Action plan for optimizing the design of clinical trials in chronic kidney disease

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High-quality clinical trials are the cornerstone of evidence-based prevention and treatment of a disease, but nephrology has a strikingly weak base of such trials. Building the evidence base to improve outcomes for people with a kidney disease, therefore, requires both greater quantity and quality of clinical trials. To address these issues, we propose that we aim to enroll 30% of people with chronic kidney disease in trials by 2030. Goal 1: Strongly encourage and promote the conduct of clinical trials in people with chronic kidney disease to increase the number of clinical trials conducted. Goal 2: Optimize the design of clinical trials in people with chronic kidney disease. Goal 3: Increase the capacity for conducting clinical trials in people with chronic kidney disease.

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High-quality clinical trials are the cornerstone of evidence-based prevention and treatment of a disease, but nephrology has a strikingly weak base of such trials. The number of clinical trials conducted in nephrology is less than that for any other specialty and shows little evidence of improvement (Figure 1).¹ Available clinical trials in chronic kidney disease (CKD) populations tend to be smaller than those in other medical specialties and are less likely to be randomized or blinded.² Building the evidence base to improve outcomes for people with CKD, therefore, requires both greater quantity and quality of clinical trials, which in turn requires better coordination and collaboration across larger groups of stakeholders to overcome a range of factors that contribute to the inadequate clinical trial base underpinning treatment and prevention (Table 1). This article expands on the recently published International Society of Nephrology CKD roadmap³ to describe an action plan for optimizing the design of clinical trials in CKD.

DEVELOPING AND DESIGNING CLINICAL TRIALS

Encouraging the development of and conducting clinical trials in CKD

The number of biologic targets for therapeutic agents to prevent the development, delay the progression, and treat complications of CKD is limited but growing. In principle, different specific causes of CKD may require targeted therapies to prevent the initiation of CKD or to effectively treat early stages of their disease, thus requiring clinical trials to be limited to populations with the same disease. When considered individually, the total populations affected may be

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Figure 1 | Number of randomized controlled trials published in nephrology and 12 other medical specialties from 1996 to 2010. Reproduced with permission from Palmer SC, Sciancalepore M, Strippoli GFM. Trial quality in nephrology: how are we measuring up? *Am J Kidney Dis.* 2011;58:335–337.¹

considered to be small, inhibiting investment into the development of new treatments, but it should be recognized that many of the underlying processes may share important aspects of disease progression. Examples of this include the role of immune dysregulation in many kidney diseases such as IgA nephropathy and lupus nephritis and that of hyperglycemia in the initiation and early progression of CKD in type 1 and type 2 diabetes. Furthermore, some mechanisms for progression may be similar in the later stages of CKD regardless of the etiology, allowing clinical trials to recruit populations with heterogeneous causes of disease. An example of this is the importance of glomerular hypertension in a number of diseases and the resultant benefits for RAS blockade treatment that was confirmed in individuals with proteinuric type 1 diabetes,⁴ type 2 diabetes,⁵ and IgA nephropathy.⁶ Treatments to prevent the complications of CKD are also likely to be largely disease independent. As CKD affects approximately 10% of the population in most countries,⁷ it should have a higher priority in the development of new potential treatments, and the CKD community should play an important role in articulating this need and advocating for a change.

In other diseases, new clinical trials of drugs are often designed in patients with late stages of the disease, where the required number of endpoints can be achieved by enrolling a

smaller number of participants with a shorter duration of follow-up. An example of this is the development of interventions to prevent cardiovascular events, where early clinical trials are frequently performed in people with advanced disease (tertiary prevention) due to their high risk, leading to smaller and more efficient clinical trials. If successful, clinical trials are then undertaken for earlier stages of the disease (secondary prevention) or in populations with an increased risk for developing a disease (primary prevention), where a substantially larger investment is required for the enrolment of a larger number of participants and for a longer follow-up to accrue the required number of endpoints.

In CKD, it is less clear whether treatments that are effective at later stages of disease may be more or less effective at earlier stages of the disease and *vice versa*. Knowledge of mechanistic transitions across the course of CKD is extremely important for both biomarker and therapeutic development. Additional studies conscious of the disease stages are required, as most clinical trials assessing CKD prevention include individuals with relatively advanced CKD, largely due to the lack of suitable endpoints during the earlier stages of the disease.

Another factor discouraging the development of new clinical trials in CKD is a perception that research in CKD is a high-risk endeavor for sponsors. Many phase 2 to 4 clinical trials in CKD populations have not shown a benefit at their primary endpoints, and several have been stopped due to safety concerns.³ Clearly the inclination for investment in new therapies for CKD by the private sector is driven by a clinical need but is hampered by the high risk of failure that is reinforced by the history of disappointing large clinical trials that led to high costs and the lack of validated intermediate endpoints and biomarkers.

The selection of valid and appropriate endpoints in CKD clinical trials has proved to be especially problematic. The most clinically objective outcome, and one that is universally accepted as important in patients with CKD, is kidney failure that requires dialysis or transplantation or that leads to death. However, this endpoint typically develops over many years (or decades), so defining the effects of interventions on this endpoint is often difficult, if not impossible. To make clinical trials feasible, many trials enroll large numbers of people with advanced stages of CKD, where progression is considered to be more predictable than in earlier stages. However, interventions that slow progression during earlier stages of CKD may not be effective during later stages. A doubling of serum creatinine level (equivalent to a 57% decline in estimated glomerular filtration rate) has been accepted as a surrogate measure for the development of kidney failure for many years. A workshop convened by the US National Kidney Foundation and US Food and Drug Administration recommended that the threshold may be reduced to 40% or even 30% glomerular filtration rate decline under specific circumstances, improving clinical trial feasibility.⁸ Further innovations are required, particularly for people with relatively preserved kidney function with a slowly progressive loss of kidney function.

Table 1 | Factors contributing to inadequate evidence base of clinical trials in nephrology

Limited number of biological targets for therapeutic agents
Differential effectiveness of therapies at early versus late stages of chronic kidney disease (CKD)
Lack of relevant endpoints and validated surrogates
Perception that CKD clinical trials are expensive and a high-risk proposition
Lack of innovation in clinical trial design
Inadequate capacity in conducting clinical trials
Insufficient power and high risk of bias in conducted clinical trials
Inappropriate comparator groups
Unnecessary duplication of previous research
Mismatch between clinical need and focus of the clinical trial
Lack of overall strategy for clinical trials across the CKD community

Designing better clinical trials

The science of designing clinical trials also needs innovation but has received limited attention to date in nephrology, with no dedicated discussion forum and a relatively low profile at existing major kidney meetings. As a result, designs have been relatively static. There has been little discussion of the role of novel clinical trial designs that might be particularly relevant to people with CKD.

Large amount of data is collected on a very frequent basis from individuals with kidney failure who require dialysis, effectively offering opportunities for developing high-quality registries, but these data are rarely used in clinical trials. The recent move toward registry-based randomized trials⁹ thus offers a key opportunity in dialysis. Other innovations in clinical trial design, such as enrichment approaches,¹⁰ adaptive designs,¹¹ and perhaps even platform and/or umbrella approaches,¹² might also be valuable in CKD. Further exploration of these approaches in CKD is required.

Finally, clinical trials have mostly focused on the needs of high-income countries to date, with little input from (and limited relevance to) low- and middle-income countries.¹³ Increased involvement of low- and middle-income countries in the design as well as the conduct of clinical trials is thus urgently required. The International Society of Nephrology has established the Advancing Clinical Trials group to increase the number of international high-quality clinical trials in nephrology, providing optimal prevention and treatment strategies of CKD and their complications for the benefit of patients (Table 2).¹⁴ The group is also working to address some of these challenges.

CONDUCTING CLINICAL TRIALS

Compared to other specialty communities, the nephrology community has a relative lack of experience, infrastructure, and capacity in conducting clinical trials.³ Many of the existing clinical trials in nephrology have been funded by the industry, without a clear, overarching framework for the engagement of participating centers. Similarly, there is little support for multicenter clinical trial groups from government sponsors, such as the National Institutes of Health in the USA. Collaboration among national, regional, and global

trial networks has been limited and *ad hoc*, leading to the underutilization of existing resources. Interaction with other health care providers (such as nurses, allied health professionals, primary care givers, and other specialists) has also been underdeveloped. Finally, limited training and capacity development opportunities have also implied that little infrastructure exists in many parts of the world. This leads to limitations in recruitment capacity and increased challenges for conducting clinical trials in CKD in countries with large affected populations.

THE PATH FORWARD

The sum effect of these factors is that clinical trials in CKD are not prioritized and are seen as a relatively high-risk endeavor compared to clinical trials of other therapeutic areas.

A broad, strategic, sustained, and collaborative approach is required to address these major challenges; it requires prioritization of CKD trials, better clinical trial design, and increased capacity to deliver these clinical trials. Table 3 describes the goals, activities, key partners, and deliverables pertinent to this theme.

As a stretch goal for the community of people concerned with CKD, ***we propose that 30% of patients with CKD should be involved in relevant clinical trials by 2030.*** This will require transformative changes and big ideas but will dramatically improve methods for preventing and treating CKD.

Goal 1: Strongly encourage and promote the conduct of clinical trials in people with CKD to increase the number of clinical trials conducted

Activity 1: Develop a value proposition for clinical trials in CKD. Greater investment in CKD clinical trials and a business-style approach are required, with clear articulation of the benefits that are achievable and the value for money gained. This will involve a multipronged strategy, starting with advocacy from relevant parties, and will include the identification of both health and financial benefits of conducting clinical trials in this field. For example, hospitalization is a common and expensive outcome in CKD that needs to be more fully considered and assessed.

Activity 2: Promote clinical trials in areas of unmet need and orphan diseases, including novel endpoint development (e.g., biopsy and hospitalization). Many individual CKDs are uncommon or rare, so hard outcome studies may not be feasible. Key parties must play a central role in advocacy for research in these areas and in the development of appropriate, meaningful, and feasible endpoints for such clinical trials. Markers of kidney damage, including biopsy findings or biomarkers of disease activity, might be suitable in some CKDs. For example, the US Food and Drug Administration has approved total kidney volume as a prognostic marker for polycystic CKD clinical trials, but this required substantial scientific collaboration by members of the Polycystic Kidney Disease Outcomes Consortium.¹⁵

Table 2 | Goals of International Society of Nephrology-Advancing Clinical Trials¹⁴

1. To bring together people undertaking clinical trials and related studies in nephrology in order to facilitate interaction, sharing of experiences, and collaboration
2. To provide a forum for the discussion of key scientific, operational, and analytical issues that are faced by clinical trial researchers studying chronic kidney disease
3. To increase the capacity of the global nephrology community to conduct high-quality clinical trials and studies by connecting researchers with different levels of experience and through specific training initiatives within the International Society of Nephrology (ISN) framework
4. To develop ISN-led and/or -supported activities that help to standardize high-quality clinical trial conduct in nephrology

Table 3 | Action plan for optimizing the design of clinical trials in CKD³

Goals	Activities	Partners	Possible deliverables
Strongly encourage and promote the conduct of clinical trials in people with CKD	1. Develop a value proposition for clinical trials in CKD	Health economists and funders	Published position statement
	2. Promote clinical trials in areas of unmet need and orphan diseases, including outcome development (e.g., biopsy and hospitalization)	Advocacy organizations, regulatory authorities, and KDIGO	Consensus conference with published report
	3. Engage active patient groups, funders, and other stakeholders to substantially increase the number of clinical trials in CKD	Advocacy organizations, major funders, and WHO	Clinical trial stakeholder workshop within 2 yr Increase in the number of clinical trials in nephrology
	4. Promote models for early conditional approval of new therapies to encourage investment	Regulatory authorities and KHI	Position statement
	5. Increase the number of people with CKD who are included in CV, diabetes, and oncology trials to reflect the prevalence of CKD in such patient populations.	Regulatory authorities, FDA, EMA, and non-nephrology disciplines	Position statement Inventory of CKD-related inclusion and exclusion criteria in major nonkidney trials to monitor implementation Increase in the number of clinical trials with CKD included (vs. excluded) as important subgroup
	6. Develop a regular stand-alone meeting to review ongoing and planned clinical trials in patients with CKD on a global scale	KDIGO, KHI, global, regional, and national nephrology societies	First stand-alone meeting within 2 yr
Optimize the design of clinical trials in people with CKD	1. Develop and refine appropriate endpoints for CKD clinical trials and promote their uptake and dissemination	NKF, FDA, EMA, KHI, and SONG	Conference on albuminuria/eGFR in 2018 (US NKF, FDA, and EMA) Position statement
	2. Evaluate factors that lead to success or failure of clinical trials in CKD trials	Industry partners	Conference accompanied by a report; to be continued as part of the proposed annual meeting
	3. Facilitate strategies to preselect patients for clinical trials according to their risk for progression or likelihood to respond to an intervention	Industry partners, bioinformaticians, clinicians, and scientists	Published reanalysis of selected clinical trials to differentiate between progressors and nonprogressors and responders and nonresponders
	4. Develop innovative clinical trial designs to enhance feasibility and success of CKD clinical trials	Clinical scientists, epidemiologists, and statisticians	Integration in clinical trial meetings
	5. Implement priority-setting exercises for interventions to be tested in clinical trials, globally and regionally	ISN, KDIGO, global, regional, and national nephrology societies	Global exercise completed in 2 yr At least 2 regional processes within 3 yr
	6. Establish recommendations for clinical trials in people with CKD for use by ethical and regulatory boards and include opportunities for sample collection for future analyses	Industry partners, ISN, global, regional, and national nephrology societies	Convene a panel to address this topic, including stakeholders with appropriate expertise in relevant disciplines
Increase the capacity for conducting clinical trials in people with CKD	1. Develop networks for kidney clinical trialists that include community physicians, other specialists, etc.	Funding agencies	Convene a meeting of established clinical trial groups
	2. Catalog sites and/or centers capable of participating in CKD clinical trials	Academic research organizations	Catalog and make mechanism available by the end of 2017, with methods for linking clinical trials and centers Develop mechanisms for internationalization of clinical trials, particularly including LMICs

(Continued on next page)

Table 3 | Action plan for optimizing the design of clinical trials in CKD³ (Continued)

Goals	Activities	Partners	Possible deliverables
	3. Develop and implement professional training in clinical trial design and conduct, involving nephrology and related specialties	Clinical trial training providers, global, regional, and national nephrology societies	First course at WCN 2017, publish online by the end of 2017, roll out in at least 2 regions during 2018 Award fellowships for the planning and conduct of clinical trials Increase size and quality of clinical trials in nephrology

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, US Food and Drug Administration; ISN, International Society of Nephrology; KDIGO, Kidney Disease, Improving Global Outcomes; KHI, Kidney Health Initiative; LMICs, low- and middle-income countries; NKF, US National Kidney Foundation; SONG, Standardised Outcomes in Nephrology; WCN, World Congress of Nephrology; WHO, World Health Organization.

Activity 3: Engage active patient groups, funders, and other stakeholders to substantially increase the number of clinical trials in CKD. Motivated people with CKD, advocacy organizations, and health care funders should be included in the community of important stakeholders in CKD clinical trials. They have been inadequately engaged to date, yet are key to new partners who can advocate strongly for greater investment in CKD clinical trials.

Activity 4: Promote models for early conditional approval of new therapies to encourage investment, with appropriate safeguards to confirm efficacy and safety. In general, a key barrier to greater investment in CKD clinical trials (but especially by smaller biotechnology companies) is the long-term nature of clinical trials that are required to generate regulatory approvals and allow revenue to be generated. In other medical specialties, conditional approval is granted by regulatory agencies based on benefits of approved surrogate outcomes with the requirement that appropriate clinical trials assessing effects on hard outcomes be undertaken after approval (e.g., glucose-lowering agents approved based on glycemic effects). A similar approach in CKD would likely increase investment, and should be considered as a promoting point by kidney disease organizations, with appropriate processes to ensure that larger studies demonstrating effects on patient-level outcomes are completed in a timely manner.

Activity 5: Increase the number of people with CKD who are included in cardiovascular, diabetes, and oncology trials to reflect the prevalence of CKD in such patient populations. Many clinical trials in other medical specialties routinely exclude participants with CKD; in some clinical trials, this is due to concerns about the safety profile of novel agents, but it limits generalizability, given the high prevalence of CKD as a comorbid condition and the likelihood of approved agents subsequently being used in CKD. More generally, the inclusion of people with CKD in clinical trials should be encouraged to obtain specific data on safety and efficacy for medications that are common and effective for conditions observed in CKD populations.

Activity 6: Develop a regular stand-alone meeting to review ongoing and planned clinical trials in patients with CKD on a global scale. Unlike other medical specialties such as cardiology, CKD clinical trials lack a regular stand-alone meeting to review ongoing and planned clinical trials in patients with

CKD on a global scale. Issues that could be discussed include endpoint selection: better and more relevant endpoints are crucial to facilitate appropriate clinical trials and several initiatives are already underway. A forum is required to promote CKD clinical trials and facilitate improved design and conduct. The development of a meeting that specifically addresses these issues is a priority for the field.

Goal 2: Optimize the design of clinical trials in people with CKD

Activity 1: Develop and refine appropriate endpoints for CKD clinical trials and promote their dissemination and implementation. There continues to be debate as to the appropriate endpoints for clinical trials. While glomerular filtration rate decline is an appropriate and well-established endpoint, particularly in people with later stages of CKD, using changes in markers of kidney damage as endpoints for studying earlier stages of specific kidney diseases (e.g., albuminuria for diabetes and other glomerular diseases and total kidney volume in polycystic kidney disease) has had some validity but still requires definition, validation, and consensus. In particular, the role of changes in albuminuria as an endpoint in kidney clinical trials continues to be debated, with no clear consensus.^{16,17} Safety endpoints have received insufficient attention. Both efficacy and safety endpoints have generally been developed by researchers, with little or no input from patients, who may have very different priorities, which is now being addressed by the Standardised Outcomes in Nephrology initiative.^{18,19} Much work is still required to define appropriate clinical trial endpoints, particularly those important for patients and funders, that are applicable to early stages of CKD.

Better and more relevant endpoints are crucial to facilitate appropriate clinical trials and several initiatives are already underway. A future workshop by the US National Kidney Foundation, US Food and Drug Administration, and European Medicines Agency is being planned for 2018 to address changes in albuminuria and rates of glomerular filtration rate decline (slopes) as surrogate endpoints for studying earlier stages of CKD. This and other activities such as the Standardised Outcomes in Nephrology Initiative and Kidney Health Initiative should be aligned to ensure that a single set of appropriate endpoints, with appropriate measurement methods, is endorsed globally.

Activity 2: Evaluate factors that lead to success or failure of clinical trials in CKD clinical trials. Many high-profile clinical trials in CKDs have demonstrated evidence of harm or a lack of efficacy.^{20–24} In addition to the true absence of efficacy or presence of harm, other reasons may relate to the endpoint chosen or to aspects of the study design or conduct. Other clinical trials have designs that increase the risk of bias (lack of blinding, allocation concealment, etc.), may be inadequately powered, or are an unnecessary duplicate of previous research. The regular stand-alone meeting proposed previously offers an ideal opportunity to ensure future clinical trials learn from these experiences and are improved as a result.

Activity 3: Facilitate strategies to preselect patients for clinical trials according to their risk for progression or likelihood to respond to an intervention. The likelihood of successful clinical trials and the appropriate generalization of evidence from these clinical trials will be enhanced if participants can be enrolled based on the likelihood of a positive response as well as the risk of CKD progression. Active run-in periods are one way that this is being done, but enrichment and/or adaptive approaches are likely to add value; they will also add complexity, so more work to understand the trade-offs is required.

Activity 4: Develop innovative clinical trial designs to enhance feasibility and success of CKD clinical trials. A number of novel or alternative approaches for conducting clinical trials are being undertaken in other medical specialties, but they may be particularly well-suited for CKD. Large simple clinical trial designs have been proven useful in other diseases, and more such clinical trials are urgently required in CKD, but they may have limitations for endpoints in kidney diseases that require repeated laboratory measures for endpoint ascertainment (e.g., nephrotic syndrome). Randomized registry trials, cluster randomized trials, adaptive trials, and other approaches should be considered as methods to dramatically increase the feasibility of clinical trials in CKD. Simple trials with minimal data collection would also increase the feasibility of including more countries (with their ethnic diversity) and thus will improve the generalizability of the studies once completed.

Activity 5: Implement priority-setting exercises for interventions to be tested in clinical trials, globally and regionally. The limited capacity for conducting CKD clinical trials highlights the need to focus on studying health conditions associated with a high burden of poor outcomes and interventions that are most likely to improve outcomes for people with CKD, rather than those that will deliver commercial returns. Prioritization of these interventions is a key goal and should be done regionally as well as globally to account for local differences in needs. In parallel, the nephrology community should work on building additional capacity.

Activity 6: Establish recommendations for clinical trials in people with CKD for use by ethical and regulatory boards and include opportunities for sample collection for future analyses. The absence of symptoms in the early stages of CKD may require special consideration.

Goal 3: Increase the capacity for conducting clinical trials in people with CKD

Activity 1: Develop networks for CKD clinical trialists that include community physicians and other specialties, etc. Improving the coordination and collaboration among individuals already involved in CKD clinical trials will facilitate a more effective conduct and sharing of experiences. This is particularly important in low- and middle-income countries, where experience and capacity are often very limited so that the value of collaboration may be greatest.

Activity 2: Catalog sites and/or centers capable of participating in CKD clinical trials. A regularly updated repository of information that can provide information on centers, networks, and coordinating centers with interest (and where possible, experience) in CKD clinical trials would strongly support better collaboration and improve clinical trial feasibility.

Activity 3: Develop and implement professional training in clinical trial design and conduct, involving nephrology and related medical specialties. Growing capacity for CKD clinical trials must be a priority for the community in order to deliver on the goals described above. Training through courses, formal and informal mentorship, structured programs, and partnerships will be crucial in increasing the number and quality of CKD clinical trials.

CONCLUSION

Given the importance of clinical trials in changing clinical practice and in improving health outcomes, it is critical to increase the number of clinical trials relevant to the care of patients with CKD and to optimize the design of future CKD-related clinical trials to improve the yield of useful information from these clinical trials. Both goals will be facilitated by thoughtful efforts to build capacity for conducting clinical trials in this population, with collaboration across a broad range of stakeholders.

DISCLOSURE

VP declared board membership of George Clinical (an academic contract research organization), membership in the Executive Operations Secretariat of the Australasian Kidney Trials Network, and chairmanship of the International Society of Nephrology-Advancing Clinical Trials group; chairs or is a member of the Trial Steering Committees supported by Janssen Pharmaceutical, AbbVie, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, and Pfizer; declared honoraria for scientific presentations and/or advisory board participation from AstraZeneca, AbbVie, Boehringer Ingelheim, Eli Lilly and Company, Novartis, Servier Laboratories, Relyps, Bayer, and Merck Serono; and has a policy of honoraria being paid to his employer. CSF declared stock options in Merck and is a current employee. GGG declared consulting fees from Pisa Farmaceutica. MBG declared lecture fees from Amgen, B. Braun, Leo Pharma, Novartis, Novo Nordisk, Promopharm, Roche, Sanofi, Servier, Sophadial, and Sothema. MJJ declared consulting fees from Baxter and Boehringer Ingelheim; lecture fees from Amgen; and grant support from Baxter, Amgen, Eli Lilly and Company, and Merck. NP declared grant support from the Canadian Institutes of Health Research. BS declared consulting fees from Merck Sharp and Dohme and grant support from Amgen, Baxter, MSD, Fresenius, Eli Lilly and Company, and Otsuka. KRT declared consulting fees from Eli Lilly and Company, Boehringer

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