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EDITORIAL COMMENTARY

The urgent need for conducting clinical trials in pediatric nephrology globally

Aaron Wightman[1] · Guido Filler[2,3,4,5] · Maria Esther Díaz-González de Ferris[6]

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Abbreviations

CKD	Chronic kidney disease
FDA	Federal Drug Administration
ISN	International Society of Nephrology
IPNA	International Pediatric Nephrology Association
MRI	Magnetic resonance imaging
RCTs	Randomized controlled clinical trials

Introduction

Clinical trials form the backbone of evidence-based treatment, but, compared to other specialties, Pediatrics is underperforming with regards to prospective randomized clinical trials (RCTs), particularly Pediatric nephrology. Optimal treatment decisions require a high level of evidence about the efficacy and safety of therapies for all ages, generated by RCTs, but there are many more adult-focused than pediatric-focused studies [1]. There are conditions where using a placebo is not ethical, in which case non-inferiority trials can be considered. Examples are conditions where an effective standard of care treatment has been established, rendering a placebo-controlled trial obsolete (i.e., steroids in nephrotic syndrome [2]). Non-inferiority is determined relative to a non-inferiority margin [3].

Conducting clinical trials in the pediatric population has been difficult, in part due to the low incidence/prevalence of some health conditions, collaboration between the urban and rural practices, under-recognition of children's rights [4], and dependency on parents to sign consent. This has resulted in the 50–80% of drugs being used off label among children (depending on the age and health condition) [5]. In a review conducted in 2005, adults were more likely to be included in RCTs than children/adolescents [6]. In another US study of selected health conditions conducted between 2006 and 2011, almost 60% of the disease burden was attributable to children, but only 12% of the 2440 clinical trials reported on ClinicalTrials.gov were pediatric focused. While almost 60% of trials were conducted without industry sponsorship (relying primarily on government and non-profit organizations), pediatric trials were more likely to be adequately registered and published [1]. Furthermore, including children in combined adult/pediatric RCTs does not provide the same benefit, as subset analysis for children/adolescents is rarely performed [7].

This editorial commentary discusses barriers for clinical trials including the ethical approach to acquiring high level evidence for optimal decision making, lack of funding, paucity of partners, low interest from the pharmaceutical industry, regulatory issues, under-recognition of children's rights, and autonomy and attitudes of patients/caregivers and providers. Furthermore, we discuss the complex barriers using an ethical framework based on the principles of beneficence, nonmaleficence, autonomy, and justice, along with barriers and ethical implications of underperformance of clinical trials in pediatric nephrology. Finally, we offer strategies to optimize the culture of designing clinical trials and enrolling pediatric nephrology patients with particular attention to equity, justice, and inclusion of diverse populations.

✉ Maria Esther Díaz-González de Ferris
maria_ferris@med.unc.edu

1 Department of Pediatrics, Divisions of Nephrology, Bioethics and Palliative Care, University of Washington School of Medicine, Seattle, WA, USA

2 Department of Pediatrics, Schulich School of Medicine & Dentistry, Western University, London, ON N6A 5W9, Canada

3 Department of Pathology and Laboratory Medicine, Schulich School of Medicine & Dentistry, Western University, London, ON N5A 5A5, Canada

4 Department of Medicine, Schulich School of Medicine & Dentistry, Western University, London, ON N6A 5W9, Canada

5 The Lilibeth Caberto Kidney Clinical Research Unit, London Health Sciences Centre, London, ON, Canada

6 Department of Pediatrics, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Differences between pediatric subspecialties

Within the various pediatric subspecialties, there are great differences in clinical trials by subspecialty. In a 2005–2010 study of ClinicalTrials.gov, 5035 (7%) trials involved children in the following areas: 1176 (23%) pediatric infectious disease, 664 (13%) pediatric mental health, 346 (7%) pediatric hematology/oncology, and 213 (4.2%) pediatric cardiology [8]. An updated study from 2008 to 2019 revealed little change, reporting small-scale trials with significant heterogeneity in funding, conditions, and study design [9]. Pediatric nephrology is underrepresented, especially when nephrologists report little or no exposure to RCTs [10], or patient enrollment is not ideal [11]. In fact, a citation analysis demonstrated that published RCTs in adults are increasing at a faster pace than in children, with pediatric nephrology being in the last place [12], despite serving patients whose conditions are among the costliest to payors. The Federal Drug Administration mandated pediatric hypertension trials, but the few RCTs in children/adolescents pertain to non-medication interventions [13]. Nonetheless, RCTs are the gold standard for therapeutic effectiveness/safety [14].

Examples of some pediatric nephrology studies

While retrospective or observational studies have utility (e.g., International Study of Kidney Disease in Children [15], the Chronic Kidney Disease in Children [16], CureGN [17], PICCOLO MONDO [18], the International Peritoneal Dialysis Registry [19]), they cannot replace RCTs. Few trials in nephrotic syndrome have considerable successes [2]. However, our PubMed search (randomized[title] clinical trial nephrotic syndrome children) yielded 58 manuscripts from 1979 to 2022, while a similar search for acute lymphoblastic leukemia yielded 155 publications for the period 1982–2022.

Ethical considerations and harms

Ethical considerations must be based on beneficence, nonmaleficence (i.e., safety), autonomy, and justice. Scientific necessity, good risk/benefit ratio, and minimized burden are also paramount [20]. It is important to respect children's rights and have representation of patients from rural settings or low- or middle-income countries [4]. Table 1 elaborates on these ethical considerations and some of the harms.

Harms from limited enrollment in clinical trials

Harm can occur when providers assume a new standard of care without trials. Here are a few examples: aluminum was used as phosphate binder in the 1970–1980s without data on safety/toxicity. Children on dialysis or with chronic kidney disease (CKD) developed aluminum toxicity syndrome including encephalopathy, osteomalacia, and anemia [21]. In 1985, a trial of 12 CKD children compared aluminum with calcium carbonate and found equivalence of both interventions [22].

Table 1 Ethical consideration and harms for pediatric clinical trials

Ethical consideration	
Beneficence	Persons are treated in an ethical manner if their decisions are respected, protected from harm, and efforts secure their well-being. We are obliged to do no harm and to maximize benefits [25]
Nonmaleficence	There are ethical considerations about clinical studies or limitations for certain populations to be considered in the field of pediatric nephrology and other specialties
Autonomy	Autonomy is about respect for individuals who should be treated as autonomous agents, and persons with diminished autonomy, such as minors, are entitled to protection [25]. Not every human being is capable of self-determination, for instance children, who depend on their caregivers. The capacity for self-determination matures during an individual's life, while other individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated requires protection as they mature or while they are incapacitated [25]
Harms	
Harm to research generation of knowledge	Under-enrollment or including an overly selected population results in limited generalizability of findings [36]
Harm to society	Society can be impacted beyond lack of knowledge generation, namely through waste of funding [37]
Harms from limited enrollment in clinical trials	If there is a complete lack of prospective clinical trials, or inferring evidence from adult studies, will result in little progress and in the development of treatments without evidence base [26]

Another example is oxygen in neonates, as there is uncertainty about the optimal oxygen saturation level [23]. Other examples include bicarbonate supplementation in critically ill neonates, thalidomide, chloramphenicol, tetracycline, and aspirin, to name a few. Drugs used during pregnancy are woefully understudied [24].

Harms to women, children, minorities, rural populations, and those who speak different languages

Women, children, minorities, rural populations, and those who speak different languages are particularly understudied in RCTs, and this problem has been identified for some time. While there is some progress with including women over the past two decades [25], pregnant women, minorities, and children remain ignored. The same applies for studies in developing countries [26]. RCT recruitment in rural areas is also lacking, as most of the research occurs in the academic health centers typically located in large urban areas [27]. The lack of inclusion of these groups poses harm to participants and raises concerns about justice and lack of generalizability [28].

Barriers to clinical trials

These include patient-, caregiver-, or investigator-related barriers, funding, industry partnership, regulatory issues, disease-specific concerns, and multicenter/multinational collaboration.

Patient-related and condition-specific barriers

All minors are dependent on their caregivers, but as they age, their independence rises. Pediatric patients with CKD are at risk for abnormal cognition and poor academic performance, placing them at risk for understanding assents [29]. Abnormal cognition appears to be related to neurological dysfunction based on functional magnetic resonance imaging (MRI) [30] and MRI brain perfusion [31]. However, the multiple co-morbidities of CKD or kidney failure, such as anemia, hypertension, uremia, and acidosis, may play a significant role. While understudied in children, literacy level also worsens with CKD progression [32]. Lower quality of life has been reported in children with CKD who have high medication burden [33], short stature, are dialysis dependent, or from lower socioeconomic backgrounds [34]. Sex differences in mortality among pediatric patients with kidney failure has been reported in a US cohort, and this must be elucidated [35]. For ultra-rare conditions [36], there is no easy treatment solution. Other diseases may be highly unpredictable in their course, for instance, typical hemolytic uremic syndrome (HUS).

Caregiver-related barriers

Caregivers must allow their children to participate in RCTs, but they have an issue with randomization [37] or assent from their children [38]. Caregivers struggle with perceived benefits, better care for their children, access to new treatments, fear of potential side effects, being randomized to an ineffective treatment, and the inconvenience of participation [39]. Often, RCTs and outcomes are not necessarily meaningful and prioritized by patients/families, so it is vital to target patient-prioritized outcomes, consulting all stakeholders [40, 41].

Investigator-related barriers

There is limited experience on clinical trials among pediatric nephrologists [12]. Without a culture that supports RCTs, there may be limited engagement with developing trial protocols. Trainees are exposed to their mentors' biases, who use protocols from the center where they were trained. Providers may also have a concern about having a placebo arm [42]. The perceived or real risks of placebo interventions are twofold: the risks of the placebo intervention itself and any risks participants face because of receiving placebo, rather than potentially effective treatment [43]. Furthermore, providers may have the desire to treat the individual patient whom they deem will have the best approach/outcome. Finally, providers may not have the training to counsel patient/families about research.

Funding and partnership-related barriers

Unlike in the adult-focused setting, there is no urgent push from industry for new treatments for children/adolescents. Pediatric nephrology patients constitute a small population with little incentive for drug companies to develop novel treatments and fund trials. Even for common diseases such as typical HUS, proper RCTs of a new drug have not occurred since 2003 [44]. The problem with typical HUS is that interventions usually do not take place in the emergency room, where patients first present. Furthermore, there have not been proper RCTs for atypical HUS [45]. Fortunately, the National Institute of Health identified this problem and funded an RCT for focal and segmental glomerulosclerosis [11].

Recently, a few new drugs have become available for rare diseases, such as X-linked hypophosphatemic rickets [46], Fabry disease [47], hyperoxaluria type 1 [48], or new formulations of cysteamine [49, 50]. This is due to drug companies running low on the development of blockbuster drugs and shifting their business models to rare diseases with orphan drugs that may have easier approval from the Federal Drug Administration [51]. It is

unclear why other rare disorders (i.e., spinal muscular atrophy) are more successful in funding new drug development [52].

Multicenter and multinational collaboration barriers

The low incidence/prevalence of some pediatric kidney diseases are barriers for RCTs, requiring multi-center collaboration, as in the FSGS trial [11], yet this may lead to prioritization of large centers, potentially excluding other communities/populations. Multi-center studies also raise concerns about authorship in scientific publications. There are few clinical trial networks that are multinational, for instance, with the pediatric transplantation trial comparing microemulsified cyclosporine and tacrolimus [53] or the Canadian KidsCAN Trial Network [54]. These networks may over-represent Caucasian participants. Gene polymorphisms among other ethnicities such as Hispanics or Africans, for example, the CYP3A5*1 gene polymorphism, may limit generalizability [55].

Barriers to enrollment in clinical trials—regulatory side

Barriers regarding the regulatory side include little or no access to centralized research ethics boards. Informed consents/assents must be at universal literacy levels, and trial designs and outcomes acceptable to all regions (i.e., financial incentives are permitted in the USA, but not in Europe as there is a concern for exploitation of patients/caregivers [56]).

Social determinants of health and injustice

Social determinants of health play a role for participation in RCTs. Lower caregiver literacy has been associated with their children's poor outcomes [57]. Caregiver low socioeconomic status is associated with the risk of poor growth among their children with CKD [58]. Although socioeconomic status plays a role in patient outcomes among adults with kidney failure, the data in children still needs to be clarified; for example, living in rural areas has been associated with lower pre-emptive transplantation [59]. There may be an added cost to the inclusion of diverse populations, disproportionately impacting communities of color and/or low socioeconomic status. Historical injustices have resulted in mistrust of research, highlighting the need to rebuild trust [60]. There may also be community-specific factors where families may agree to anything their physician suggests. A major omission is the lack of sharing the results of the studies with the participants [61].

We must do justice

Research must be generalizable and inclusive of all populations [20]. There is a need to develop competency among nephrologists to participate in clinical trials. The adult-focused International Society of Nephrology (ISN) has implemented the ISN-Advancing Clinical Trials (ISN-ACT) program, to encourage existing infrastructures within ISN to improve participation in clinical trial research by the global nephrology community (https://www.theisn.org/in-action/research/clinical-trials-isn-act/, accessed 23-Nov-2022). We must find ways to make treatments available to patients from low- and middle-income countries, where new therapies are costly. The substantial gaps between when FDA-approved drugs are evaluated and when they become available need to be reduced [62].

We must foster research to determine what is relevant to patients and their caregivers globally. For instance, in a meeting with patient representatives of the CHILDNEPH study group [63], the pressing question of what to choose as second-line agent after steroids for childhood nephrotic syndrome was of much lower importance to the patient representatives as compared to simpler steroid taper protocols.

We need to develop greater flexibility in protocols that include technology and reduce visit frequency. We need to create therapeutic education material at a universal functional literacy level for patients/caregivers. We need to develop partnerships between the International Pediatric Nephrology Association (IPNA) and other regional associations, focusing on community-based participatory research. We need to foster a culture for pediatric nephrologists toward participation in global collaborations, with the commitment to dismantle the lasting impacts of structural or institutional racism and colonialism.

Strategies to increase pediatric-focused clinical trials

In a systematic review, 80 studies described issues with protocol development/pre-trial planning, trial marketing, educational tools, communication strategies, community involvement, incentives, and structural changes [64]. In a survey of rural and urban healthcare staff ($n=145$, 79% response rate) across Kansas, USA, rural providers were less supportive of recruiting patients in their practices and more likely to refer them to urban centers [65]. In that same study, providers identified potential incentives for participation in clinical trials: compensation for time and travel,

child support, tests and medications not covered by insurance, opportunity at local practices, and telehealth [65].

There is an urgent need to make progress in RCTs that serve neonates, infants, children, adolescents, and young adults with kidney and urinary tract conditions, with an ethical, evidence-based, and equitable approach. The development of dedicated pediatric nephrology trial networks is imperative and must include input from patients, caregivers, advocacy groups, researchers, pharmaceutical companies, and regulatory agencies. Ideally, clinical trials would be multicenter and multinational with a centralized institutional review board.

All trials need to be conducted following ethical considerations based on beneficence, nonmaleficence, autonomy, justice, a good risk/benefit ratio to minimize burden, and recognizing children's rights. However, pediatric nephrology studies are at significant risk for bias, given that the small centers may not be able to enroll patients, and limited opportunities for participation exist among Black, Indigenous

Table 2 Strategies to increase and improve pediatric-focused clinical trials

Area to address	Strategy
Ethics and justice	Follow ethical considerations based on beneficence, nonmaleficence, autonomy, justice, a good risk/benefit ratio to minimize burden, and recognizing children's rights
Patient and caregiver concerns	Universal literacy and cognition-sensitive material on study design, concept of randomization, and assent Ready availability of investigators
Investigator concerns	Understand patient/caregiver research and outcome priorities Utilize ethical and just principles in patient enrollment Train study staff on motivational interviewing and study protocol (videos can be used)
Small practices or sample size	Development or expansion of trial networks such as the Pediatric Nephology Research Consortium, NAPRTCs, the International Pediatric Peritoneal Dialysis Registry, PICCOLO MONDO, IPNA, or regional pediatric nephrology associations
IRB	Central and international Institutional Review Board (IRB)
Representation	Include and support rural practices or small groups. Community-based participatory models
Inclusivity	Purposive samples in all studies to include all races/ethnicities, urban and rural populations Universal literacy material Identify barriers for participation among those with lower socioeconomic backgrounds and develop a plan to resolve those barriers
Special populations	Expand on ongoing cohorts as ancillary studies, such as the Neonatal network, Children's Oncology Group, CureGN, NEPTUNE, or CKiD
Rare diseases	Artificial intelligence and electronic health record–generated data to identify patients. Leverage patient advocacy groups, non-profits, and pharmacy industry to ask for support
Access	Use telemedicine technology for follow-up visits
Study marketing and participant retention	Acknowledge the patients' and caregivers' generosity for participating in research studies, as they are doing us and other patients a favor Develop a culturally appropriate and sensitive enrollment and retention plan, involving all stakeholders and attending to all participants' needs Develop a refusal conversion plan with properly trained "study closers" Develop and update a comprehensive locator form with several family contact numbers (up to 10 contacts per participants has been successful in hard-to-reach populations) Send birthday and holiday greetings to participants Create a protocol for persistent teamwork and to approach doggedness Foster and maintain strong relationships with pediatric patients and their caregivers Ask patients/caregivers for what they foresee as potential study participation and retention barriers while suggesting how to overcome them Flexible schedules and locations of study visits (in-person or through technology) Understand participant mistrust of research, losing contact Remove logistical barriers such as transportation, childcare, scheduling, and stipends for parking or meals as needed Share study results with participants through newsletters or lay abstracts of resulting manuscripts Measure the efficacy of newer approaches to participant retention such as videos with peer-to-peer appeals, video animation, and the use of social media for marketing or to track patients

people of color, those who speak different languages, rural families, and those from lower socioeconomic backgrounds. In terms of addressing patient and caregiver participation, using study-related material that is at a universal literacy level and being available for in-person discussions of trials may overcome some of these barriers**.**

Clearly, we must identify and test new techniques to recruit and retain underserved or hard-to-reach populations in pediatric RCTs. The role of community-based participatory research models needs to be explored [66]. Would using a peer-to-peer method with videos from trial participants to encourage potential patients to enroll in studies be more effective than using social media influencers or other new platforms such as social media [67] or video animation [68]? Would utilizing electronic health records or artificial intelligence data alleviate some of our deficits in study design and patient recruitment? Please refer to Table 2 for expansion on these strategies.

Conclusions

There are more adult- than pediatric-focused clinical trials and among all pediatric specialties, pediatric nephrology has the lowest number of clinical trials published. Pediatric nephrology patients are among the costliest to all payors, yet they constitute a small population, providing little incentive for drug companies to develop novel treatments or fund trials. In fact, most studies are funded by government or non-profit agencies.

Differences by age, sex, and socioeconomic factors must be understood and addressed with RCTs that focus on neonates, infants, children, adolescents, and young adults with CKD/kidney failure from multiple populations and ethnicities. Patient, caregiver, provider, and institutional factors must be identified and addressed to ensure diversity, equity, and inclusion in clinical trials for these patients who have great survival to adulthood.

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