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

Vlado Perkovic[1,21], Jonathan C. Craig[2,3], Worawon Chailimpamontree[4], Caroline S. Fox[5], Guillermo Garcia-Garcia[6], Mohammed Benghanem Gharbi[7], Meg J. Jardine[8,9], Ikechi G. Okpechi[10,11], Neesh Pannu[12], Benedicte Stengel[13,14,15,16], Katherine R. Tuttle[17], Katrin Uhlig[18,19] and Andrew S. Levey[20,21]

[1]The George Institute for Global Health, University of New South Wales Sydney, New South Wales, Australia; [2]Department of Nephrology, School of Public Health, University of Sydney, Sydney, New South Wales, Australia; [3]Centre for Kidney Research, Children's Hospital at Westmead, Westmead, Australia; [4]Nephrology Division, Department of Medicine, Bhumibol Adulyadej Hospital, Bangkok, Thailand; [5]Genetics and Pharmacogenomics, Merck Research Laboratories, Boston, Massachusetts, USA; [6]Servicio de Nefrologia, Hospital Civil de Guadalajara Fray Antonio Alcalde, University of Guadalajara Health Sciences Center, Hospital 278, Guadalajara, Jalisco, Mexico; [7]Urinary Tract Diseases Department, Faculty of Medicine and Pharmacy of Casablanca, University Hassan II of Casablanca, Casablanca, Morocco; [8]Renal & Metabolic Division, The George Institute for Global Health, University of New South Wales Sydney, New South Wales, Australia; [9]Nephrology Unit, Concord Repatriation General Hospital, Sydney, New South Wales, Australia; [10]Division of Nephrology and Hypertension, University of Cape Town, Cape Town, South Africa; [11]Kidney and Hypertension Research Unit, University of Cape Town, Cape Town, South Africa; [12]Department of Medicine, Division of Nephrology, University of Alberta, Edmonton, Alberta, Canada; [13]Centre for Research in Epidemiology and Population Health (CESP), French National Institute of Health and Medical Research (INSERM), Villejuif, France; [14]University Paris Sud, Villejuif, France; [15]University of Versailles Saint-Quentin (UVSQ), Villejuif, France; [16]University of Paris-Saclay, Villejuif, France; [17]Providence Medical Research Center, Providence Health Care Kidney Research Institute, Nephrology Division and Institute for Translational Health Sciences, University of Washington, Spokane, Washington, USA; [18]Clinical Development, Keryx Biopharmaceuticals, Boston, Massachusetts, USA; [19]Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA; and [20]Department of Medicine, Division of Nephrology, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA

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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Correspondence: *Andrew S. Levey, Division of Nephrology, Box 391, Tufts Medical Center, 800 Washington Street, Boston, Massachusetts, USA. E-mail: alevey@tuftsmedicalcenter.org*

[21]GKHS Working Group Co-chairs.

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 roadmap[3] 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

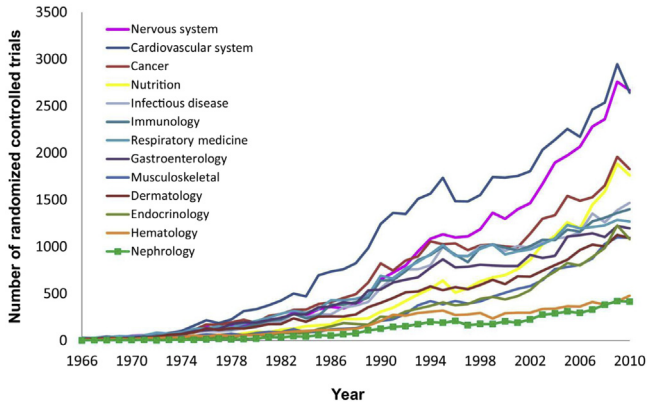

Figure 1 | Number of randomized controlled trials published in nephrology and 12 other medical specialties from 1996 to 2010. Reproduced with permission from Palmer SC, Sciancalepore M, Strippoli GFM. Trial quality in nephrology: how are we measuring up? *Am J Kidney Dis*. 2011;58:335–337.[1]

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.

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

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.