Innovating and invigorating the clinical trial infrastructure for glomerular diseases

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In 2004, the nephrology community took an introspective look at the state of clinical trials for kidney disease and realized the subspecialty holds the dubious distinction of being in last place in the performance and completion of trials compared with other disciplines.[1] However, some recent successes, including US Food and Drug Administration–approved drugs for autosomal dominant polycystic kidney disease, diabetic kidney disease, and anti–neutrophil cytoplasmic antibody–associated vasculitis and positive interventional trials in focal segmental glomerular sclerosis and lupus nephritis, provide cause for encouragement. It is critical that the community sustains and increases the momentum of bringing novel therapeutics to trial. In this regard, the treatment of glomerular diseases could lead the way.

The current treatment of glomerular diseases is based largely on expert opinion, and small clinical studies from many years ago. Thankfully, there has been recent intense interest from the pharmaceutical industry in bringing drugs for glomerular diseases to trial, despite past failures. This is due, in part, to research efforts that have increasingly revealed molecular mechanisms of disease, facilitating the development of targeted therapeutics, as well as work undertaken by the larger nephrology community to support the use of surrogate end points, such as proteinuria, as efficacy end points in clinical trials of glomerular disease.[2–4] Such efforts highlight how effective data sharing can greatly facilitate drug development for rare diseases.

A quick look at current and actively enrolling trials for primary glomerular diseases is impressive (Table 1) but highlights several issues the nephrology community needs to address to optimize the likelihood of success. A growing number of trials are competing for the same patient populations, and as glomerular diseases are rare diseases, the difficulty to recruit is compounded. Novel therapeutics with a wide array of putative mechanisms of action are being studied in glomerular diseases, raising the question of how to choose the most appropriate trial for an individual. Finally, there are concerns about manpower. For example, in the United States, of the approximately 11,000 practicing nephrologists, <350 are glomerular disease experts conducting clinical trials (NephCure Kidney International [NephCure] database). The glomerular disease space is thus ripe for innovation and culture change to facilitate clinical trials and clinical investigation.

Even if patients are not eligible for a formal pharma interventional clinical trial, enrolling in observational studies and investigator-initiated trials is also essential to improve our understanding of glomerular diseases. Investigator-initiated trials offer a pathway to test real-world management strategies with novel drugs, and often provide mechanistic information not readily available from strictly structured traditional trials. We anticipate that the success of current clinical trials will spawn many new investigator-initiated trial ideas. Implementation of these will require investment on the part of all glomerular disease stakeholders, including pharma, to provide support for infrastructure.

Nephrologists

Patients are usually recruited into trials by their physicians, but many physicians are not trained in clinical research and do not understand how to properly recruit patients into studies and trials. Clinical research training is often not part of a regular fellowship, and developing expertise takes time. In addition, interest in joining the nephrology workforce has been waning the last few years (American Society of Nephrology Workforce Report). We encourage current clinical trial centers of excellence to share their expertise and develop training programs with added certification to graduate *bona fide* clinical trialists. Advanced training programs have worked well for other areas of nephrology, such as onconephrology. For peritoneal dialysis, industry and academia have collaborated to create "PD Universities" to teach the nuances of peritoneal dialysis. Interest

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Table 1 | A sampling of recent clinical trials in primary glomerular diseases

Trial (sponsor)	ClinicalTrials.gov identifier/phase	Disease targeted	Children included	Drug/compound	Mechanism of action
DUPLEX (Retrophin)	NCT03493685/ phase 3	FSGS	Yes	Sparsentan	Endothelin antagonism plus angiotensin receptor blockade
PODO (Pfizer)	NCT03448692/ phase 2	FSGS	No	PF-06730512	SLIT2 antagonism
VX-147 in APOL1-Mediated FSGS (Vertex)	NCT04340362/ phase 2	FSGS	No	VX-147	APOL1 inhibition
ACTION (Dimerix)	NCT03649152/ phase 2	FSGS	No	Propagermanium	Chemokine receptor inhibition
TRPC5 Channel Inhibitor in FSGS and Resistant MCD (GoldFinch)	NCT04387448/ phase 2	FSGS or MCD	No	GFB-887	Ion channel blockade
Abatacept in FSGS or Minimal Change Disease (Bristol-Myers Squibb)	NCT02592798/ phase 2	FSGS or MCD	Yes	Abatacept	CD80 antagonism
Liposorber LA-15 System for Children With FSGS (Kaneka)	NCT02235857/ postapproval	Recurrent or primary FSGS	Yes	Liposorber LA-15 system	Lipoprotein removal
Bleselumab to Prevent Recurrent FSGS (Astellas)	NCT02921789/ phase 2	Recurrent FSGS	No	Bleselumab	CD40 antagonism
Cemdisiran in IgAN (Alnylam)	NCT03841448/ phase 2	IgAN	No	Cemdisiran	Complement system antagonism
Nefigard (Calliditas)	NCT03643965/ phase 3	IgAN	No	Nefecon	Gut-targeted steroid
PROTECT (Retrophin)	NCT03762850/ phase 3	IgAN	No	Sparsentan	Endothelin antagonism plus angiotensin receptor blockade
Efficacy and Safety of OMS721 in IgAN (Omeros)	NCT03608033/ phase 3	IgAN	No	Narsoplimab	Complement system antagonism
Atacicept in IgA Nephropathy (EMD Serono)	NCT02808429/ phase 2	IgAN	No	Atacicept	B-cell survival
LNP023 in IgAN (Novartis)	NCT03373461/ phase 2	IgAN	No	LNP023	Complement system antagonism
BION-1301 in IgAN (Aduro Biotech)	NCT03945318/ phase 1	IgAN	No	BION-1301	B-cell survival
AVB-S6-500 in IgAN (Aravive)	NCT04042623/ phase 2	IgAN	No	AVB-S6-500	AXL signaling inhibitor
VIS649 in IgAN (Visterra)	NCT04287985/ phase 2	IgAN	No	VIS649	B-cell survival
ACCOLADE (ChemoCentryx)	NCT03301467/ phase 2	C3G	Yes	Avacopan	Complement system antagonism
LNP023 in C3G; LNP023 in MN (Novartis)	NCT0382114; NCT04154787/ phase 2	C3G MN	No	LNP023	Complement system antagonism
M-PLACE (MorphoSys)	NCT04145440/ phase 1	MN	No	MOR202	Plasma cell inhibition

ACCOLADE, Controlled Trial Evaluating Avacopan in C3 Glomerulopathy; ACTION, Action for Focal Segmental Glomerulosclerosis; APOL1, apolipoprotein L1; AXL, AXL receptor tyrosine kinase; DUPLEX, Study of Sparsentan in Patients With Primary Focal Segmental Glomerulosclerosis; FSGS, focal segmental glomerular sclerosis; IgAN, IgA nephropathy; M-PLACE, Trial to Assess Safety and Efficacy of MOR202 in Anti-PLA2R + Membranous Nephropathy; MCD, minimal change disease; MN, membranous nephropathy; Nefigard, Nefecon in Patients With Primary IgA (Immunoglobulin A) Nephropathy; PODO, A Study to Evaluate PF-06730512 in Adults With Focal Segmental Glomerulosclerosis; PROTECT, A Study of the Effect and Safety of Sparsentan the Treatment of Patients with IgA Nephropathy; SLIT2, slit guidance ligand 2; TRPC5, Transient receptor potential cation channel, subfamily C, member 5.

in clinical trialist programs is certain to be enhanced through emerging and ongoing investigator training initiatives from the American Society of Pediatric Nephrology, the Kidney Health Initiative, the Kidney Research Network, Connect 4 Children (Europe), and the Glomerular Disease Study and Trial Consortium (https://glomcon.org). These programs are intended to excite and educate clinicians, pathologists, researchers, and industry partners about glomerular diseases and inform these stakeholders of ongoing clinical trial initiatives. Increasing interest in a career as a clinical trialist may also have the important downstream effect of renewing interest in nephrology as a subspecialty.

Training new trialists is an important investment for the nephrology community, but

most patients are not followed at clinical trial centers of excellence. To improve the volume and matching of "recruitable"/eligible patients, trial centers and community nephrologists will need to cooperate/collaborate. There have been several proposed reasons as to why community physicians do not refer patients for trials. These include loss of control, financial disincentives, lack of awareness of ongoing trials, mistrust of academic clinical trial centers, and the possibility of randomization to placebo. These barriers need to be verified, and then addressed systematically to engage community physicians to become partners in trials of glomerular therapeutics. As a step in this direction, NephCure, through its Gateway Initiative, launched a website (KidneyHealthGateway.com) to help inform the broader nephrology community of current clinical trials. The site will sync with a new renal pathology site to aid in clinical trial recruitment (see below). NephCure has developed a process to identify glomerular disease experts and is working on a mechanism to facilitate comanagement of patients enrolled in clinical trials. A physician portal was created (https://kidneyhealthgateway.com/healthcare-provider/) to enable clinical nephrologists to quickly identify trial opportunities for their patients based on diagnosis, eligibility criteria, and geographic location.

Renal pathologists

Renal pathologists can play a critical role in the cultural and structural changes needed for clinical trial innovation. They are ubiquitously present at the time of diagnosis. The pathologist is ideally positioned to address trial recruitment by appropriately classifying patients during diagnosis, identifying potential trial candidates, and communicating relevant information to the referring nephrologist. This is not a novel concept. In oncology, molecular pathology reports often include the genomic variants found in tumors and trials for which a patient may be qualified.[5] A barrier to renal pathologists' participation in this process has been the lack of accessibility to information on current clinical trial options and trial-specific histologic and molecular requirements or exclusions. To remove this barrier, ongoing clinical trials and their details are now posted and will be kept current on the Renal Pathology Society website (https://renalpathsoc.wildapricot.org/Clinical-Trials-for-Renal-Diseases).

Beyond recruitment, nephropathologists could play several additional roles in promoting the success of glomerular disease clinical trials. Historically, pathologists have not participated in trial design, resulting in clinical trials using outdated morphologic classifications or criteria disconnected from a drug's presumptive mechanism of action to assess patient eligibility. Embedding nephropathologists into clinical trial design teams would optimize eligibility criteria and help identify histologic descriptors that reflect disease pathogenesis to connect with a drug's mechanism of action. We envision a future in which designation of glomerular diseases as primary or secondary is replaced by a comprehensive clinical, morphologic, and mechanistic evaluation to identify phenotypes that will be used to pair individual patients with a clinical trial best fit to their disease mechanism. In addition, given the considerable clinical, morphologic, and molecular heterogeneity of glomerular diseases, and the suboptimal diagnostic reproducibility among pathologists, central screening of kidney biopsies might help ensure more accurate patient classification and recruitment into studies. A centralized biopsy adjudication strategy also lends itself to standardization of the data collected, information that would undoubtedly be useful in stratifying patients before randomization, during analysis of trial data, and during comparison of data across trials. Application of artificial intelligence and machine learning methods to the evaluation of kidney biopsies may facilitate the inclusion of pathologists' input into the design of trials for glomerular disease.

Patients

Although clinical trials are conducted to benefit patients, the patient has historically been neglected in the design and operation of clinical trials. Patient engagement and patient-centered care models have only recently become mainstream ideas. Patients can and should contribute to clinical trials not just as study participants but throughout the process, including study design, recruitment, retention, data analysis, dissemination of results, and return of findings, including experimental data, to study participants. This has been helpful in National Institutes of Health–funded Kidney Precision Medicine Project (KPMP) and APOL1 Long-Term Kidney Transplantation Outcomes Consortium (APOLLO) studies.[6] Patient advisory groups, focus groups, and

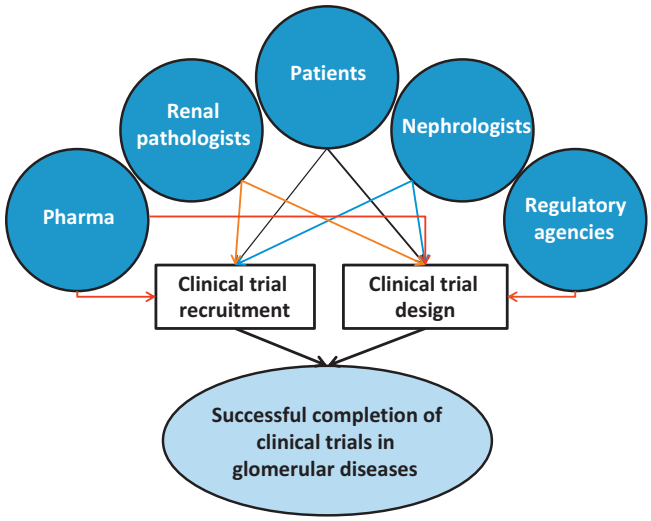

Figure 1 | Changing the culture surrounding clinical trials for glomerular diseases. A well-designed trial will facilitate success and is dependent on the input of patients, clinicians, pathologists, industry, and regulatory agencies. Recruitment can be optimized if renal pathologists identify trial candidates and if patients, empowered with trial information, inform their physicians about available trials and their desire to participate. Nephrologists at trial centers and nephrologists in the community need to collaborate to ensure timely patient referrals and need to communicate results to ensure continued collaboration.

consultative workshops are some potentially impactful strategies to accomplish this. The Standardized Outcomes in Nephrology initiative (www.songinitiative.org) has embraced this philosophy. Standardized Outcomes in Nephrology is an international collaboration of patients, caregivers, clinicians, researchers, and policy makers, developing a set of core outcomes and outcome measures for all types of kidney disease, including glomerular disease.[7] These outcomes are intended to be meaningful and relevant to patients, family members, and physicians, and to be used in future clinical trials. In the spirit of patient engagement and empowerment, NephCure's clinical trial website (discussed above) is patient centric, with the goal of helping patients with nephrotic syndrome become aware of cutting-edge clinical trial opportunities. The hope of this tool is that a well-informed patient will seek out participation in a trial, or more likely bring these trial opportunities to his/her own physician, increasing awareness of glomerular disease trials in the community and, as a consequence, improving trial recruitment.

The implementation of these suggestions will be difficult but has already started. In an effort to assemble all stakeholders in one room, NephCure has taken the reins. In enthusiastic collaboration with the National Institutes of Health, the American Society of Nephrology, the Kidney Health Initiative, and the US Food and Drug Administration, NephCure brought together many of the key members of the nephrology communities of the United States and Europe for an initial meeting in November 2018. Participants included clinical investigators, basic scientists, government regulatory officers, representatives from industry, patient advocacy groups, patients, and care providers. At this meeting, an ambitious agenda to assure successful patient recruitment was defined. Several work groups, covering key topics, such as glomerular disease registries, clinician engagement, renal pathology, inclusion of children and adolescents, and international collaboration and integration, were convened to address the key aspects of trial recruitment and the infrastructure needed for success. More important, as leaders in this ambitious collaborative effort, patients and caregivers provided direction and context for all the work groups, and reminded attendees that, for some glomerular diseases, pediatric patients make up about 40% of the affected population. The ongoing charge of each group is to develop near-term actionable solutions to barriers of patient recruitment. Follow-up meetings of this large consortium are on the calendar so no momentum is lost.

This is a challenging and exciting time for nephrologists interested in glomerular diseases. To sustain a robust pipeline of novel, mechanism-based, targeted therapeutics, the community should consider the current growth

in the number of clinical trials as a call to action to come together and break down existing cultural barriers to clinical trial recruitment and success for our patients. If we cannot recruit to trials in a timely manner, we risk losing our biopharma pipeline to other diseases. Considering the clinical burden of glomerular disease, that would be a tragic failure. We are optimistic that the ideas offered herein represent a blueprint for us to make the best use of these opportunities (Figure 1).

DISCLOSURE

All the authors declared no competing interests with the material in this article.

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