

Equity in evidence: overcoming barriers to kidney trials in low-resource settings



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Interventions to address complex kidney care challenges require quality trial-based evidence. Randomized controlled trials remain the gold standard for evaluating the safety and efficacy of such interventions. With recent advances in novel trial designs and international collaboration, many successful clinical trials in nephrology have resulted in new drugs targeting a wide spectrum of kidney diseases. Despite low- and middle-income countries (LMICs) bearing over 30% of the global chronic kidney disease burden, participation in clinical trials is mainly limited to high-income countries (HICs) and upper-middle-income countries.¹ Landmark nephrology trials such as those involving sodium-glucose cotransporter-2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, glucagon-like peptide-1 analogs, and other targeted therapies have historically under-represented participants from LMICs. Although some trials have included sites from selected lower-middle-income regions, overall participation from LMICs remains disproportionately low, with most countries in Africa and South Asia being completely excluded from trial enrollment. Globally, less than 35% trials included LMICs and virtually no low-income countries, with only 6.3% of the global trial population belonging to these regions. This under-representation questions the validity and applicability of trial findings in the settings that need them most.

Clinical trial participation in LMICs is increasing, but it remains heavily concentrated in a small number of countries, primarily in Southeast Asia and Latin America. These countries have diverse treatment-naïve populations, sufficient research infrastructure and expertise, relatively low implementation costs, and growing engagement from private health care sectors. Even within these regions, trial participation is confined mainly to major urban centers, highlighting the gap in rural research capacity and the need for more representative trial networks.

In this policy forum, we examine the key barriers and challenges to conducting nephrology trials in LMICs and propose strategies to improve access to research in these under-resourced and underserved settings.

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Barriers to conducting clinical trials in kidney diseases

There are many challenges in implementing clinical trials in LMICs.^{2,3} These include limited research capacity (infrastructure and resources) and research capability (skills and

expertise), as well as difficulties in patient recruitment and trial execution.

Financial constraints and competing priorities. Clinical trials are inherently resource-intensive, requiring considerable financial, human, and infrastructural investments. In most LMICs, constrained health care budgets prioritize funding for communicable diseases such as tuberculosis, maternal and child health, and noncommunicable diseases such as cardiovascular disease and cancer. Limited resources are allocated to research, often perceived as secondary to immediate clinical needs. Government funding for investigator-initiated trials is scarce. Researchers face difficulties in accessing international funds, as trials led by HICs may not align with local health needs.

Workforce and capacity constraints. A major barrier to conducting trials in low-resource settings is the lack of adequately trained personnel, including investigators, study coordinators, research nurses, and trial assistants, without whom participant identification, recruitment, and follow-up are compromised. Clinical trial and research training are underdeveloped because of limited institutional capacity and expertise. Opportunities for research mentorship, continuing professional development, and international collaboration are limited, further impeding the growth of a skilled research workforce. Health professionals are hesitant to engage in trials because of excessive clinical workload, operational impediments, and lack of career incentives. A global survey reported that only 8.1% of nephrologists from LMICs would enroll/refer patients with IgA nephropathy to clinical trials, despite most being aware of ongoing trials in their regions.⁴

Ethical and regulatory hurdles. Rigorous regulatory and ethics review is essential to protect research participants and uphold research integrity. However, in many LMICs, these processes are limited because of structural and capacity constraints. Centralized ethics review authorities and expertise are lacking, and local committees may not have the necessary capability or resources to evaluate complex trial protocols. Similarly, the absence of a competent drug regulatory authority may contribute to fragmented oversight and prolonged review timelines. Although judicious regulations are necessary to prevent exploitation of the vulnerable, these hurdles often result in substantial delays in trial approvals and subsequent protocol amendments. Involving patients from diverse backgrounds requires translating consent forms and patient-facing materials into multiple languages, with careful consideration of language and cultural diversity. This process is time-consuming and can cause delays.

Operational barriers. It may be challenging to provide care to trial patients because of a shortfall of hospital beds and dialysis facilities. Laboratories may not be accredited, and access to research equipment may be restricted by excessive clinical workload and lack of multidisciplinary collaboration. Critical research equipment, such as -80°C refrigerators, cold centrifuges, and incubators essential for

processing and storing samples, may be unavailable. Unreliable electricity supply and internet connectivity pose significant barriers to trial implementation. These infrastructure gaps also limit proper storage of investigational products and hinder patient participation, particularly in rural and remote regions. Transportation and communication networks, including cold chain facilities, may be untrustworthy, which interferes with the seamless transportation of patients' samples to centralized laboratories and affects bio-samples' viability. Wide variability in data collection methods, monitoring, and reporting leads to inconsistencies in data integrity. The lack of electronic medical records may render data retrieval difficult and erroneous. Complex and ambiguous legal and insurance frameworks hinder trial implementation and discourage local and international stakeholders from initiating trials in LMICs.

Difficulty in patient recruitment and retention. Patient enrollment in trials is often slow and limited in LMICs because of socioeconomic, cultural, and operational factors. The lack of clinical registries and longitudinal cohorts limits the ability to identify eligible patients systematically. Clinical trial participation is lower among patients with cancer from minority backgrounds, low socioeconomic status, limited education, and remote regions, even in HICs.⁵ In the United States, patients earning under \$50,000 annually have 32% lower odds of participating in clinical trials. These barriers are likely to be more pronounced and widespread in LMICs. Compensation for trial participation is often inadequate as patients face out-of-pocket expenses and indirect costs for trial visits, such as time off work, caregiving duties, and lodging (when traveling from distant locations). Low health literacy and limited awareness fuel concerns about adverse events and treatment benefits.

Religious and cultural beliefs also shape patients' skepticism of medical research and trials. Enrollment of women may be limited in patriarchal societies where male family members make health care decisions. As they are advised to avoid conception during trials, young women of childbearing age may often decline participation because of family and societal pressures.

Lack of stakeholder engagement. Communication and collaboration with key stakeholders, including patients, caregivers, clinicians, researchers, policymakers, regulatory authorities, and industry sponsors, is essential for conducting high-quality clinical trials. Global trials are often designed in HICs without consulting local stakeholders, particularly consumers from LMICs. Consequently, they may have eligibility criteria and requirements that are not feasible locally, limiting patient recruitment. For example, a history of tuberculosis is an exclusion criterion in most trials of immunosuppressive drugs. This creates a significant hurdle in countries where tuberculosis is endemic. Further, diagnostic criteria to exclude patients with tuberculosis in HICs may not be feasible in these regions.⁶ Patients in LMICs have unique perspectives that are not incorporated in trial designs, creating hurdles in implementation. Lack of

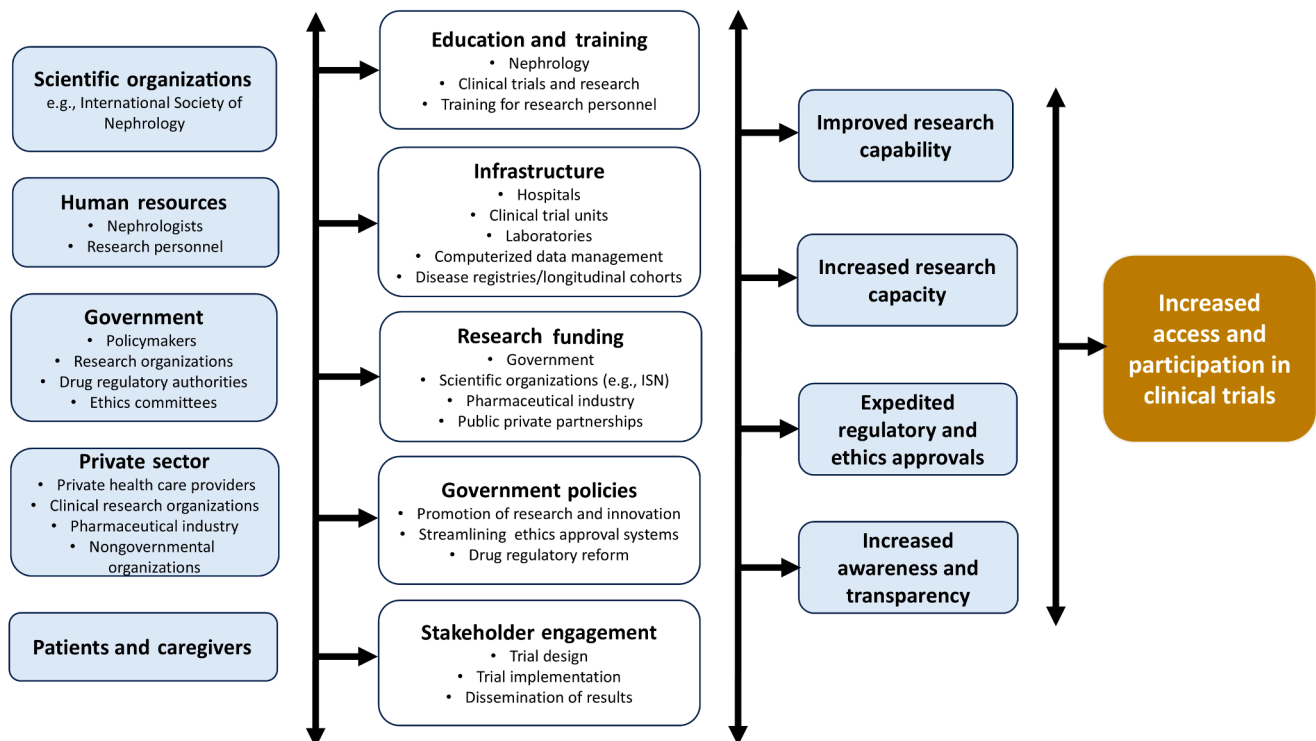


Figure 1 | Strategies to improve representation of low- and middle-income countries in global trials. ISN, International Society of Nephrology.

communication with consumers leads to ignorance regarding the availability of trials and fosters mistrust regarding investigators and trial sponsors.

Strategies to improve trial participation in LMICs

Work is underway to address the disparities and inequities in access to nephrology trials in LMICs. Initiatives led by the International Society of Nephrology (ISN), including fellowships, the sister renal centers program, research grants, and advocacy, have contributed to the expansion of the nephrology workforce, international collaborations, and research opportunities. The ISN-Advancing Clinical Trials, an initiative by the ISN to increase the involvement of the global nephrology community in trials, needs to focus on improving access in resource-limited countries. Although some countries have seen notable progress, significant gaps remain. Multifaceted interventions (Figure 1) are needed to correct this inequity in access to research.

Research advocacy and stakeholder collaboration. In LMICs, competing health priorities often marginalize research in kidney disease. The nephrology community must actively engage and incentivize key stakeholders to shape health policy by showing the actual burden of disease, including its broader societal and economic impacts. Meaningful engagement with both public and private institutions and consumers can help identify and overcome

barriers to trial implementation, improve transparency and overall efficiency, enhance awareness, and coordinate research efforts.

Targeted research funding and capacity building. Federal programs in countries such as India, the Philippines, and Indonesia are supporting the development of locally developed therapeutics. The nephrology community should collaborate with national health authorities to increase research funding for kidney disease, prioritizing clinically relevant, investigator-initiated trials that address local needs. Notably, investigator-initiated trials in LMICs, particularly studies conducted in India, have informed Kidney Disease: Improving Global Outcomes recommendations for childhood nephrotic syndrome.⁷ Beyond evaluating novel and unaffordable therapies, strategic repurposing of accessible generic drugs offers a practical way to affordable solutions. Dedicated training and mentorship programs for nephrologists and research personnel are essential. Funding should be merit-based and aligned with local health priorities, with regular evaluations to ensure efficient resource use, accountability, and measurable impact.

Regulatory reforms. Regulatory policy interventions developing standardized guidelines and streamlining ethics and trial submission processes can help avoid undue delays in trial approvals and attract more global clinical trials, as seen in India following the New Drugs and Clinical Trials Rules, 2019.⁸ National centralized ethics committees,

replacing separate site-specific approvals, can expedite the review process.

Public-private collaboration. A coordinated effort is needed to engage industry partners and philanthropic funding to build long-term research capacity and expertise, as demonstrated in infection and oncology research. Reducing administrative and regulatory barriers is essential to foster innovation and partnerships.⁸ LMICs have seen occasional successes by leveraging local expertise and industry support, including locally produced vaccines in India and Indonesia, and chimeric antigen receptor T-cell (CAR-T cell) therapy in India.⁸ Equitable industry, academia partnerships, modeled on those in HICs, are vital for therapeutic advances. International collaborations with public hospitals, exemplified by the renowned KEMRI-Wellcome Trust Research Unit in Kenya and industry collaboration with initiatives like the Clinical Trials Community Africa Network and the Cancer Research and Clinical Trials Centre in Vietnam, have helped build sustainable research capacity and increase trial participation.⁹

Ensuring equitable trial participation. Global trials should include participants from LMICs in a manner that reflects the actual chronic kidney disease burden, similar to clinical trials that focus on infectious diseases, including HIV and malaria, rather than tokenistic representation.⁹ Efforts should be made to include more participants in countries with existing infrastructure while implementing strategies to develop facilities in other regions. Local investigators should lead in setting priorities, designing, and conducting globally relevant local trials. Approaches to increase trial participation must be local and culturally sensitive, such as engagement with community leaders and local health workers, adapting consent to local norms, and using telehealth for remote follow-up. Innovative trial designs such as remote, adaptive, and pragmatic trials, and trials embedded in routine care can facilitate participation by reducing logistical burdens, increasing flexibility, and using existing health care systems. Trial sponsors, regulators, and researchers must ensure post-trial access to approved drugs for participants, in accordance with the Declaration of Helsinki.

Ultimately, trials must go beyond recruitment by planning for equitable access to build trust among other stakeholders. For example, lenacapavir (an antiretroviral drug) was tested in Uganda with a generic access plan for 120 LMICs, and new antimalarials cipargamin and cabamiquine are being trialed in Africa with strategies to ensure sustainable supply.⁹ All these initiatives can increase patient recruitment and

retention, ensuring contextually relevant research that is more likely to drive meaningful clinical and policy change.

Established programs and frameworks from other specialties, particularly infectious diseases and oncology, should be leveraged and emulated to make kidney research more sustainable in LMICs. Finally, we should acknowledge the considerable variability in research readiness across LMICs and recognize that dichotomizing countries into LMICs and HICs may risk oversimplifying the issue, further accentuating inequities in nephrology care and research.

In summary, despite bearing a significant burden of kidney disease, LMICs remain under-represented in nephrology trials. Equitable inclusion, local capacity-building, funding, and regulatory reforms are needed to drive transformational change and ensure that research benefits are accessible in these settings.

DISCLOSURE

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