kidney disease clinical trials may include 1) adults and children simultaneously when there is a potential for direct benefit in the background of limited or unfeasible options for children, 2) children after demonstration of preliminary or robust evidence suggesting efficacy in adults, or 3) children alone when the disease under study does not occur in adults. Early consultation with experts in the pediatric nephrology community, with patients and family caregivers, and with members of the regulatory agencies such as the US Food and Drug Administration (FDA) can help to guide the clinical development plan.

## Improving opportunities for pediatric drug development: legislation and regulation

The limited drug development for children has been acknowledged by the United States government and the FDA. A series of legislative initiatives have provided incentives to include children in drug development activities by adding a 6-month extension on marketing exclusivity (3) and by establishing a framework for the FDA to request testing of prioritized therapies in children (4). Proposals are requested by the National Institute of Child Health and Human Development for priority (off-patent) drugs and therapeutic areas for testing. The Best Pharmaceuticals Act for Children program pro-

**In 1963, Dr. Harry C. Shirkey observed that “By an odd twist of fate, infants and children are becoming therapeutic or pharmaceutical orphans.”**

vides an opportunity for the pediatric nephrology community to advocate for therapeutics testing for children with kidney disease (5).

In 2007, the Pediatric Research Equity Act included the option for the FDA to require a pediatric investigation plan for new drug applications. However, orphan diseases (defined by the FDA as rare diseases and disorders that affect fewer than 200,000 people in the United States, or that affect more than 200,000 persons but for which drug development is not expected to recover the costs of developing and marketing a treatment drug) are excluded from these pediatric testing requirements. Despite the implementation of a series of legislative initiatives, rare and orphan diseases remain a neglected area of drug development.

The RACE for Children Act was enacted as a part of Title V of the FDA Reauthorization Act (FDARA) in 2017. This act requires the evaluation of new molecularly targeted drugs and biologics for oncology indications to be tested for use in children. Importantly, this act eliminates the orphan exemption for pediatric studies for new molecularly targeted cancer drugs. This legislation and the resulting program provide an example that may be replicated for children with kidney diseases in which precision medicine trials are emerging.

## Building a new reality of drug development for children with chronic kidney diseases

In partnership with experts from American Society of Nephrology’s (ASN) KHI, NephCure Kidney International’s (NKI) Gateway Initiative, and the American Society of Pediatric Nephrology (ASPN) Therapeutics Development Committee, complementary programs are

being launched to facilitate pediatric drug development for children with kidney diseases. All three entities are identifying ways to collaborate to improve the national capacity to conduct clinical trials in children.

KHI launched the Kidney-PATCH (Pediatric Accelerator Trial Clearing House) program in 2018. The program implementation committee is being led by H. William Schnaper, MD, of Northwestern University, who summarized the objective of Kidney-PATCH: “We’d like to serve as an honest broker for sponsors to conduct trials in children with CKD.” The goals of Kidney-PATCH are as follows:

- To enable feasibility assessment in terms of the available patient populations through data sharing and access to CKD pediatric registries.
- To facilitate assessment of the capacity of various pediatric kidney clinical trial organizations.
- To assist with the identification of expertise that can provide consultation on study planning.

Subject matter expertise has been identified from the United States and Europe to participate in the pilot phase of this program. Additional information about Kidney-PATCH and the request form can be accessed through the KHI website: [www.kidneyhealthinitiative.org](http://www.kidneyhealthinitiative.org).

NKI’s Gateway Initiative is bringing patients and family caregivers, clinicians, industry partners, and regulatory authorities together with professional society and foundation leadership to improve the clinical trial development and participation by individuals affected by glomerular disease. This initiative includes a Pediatric Working Group specifically charged to assist with strategies for the inclusion of children in clinical trials and for expanding the participation of patients and pediatric nephrology practices in glomerular disease clinical trials (KidneyHealthGateway.com).

“The success of the Gateway Initiative Pediatric Work Group is essential to drug development for glomerular disease,” said Joshua Tarnoff, chief executive officer, NephCure Kidney International. “With the wonderful evolution of regulatory pathways, there are currently 20 clinical nephrotic syndrome trials under way, up from only two a few years ago. Clinical trials simply must include adults and children in order to enroll the necessary population to bring trials to completion and drugs to market for the rare glomerular diseases.”

The opportunities for new pathways for drug development for children with kidney diseases are tremendous. We are observing an alignment of interest in drug development from the full spectrum of stakeholders, and we fully intend that children with kidney diseases will be the beneficiaries of this collective effort. ■

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