CJASN Clinical Journal of the American Society of Nephrology

Understanding and Overcoming the Challenges Related to Cardiovascular Trials Involving Patients with Kidney Disease

Journal:	*Clinical Journal of the American Society of Nephrology*
Manuscript ID	CJASN-1756-11-20.R1
Manuscript Type:	Invited Features
Date Submitted by the Author:	n/a
Complete List of Authors:	Ishida, Julie; Gilead Sciences Inc Herzog, Charles; Hennepin County Medical Center, Medicine Chauhan, Cynthia Gillespie, Barbara; Covance Global CRO; University of North Carolina, UNC Kidney Center Gruchalla, Ken McCullough, Peter; Baylor University Medical Center, Medicine Quella, Susan Romero, Alain; Relypsa Inc Rossignol, Patrick; Université de Lorraine, INSERM CIC-P 1433, CHRU de Nancy, INSERM U1116, FCRIN INI-CRCT Wheeler, David; University College London Malley, Meaghan; American Society of Nephrology West, Melissa; American Society of Nephrology
Keywords:	cardiovascular, kidney disease, cardiorenal, cardiovascular trials

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Title: Understanding and Overcoming the Challenges Related to Cardiovascular Trials Involving Patients with Kidney Disease

Running head: Patients with Kidney Disease in Cardiovascular Trials

Manuscript Type: Invited Features

Manuscript Category: Feature CUST_CHOOSE_A_MS_CATEGORY_FOR_UNSOLICITED_FEATURES :No data available.

Funders: US Food and Drug Administration, (Grant / Award Number: '2R18FD005283-06 ')

Financial Disclosure: Yes
Dr. Herzog is currently employed by Hennepin Healthcare System. Dr. Herzog reports receiving grants from Amgen, BMS, and Relypsa; receiving honoraria from the American College of Cardiology and UpToDate; serving as a consultant for AbbVie, Amgen, AstraZeneca, Corvidia, DiaMedica, FibroGen, Janssen, NxStage, OxThera, Pfizer, Relypsa, and University of Oxford; and serving as a scientific advisor or member of American Heart Journal Editorial Board, KDIGO Planning Committee for CKD, Heart and Vasculature conference series, and the Kidney Health Initiative; and has ownership interest in Boston Scientific, General Electric, Johnson & Johnson, and Merck; all outside of the submitted work. Dr. Ishida was employed by the University of California San Francisco during the initiation and development of this project and is currently employed by and has ownership interest in Gilead Sciences outside of the submitted work. Ms. Chauhan has nothing to disclose. Dr. Gillespie is currently employed by Covance CRO. Dr. Gillespie reports having ownership in LabCorp; receiving honoraria from NephCure Gateway Initiative; and serving as a scientific advisor or member of the Kidney Health Initiative Board of Directors, National Kidney Diseases CKD Registry steering committee and scientific advisory board, and CardioRenal Society of America Board of Directors; all outside of the submitted work. Dr. Gruchalla has nothing to disclose. Dr. McCullough is currently employed by Baylor University Medical Center. Ms. Quella has nothing to disclose. Dr. Romero is currently employed by and has ownership interest in Chinook Therapeutics. Dr. Romero reports serving as a consultant for Respira Therapeutics; receiving grants from Relypsa; receiving honoraria from Respira Therapeutics; serving as a scientific advisor or member of Respira Therapeutics, and the Kidney Health Initiative; all outside of the submitted work. Dr. Rossignol is currently employed by University of Lorraine Clinical Investigation Center-INSERM-CHRU of Nancy. Dr. Rossignol reports serving as a consultant for Idorsia; receiving honoraria from AstraZeneca, Bayer, CVRx, Fresenius, Grunenthal, Novartis, NovoNordisk, Relypsa, Servier, Stealth Peptides, and Vifor Fresenius Medical Care Renal Pharma; receiving travel grants from AstraZeneca, Bayer, CVRx, Novartis, and Vifor Fresenius Medical Care Renal Pharma; having ownership interest in G3P and a cofounder of CardioRenal; all outside of the submitted work. Dr. Wheeler is currently employed by University College London. Dr. Wheeler reports serving as a consultant for Amgen, AstraZeneca, Boehringer Ingelhiem, Janssen, Napp, Mundipharma, GalaxoSmithKline, Gilead, Tricida, and Vifor Fresenius receiving honoraria from Amgen, Astellas, AstraZeneca, Boehringer Ingelhiem, Janssen, Napp, Mundipharma, Merck, Sharp and Dohme, GalaxoSmithKline, Napp, Ono Pharma, and Vifor Fresenius; and serving as a scientific advisor or member of George Institute for Global Health and the Kidney Health Initiative; all outside of the submitted work. Ms. Malley and Ms. West are currently employed by the American Society of Nephrology.

Total number of words: 3518

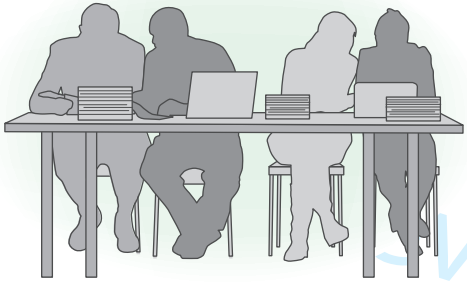
Abstract: Cardiovascular disease is a prevalent and prognostically important comorbidity among patients with kidney disease, and individuals with kidney disease comprise a sizeable proportion (30% to 60%) of patients with cardiovascular disease. However, several systematic reviews of cardiovascular trials have observed that patients with kidney disease, particularly those with advanced kidney disease, are often excluded from trial participation. Thus, currently available trial data for cardiovascular interventions in patients with kidney disease may be insufficient to make recommendations on the optimal approach for many therapies.

The Kidney Health Initiative (KHI), a public-private partnership between the American Society of Nephrology (ASN) and the US Food and Drug Administration (FDA), convened a multi-disciplinary, international workgroup and hosted a stakeholder workshop intended to understand and develop strategies for overcoming the challenges with involving patients with kidney disease in cardiovascular clinical trials, with a particular focus on those with advanced disease. These efforts considered perspectives from stakeholders including academia, industry, contract research organizations, regulatory agencies, patients, and care-partners.

This article outlines the key challenges and potential solutions discussed during the workshop centered on the following areas for improvement: building the business case, reexamining study design and implementation, and changing the clinical trial culture in nephrology. Regulatory and financial incentives could serve to mitigate financial concerns with involving patients with kidney disease in cardiovascular trials. Concerns that their inclusion could impact efficacy or safety results could be addressed through thoughtful approaches to study design and risk mitigation strategies. Finally, there is a need for closer collaboration between nephrologists and cardiologists and systemic change within the nephrology community such that participation of patients with kidney disease in clinical trials is prioritized. Ultimately, greater participation of patients with kidney disease in cardiovascular trials will help build the evidence base to guide optimal management of cardiovascular disease for this population.

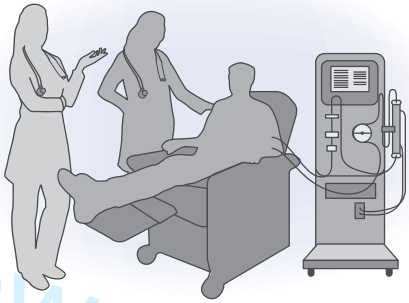
Building the Business Case

- Incentives



Study Design and Implementation

- Mitigate Safety Concerns
- Design Innovations



Changing Research Culture

- Collaboration
- Engagement

Understanding and Overcoming the Challenges Related to Cardiovascular Trials Involving Patients with Kidney Disease

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Abstract Word Count: 300

Manuscript Word Count: 3,518

Running Title: Patients with Kidney Disease in Cardiovascular Trials

ABSTRACT

Cardiovascular disease is a prevalent and prognostically important comorbidity among patients with kidney disease, and individuals with kidney disease comprise a sizeable proportion (30% to 60%) of patients with cardiovascular disease. However, several systematic reviews of cardiovascular trials have observed that patients with kidney disease, particularly those with advanced kidney disease, are often excluded from trial participation. Thus, currently available trial data for cardiovascular interventions in patients with kidney disease may be insufficient to make recommendations on the optimal approach for many therapies.

The Kidney Health Initiative (KHI), a public-private partnership between the American Society of Nephrology (ASN) and the US Food and Drug Administration (FDA), convened a multi-disciplinary, international workgroup and hosted a stakeholder workshop intended to understand and develop strategies for overcoming the challenges with involving patients with kidney disease in cardiovascular clinical trials, with a particular focus on those with advanced disease. These efforts considered perspectives from stakeholders including academia, industry, contract research organizations, regulatory agencies, patients, and care-partners.

This article outlines the key challenges and potential solutions discussed during the workshop centered on the following areas for improvement: building the business case, reexamining study design and implementation, and changing the clinical trial culture in nephrology. Regulatory and financial incentives could serve to mitigate financial concerns with involving patients with kidney disease in cardiovascular trials. Concerns that their inclusion could impact efficacy or safety results could be addressed through thoughtful approaches to study design and risk

mitigation strategies. Finally, there is a need for closer collaboration between nephrologists and cardiologists and systemic change within the nephrology community such that participation of patients with kidney disease in clinical trials is prioritized. Ultimately, greater participation of patients with kidney disease in cardiovascular trials will help build the evidence base to guide optimal management of cardiovascular disease for this population.

INTRODUCTION

Kidney disease is highly prevalent (30% to 60%) among patients with cardiovascular disease and is a risk factor for worse cardiovascular outcomes (1, 2). Thus, management of cardiovascular disease in patients with kidney disease is a common and important clinical problem, yet the evidence base to guide optimal treatment recommendations is limited. Previous reports have observed that the quantity and quality of nephrology trials have been low (2-6), and patients with kidney disease have been underrepresented in cardiovascular trials (1, 2, 7, 8). However, extrapolation of results from cardiovascular trials conducted in the general population to patients with kidney disease may not be appropriate.

The exclusion of patients with kidney disease from cardiovascular trials has been well-documented. Two systematic reviews published in 2006 (1, 2) observed that 56% to 80% of randomized, controlled trials of cardiovascular interventions excluded patients with kidney disease. Although the authors issued strong recommendations for greater inclusion of these patients, their underrepresentation persists. More recently published reviews found that 46% to 57% of cardiovascular trials likewise excluded patients with kidney disease, many of whom had advanced kidney disease (stage 4 chronic kidney disease [CKD]) and kidney failure (7, 8).

These reviews highlight the need for more data to assess the risks and benefits of cardiovascular interventions among patients with kidney disease, a sizable and prognostically important subgroup that bears a high burden of cardiovascular disease (9). To better understand and develop strategies for overcoming the challenges with involving patients with kidney disease in cardiovascular trials, with an emphasis on those with advanced disease, the Kidney Health

Initiative (KHI), a public-private partnership between the American Society of Nephrology (ASN) and the US Food and Drug Administration (FDA) (10), assembled a multi-disciplinary, international workgroup with representation from a variety of stakeholders, including academia, industry, contract research organizations, regulatory agencies, and patients. The workgroup developed and implemented an informal polling mechanism designed to elicit the viewpoints of experts engaged in cardiovascular trials, patients, and care-partners (**Supplemental Material**). Based on this feedback, the group identified key methodologic, operational, and regulatory considerations for the design and conduct of cardiovascular trials involving patients with kidney disease.

To discuss these challenges and to develop actionable strategies to overcome them, a KHI-sponsored workshop was held in September 2018, convening a diverse group of stakeholders including academic and industry trial sponsors, academic and contract research organizations, regulatory agencies, and patients, whose input was considered critical to the workshop's deliberations.

The workshop underscored the urgent need for action to successfully achieve the goal of greater participation of patients with kidney disease in cardiovascular trials. Since the time of the workshop, major nephrology trials (CREDENCE, DAPA-CKD, and FIDELIO-DKD) have been published that evaluated cardiovascular outcomes in patients with kidney disease (11-13). However, these trials did not enroll those with estimated glomerular filtration rate (eGFR) less than 25 ml/min/1.73 m^2, indicating that an evidence gap remains (14, 15), and the concepts discussed during the workshop remain relevant. This article highlights the challenges and

solutions discussed during the workshop, focused around three key areas for improvement: building the business case, reexamining study design and implementation, and changing the clinical trial culture in nephrology (**Table** and **Figure**).

BUILDING THE BUSINESS CASE

Challenges

Patients with kidney disease represent a subgroup in which the pathophysiology of cardiovascular disease can differ from that of the general population (16), which could reduce the efficacy of a therapy if it targets a mechanism that may be less relevant in this subgroup. Additionally, patients with kidney disease have multiple comorbidities and are at risk for experiencing adverse events (17). Thus, trial sponsors with finite financial resources and competing priorities for investment may have concerns about supporting cardiovascular studies involving patients with kidney disease, particularly those with advanced disease, because this could potentially skew their efficacy and safety results and impact regulatory approval and product labeling. If trial sponsors collectively continue to exclude patients with advanced kidney disease from their cardiovascular trials, this may serve as a further disincentive for sponsors to deviate from this common practice.

Solutions

A business case must be made to research sponsors to articulate why patients with advanced kidney disease need to be involved in cardiovascular trials, highlighting the return on investment in this subgroup at high risk for cardiovascular events (1, 2). The financial risk of including

patients with advanced kidney disease into cardiovascular trials could be mitigated by utilization of regulatory and financial incentives that may be applicable to this population.

First, sponsors should consider early during development how existing FDA programs such as Orphan Drug Designation, Breakthrough Therapy, Fast Track, Accelerated Approval, and Priority Review could be leveraged to encourage cardiovascular trials that include patients with advanced kidney disease (18, 19). For example, the development of surrogate cardiovascular endpoints for this population could open a path to accelerated approval, reducing time to market. While not specifically related to a cardiovascular therapy, ongoing trials for IgA nephropathy and focal segmental glomerulosclerosis (FSGS) are evaluating proteinuria reduction as a surrogate endpoint to support regulatory submissions for accelerated approval (20, 21). In addition, the development of lumasiran, the first FDA-approved treatment for primary hyperoxaluria type 1, was facilitated by Orphan Drug and Breakthrough Therapy designations and involved successful collaboration among multiple stakeholders, including industry, FDA, physicians, and patients (22). KHI has championed publications that have fostered these development efforts and provides a forum for multi-disciplinary collaboration (23, 24).

In addition, financial incentives such as market exclusivity extensions for products that have demonstrated efficacy in patients with advanced kidney disease could also encourage their inclusion in trials, although this would require new legislation. Engaging Centers for Medicare & Medicaid Services and other payers early in the development process could also provide insight into how to lay the groundwork for successfully bringing a new cardiovascular therapy for patients with advanced kidney disease to market and reduce concerns about coverage or

reimbursement after approval. Finally, incorporating feedback from patients with kidney disease throughout the development process can add financial value by potentially avoiding costly protocol amendments and improving enrollment, adherence to the intervention, and retention in the trial (25).

STUDY DESIGN AND IMPLEMENTATION

Challenges

Safety Concerns

Safety concerns are viewed as a major barrier to including patients with advanced kidney disease in cardiovascular trials by trial sponsors, investigators, and patients. Patients with kidney disease suffer from multiple comorbidities and take multiple medications (26), which places them at risk for adverse events, drug interactions, non-adherence to the intervention, and withdrawal from the trial.

Trial sponsors may be reluctant to design cardiovascular studies that include this subgroup given the additional financial and logistical burden of safety monitoring and reporting and the potential reduction in data quality due to poor adherence, study drug discontinuation, and study dropout. Investigators may likewise be concerned about this increased burden and may be reluctant to enroll patients with advanced kidney disease if the investigational product impacts eGFR or may exacerbate complications of kidney disease such as hyperkalemia. Patients may be deterred from trial participation due to concerns that the intervention could worsen their kidney disease or cause adverse effects.

Efficacy Concerns

Because the pathophysiology of cardiovascular disease in patients with kidney disease can differ from that of the general population (16), a treatment may lack efficacy or have a smaller effect size in this subgroup, skewing the overall result of a trial toward the null. Additionally, the outcomes of interest may differ for some kidney disease populations. For example, arrhythmia and sudden cardiac death are leading causes of death among patients with kidney failure (27) and may be more relevant than coronary heart death in some situations. Additionally, heart failure endpoints that are suitable in the general population may need to be modified for studies in patients with kidney failure to address unique challenges related to fluid management (28-30). Thus, endpoints used in the general population may not be as relevant for patients with advanced kidney disease, and there is a need for the development of endpoints that may be more appropriate for this subgroup (28).

Lack of Innovative Protocol Designs

When designing new trials, sponsors may use templates from previous trials that excluded patients with advanced kidney disease (7, 8). These protocols may not have involved input from nephrologists who have the greatest knowledge and expertise regarding the unique characteristics of patients with kidney disease.

Recruitment Concerns

Among all patients with cardiovascular disease, a relatively small proportion have advanced kidney disease, particularly kidney failure (27). Absent specific efforts to target patients in this

subgroup, investigators may be unable to recruit and enroll sufficient numbers of patients to draw meaningful conclusions about this population.

Solutions

Manage Safety Concerns

Adverse events are anticipated to be common among patients with advanced kidney disease, and in some cases, their exclusion may be justified due to safety concerns related to a particular drug or device. However, sponsors should consider whether there are aspects of trial design that could mitigate safety risks. For example, the SONAR trial of atrasentan in diabetic patients with kidney disease incorporated a novel design that excluded participants with fluid retention to minimize risk of heart failure (31). Sponsors may consider adopting such an approach that excludes participants who are at-risk for experiencing adverse events. In addition, protocols can prohibit or restrict use of medications commonly used in this population that interact with the investigational product. If the intervention impacts eGFR, sponsors should understand the mechanism, time course of the effect, reversibility, and implications for longer-term kidney function, and they should provide appropriate education to investigators. If the intervention may exacerbate complications of kidney disease (e.g., hyperkalemia), sponsors and investigators can develop strategies to manage these risks (e.g., non-invasive potassium monitoring, potassium-lowering agents). Patient input on strategies to mitigate safety risks and maximize adherence to intervention and study participation should also be incorporated into study design and implementation. It is possible that measures to mitigate safety risks could increase costs for sponsors, but investments in such safeguards should ideally be balanced by avoidance of adverse

events and undesirable downstream consequences such as study drug discontinuation and study dropout.

Require Justification for Exclusion of Patients with Advanced Kidney Disease

Although excluding patients with advanced kidney disease may be warranted in some settings, the rationale for exclusion may not be clear or justified in all cases. Trial sponsors should carefully consider whether there is a strong rationale to exclude patients with advanced kidney disease, and individuals involved in trial conduct, including investigators, regulatory authorities, and patients, should routinely question exclusions based on level of kidney function. Requiring justification for exclusion of patients with advanced kidney disease could serve to mitigate unnecessary exclusion due to concerns about potential impact on efficacy results.

Innovative Protocol Design

To mitigate sponsor concerns over potentially diluting efficacy due to the inclusion of patients with advanced kidney disease in cardiovascular trials conducted in the general population, sponsors could be given the option of enrolling patients with an eGFR below a certain threshold but excluding them from key efficacy endpoint analyses. Given the relatively low prevalence of advanced kidney disease, it may be challenging to enroll sufficient numbers of patients to draw firm conclusions; however, this approach would allow collection of some efficacy and safety information in this subgroup rather than none.

Another option would be to conduct a *dedicated* cardiovascular trial for patients with advanced kidney disease in parallel with a cardiovascular trial in the general population that excludes

patients below a certain eGFR cutoff. This option may be particularly relevant if it is necessary to use cardiovascular endpoints that are tailored to patients with advanced kidney disease. As kidney disease advances, there is a shift towards an increasing burden of non-atherosclerotic disease (e.g., arrythmias, sudden cardiac death) versus atherosclerotic disease (e.g., coronary artery disease, ischemic stroke), and endpoints should be selected as appropriate to the study population (32).

Additionally, the endpoint definitions themselves may require modification. For example, in a trial evaluating heart failure events among participants receiving hemodialysis, the standard definition of a heart failure endpoint event may not be optimal. It may be challenging to determine whether signs and symptoms of volume overload are attributable to heart failure or kidney failure, which may be related to missed hemodialysis sessions, dry weight overestimation, or lack of adherence to diet and fluid restrictions (28). Such a trial could consider using the Acute Dialysis Quality Initiative (ADQI) proposed classification of heart failure in patients with kidney failure, which takes into account response of symptoms to renal replacement therapy/ultrafiltration, if the staging system undergoes the appropriate prospective validation (29). Cardiovascular and kidney trialists must continue collaborating on the development of standardized cardiovascular outcome definitions for patients with advanced kidney disease and kidney failure.

Nephrologists are optimally positioned to advise on how to tailor cardiovascular trial protocols to facilitate involvement of patients with advanced kidney disease, so consulting nephrologists to

guide the design and implementation of cardiovascular trials involving this population is essential.

Recruitment

Recruitment of patients with kidney disease into cardiovascular trials may be facilitated by seeking guidance from such patients on how to optimize recruitment strategies. Obtaining patient feedback on study materials (e.g., protocols) may help to ensure that study procedures will not be a deterrent to enrollment. Additionally, creation of registries for patients with kidney disease – a "virtual pool" of potential participants who may be amenable to participating in cardiovascular trials – may also support recruitment efforts. Best practices from cardiovascular trials that have been able to successfully enroll patients with stage 4 and 5 CKD (e.g., SHARP, ISCHEMIA-CKD) should be leveraged (33, 34).

CLINICAL TRIAL CULTURE IN NEPHROLOGY

Challenges

Current Culture

In addition to addressing challenges with financial concerns and study design and implementation, there is a compelling need for a broader mission to transform nephrology into an "on-study" culture in which trial participation is the norm and not the exception. The number and quality of trials in nephrology continues to be lower than that of other specialties (4-6), and until recently, there has been limited investment in drug development for treatment of kidney disease. Recently published major trials (CREDENCE, DAPA-CKD, and FIDELIO-DKD) and ongoing trials involving patients with kidney disease point to the growing clinical trial enterprise

within the field of nephrology (11-13, 35). However, because trials are not widely part of routine practice, nephrologists may be less familiar with them and may also face challenges with communicating the value of trial participation within their organizations.

Lack of Infrastructure

Nephrology lags behind other fields, such as oncology and cardiology, in terms of the infrastructure needed to support conducting clinical trials (36, 37). There are few incentives for nephrologists to participate in trials and a relatively limited number of established sites and investigators with experience enrolling patients with advanced kidney disease.

Enrollment Challenges

One topic raised at the stakeholder workshop (and receiving little attention in publications) is the practical concern of burden to site coordinators. Patients with advanced kidney disease are justifiably perceived by site coordinators to require more time and effort due a higher number of expected reportable adverse events. Given that there is not additional compensation from the sponsor for enrolling patients with advanced kidney disease, there is essentially a disincentive for site coordinators to enroll such individuals.

For patients receiving dialysis, enrollment requires partnerships with dialysis organizations, posing financial and logistical barriers such as the need for staff to perform research activities and disruptions to treatments. The RENAL-AF trial (38), which evaluated the safety of apixaban versus warfarin in hemodialysis patients with atrial fibrillation, was terminated early for slow

enrollment, exemplifying the daunting challenges facing researchers conducting cardiovascular clinical trials in dialysis patients.

Patient Involvement

Patients overwhelmingly express a willingness to participate in cardiovascular trials, citing the importance of this issue to people with kidney disease and a desire to help contribute knowledge to the field. However, patients with kidney disease may not be aware that trials are happening or how to participate. Additionally, patients with kidney disease may be unaware that they are at risk for cardiovascular disease. In the Wearable Cardioverter Defibrillator in Hemodialysis Patients (WED-HED) trial (39), which was terminated for slow enrollment, a recurring refrain from patients considering trial participation was, "What do you mean I am at risk for sudden cardiac death? If that's true, why didn't my nephrologist tell me?"

Despite their willingness to participate, patients expressed some concerns. In addition to the safety concerns discussed above, other concerns included fear of the unknown, risk of receiving placebo, polypharmacy, painful testing, inconvenience, and lack of time and sufficient compensation for participation. Patients also expressed a strong desire for the results of research studies to be communicated back to them.

Solutions

Greater participation of patients with kidney disease in cardiovascular trials will require a cultural change within nephrology in which trial participation is broadly supported. To this end, there are several strategies aimed at facilitating physician and patient engagement in trials that

could help move nephrology toward the "on-study" mindset that is more common in other specialties.

Physician Engagement

Physician participation in trials could be supported through financial and other incentives. For example, participation of academic investigators could be enhanced if nephrology and cardiology division leadership created protected time for trial activities and recognized their intrinsic value. Continuing medical education credit could also be offered for trial-related efforts. Additionally, enhancing government funding across multiple relevant institutes, subspecialty societies, and industry-sponsored funding could expand opportunities to conduct cardiovascular trials involving patients with kidney disease. Providing training in trial planning and execution, particularly among trainees and junior investigators, could also help to ensure a steady pipeline of researchers capable of conducting trials. Shared resources, such as papers and presentations, should be developed to support nephrologists' involvement as principal investigators and to spur discussions with health systems.

Collaboration

Numerous recent papers have called for specific training in cardiorenal medicine and closer collaboration between nephrologists and cardiologists (40-43). A larger community of nephrologists and cardiologists must be created, leveraging existing professional organizations. Attendance at multi-disciplinary meetings and academic meetings outside of one's specialty should also be encouraged to enhance cross-fertilization of ideas, along with coordinating efforts across existing trial networks.

Building provider networks and partnerships among other stakeholders would also help create the infrastructure needed to support trial conduct among patients receiving dialysis and greater engagement from nephrologists. For example, a network of dialysis providers could share resources (e.g., research coordinators) to facilitate trials.

Patient Engagement

In order to emphasize the clinical importance of cardiovascular disease, patients with kidney disease must be informed about the link between kidney and heart disease. Educational campaigns, coordinated by the National Institutes of Health (NIH) and specialty organizations, with support from dialysis providers and patient groups, could aid in these efforts. Patient engagement could also be strengthened through education about trial participation by personal physicians, patient advocacy groups, social media, and other patients with kidney disease. Compensation to sites to incentivize enrollment of patients with advanced kidney disease should be considered.

The creation of a trial registry as discussed above could also help allay patient concerns about lack of information about study participation opportunities. The registry would include a list of ongoing trials targeted for study populations with kidney disease, including cardiovascular trials, and would be interactive such that an interested patient could easily obtain information about a trial, answer a screening questionnaire to determine eligibility, and indicate a desire to be contacted by a study coordinator. Such a registry would empower patients to be active partners in trial participation, improve the efficiency and costs of recruitment, and ameliorate concerns

regarding investigator access to particular groups of kidney patients, such as those receiving dialysis. Finally, trial results should be communicated back to those who have participated in the trial, maintaining patient involvement from start to finish and creating a greater sense of engagement.

CONCLUSION/CALL TO ACTION

The persistent underrepresentation of patients with kidney disease in cardiovascular trials has led to insufficient evidence to guide optimal management of cardiovascular disease in this population. Our charge was to identify barriers to including patients with kidney disease in cardiovascular trials, with an emphasis on those with advanced disease, and strategies to overcome these hurdles. Many of the topics discussed in this paper are broadly applicable to nephrology trials in general. However, the challenges we identified may be magnified among the subgroup of kidney patients with cardiovascular disease, given their high mortality and morbidity.

Our workgroup identified financial, methodologic, operational, and cultural barriers to greater inclusion of patients with advanced kidney disease in cardiovascular trials, but we believe these barriers are not insurmountable. Strategies to overcome them include building a business case with regulatory and financial incentives, improving study design and implementation with greater physician and patient engagement, and creating an "on-study" culture in nephrology akin to that of other specialties. Implementation of the proposed solutions will require a multi-disciplinary effort involving a variety of stakeholders, including academia, industry, regulatory agencies, patients, government and specialty organizations in the nephrology and cardiology

community. Collectively, these strategies can increase the available data for managing cardiovascular disease among patients with kidney disease and allow providers to make more informed treatment decisions in this important subgroup.

DISCLAIMERS

The views and opinions expressed in this publication are those of the authors and do not necessarily reflect the official policies of any KHI member organization, FDA, the U.S. Department of Veterans Affairs, or the U.S. Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

DISCLOSURES

Dr. Herzog is currently employed by Hennepin Healthcare System. Dr. Herzog reports receiving grants from Amgen, BMS, and Relypsa; receiving honoraria from the American College of Cardiology and UpToDate; serving as a consultant for AbbVie, Amgen, AstraZeneca, Corvidia, DiaMedica, FibroGen, Janssen, NxStage, OxThera, Pfizer, Relypsa, and University of Oxford; and serving as a scientific advisor or member of American Heart Journal Editorial Board, KDIGO Planning Committee for CKD, Heart and Vasculature conference series, and the Kidney Health Initiative; and has ownership interest in Boston Scientific, General Electric, Johnson & Johnson, and Merck; all outside of the submitted work. Dr. Ishida was employed by the University of California San Francisco during the initiation and development of this project and is currently employed by and has ownership interest in Gilead Sciences outside of the submitted work. Ms. Chauhan has nothing to disclose. Dr. Gillespie is currently employed by Covance

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outside of the submitted work. Mrs. Malley and Ms. West are currently employed by the American Society of Nephrology.

ACKNOWLEDGMENTS

We would like to acknowledge Aliza Thompson and Kimberly Smith from the U.S. Food and Drug Administration for their thoughtful guidance on the development of this manuscript. This work was supported by the Kidney Health Initiative (KHI), a public-private partnership between the American Society of Nephrology, the U.S. Food and Drug Administration, and >100-member organizations and companies to enhance patient safety and foster innovation in kidney disease. KHI funds were used to defray costs incurred during the conduct of the project, including project management support which was provided by American Society of Nephrology staff members, Melissa West, Meaghan Malley, and Elle Silverman. There was no honorarium or other financial support provided to KHI workgroup members. The authors of this paper had final review authority and are fully responsible for its content. KHI makes every effort to avoid actual, potential or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the members of the workgroup. More information on KHI, the workgroup, or the conflict of interest policy can be found at www.kidneyhealthinitiative.org.

FUNDING

This work was supported by KHI, which is partially funded by a US FDA grant 2R18FD005283-06 and ASN.

SUPPLEMENTAL MATERIAL

Supplemental Table 1: Expert Stakeholder Poll Respondent Characteristics

Appendix 1: Expert Stakeholder Poll Questions

Supplemental Table 2: Patient and Care-partner Poll Respondent Characteristics

Appendix 2: Patient and Care-partner Poll Questions

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Table: Challenges with Involving Patients with Kidney Disease in Cardiovascular Trials and Proposed Solutions

Challenges	Solutions
Building the Business Case	
Trial sponsor concerns • Finite resources and competing priorities • Inclusion of patients with advanced kidney disease could potentially skew efficacy and safety results and impact regulatory approval and product labeling	• Consider existing FDA programs (e.g., Orphan Designation, Breakthrough Therapy and Fast Track Designation, Accelerated Approval, and Priority Review Designation) • Financial incentives such as market exclusivity extensions • Engaging CMS and other payers early in the development process • Incorporate feedback from patients throughout the development process
Study Design and Implementation	
Safety concerns • Higher risk of adverse events, drug interactions, non-adherence to the intervention, withdrawal from the trial • Financial and logistical burden of safety monitoring and reporting • Potential reduction in data quality due to poor adherence and dropout from the study due to adverse events • Concern that investigational product may impact kidney function or exacerbate complications of kidney disease	• Develop strategies to mitigate safety concerns (e.g., novel study design, prohibit or restrict medications that interact with investigational product, understand impact of investigational product on eGFR, manage risks of exacerbating complications of kidney disease such as hyperkalemia)
Efficacy concerns and lack of innovative protocol designs • Lack of efficacy or smaller effect size in subgroup with kidney disease, which could skew overall result toward the null • Endpoints used in the general population may not be as relevant for patients with advanced kidney disease • Use of protocol templates that excluded patients with kidney disease • Protocols designed without nephrologist input	• Consider whether there is adequate justification to exclude patients with advanced kidney disease • Sponsor could be offered option of enrolling patients with an eGFR below a certain threshold in a broader study but exclude them from key efficacy analyses • Conduct *dedicated* cardiovascular trial for patients with advanced kidney disease in parallel with a cardiovascular trial in general population that excludes patients below a certain eGFR cutoff • Select appropriate endpoints and develop standardized cardiovascular outcome definitions for patients with advanced kidney disease and kidney failure

	• Include nephrologists in the development of cardiovascular trial protocols
Recruitment concerns • Prevalence of patients with advanced kidney disease is relatively low and may be a barrier to trial recruitment and enrollment	• Seek guidance from patients with kidney disease on study materials (e.g., protocols) and how to optimize recruitment strategies • Create registries for patients with kidney disease in order to have "virtual" pool of potential participants • Leverage best practices from trials that have successfully enrolled patients with advanced kidney disease and kidney failure
Clinical Trial Culture in Nephrology	
Lack of "on-study" culture and trial infrastructure in nephrology • Lack of awareness and incentives for nephrologists to participate in trials • Limited number of established sites and investigators with experience enrolling patients with advanced kidney disease • Challenges with communicating the value of trial participation to health systems	• Offer financial and other incentives to physicians for participation in trials • Enhance government (e.g., NHLBI, NIDDK), subspecialty society, and industry-sponsored funding • Provide training in trial planning and execution to trainees and junior investigators • Develop resources (e.g., papers, presentations) to support nephrologists' participation in trials • Encourage cross-specialty collaboration between cardiologists and nephrologists, leveraging existing organizations (e.g., ERA/EDTA, HFSA, KCVD, Cardio Renal Society of America, INI-CRCT) and attendance at multi-disciplinary meetings (e.g., CVCT, KDCT)
Enrollment challenges • High number of expected reportable adverse events may serve as a disincentive to site coordinators to enroll patients with advanced kidney disease • Financial and logistical barriers to enrolling patients receiving dialysis	• Compensation to sites to incentivize enrollment of patients with advanced kidney disease • Build provider networks and partnerships to support trial conduct among patients receiving dialysis
Patient involvement • Patients unaware of clinical trials or how to participate • Patients with kidney disease are unaware that they are at risk for cardiovascular disease	• Increase patient knowledge about the link between cardiovascular and kidney disease via educational campaigns coordinated by NIH and specialty organizations (e.g., ASN, NKF, ISN, ERA/EDTA) with

• Patient concerns include fear of the unknown, risk of receiving placebo, polypharmacy, painful testing, inconvenience, and lack of time, sufficient compensation for participation, and communication of research results	support from dialysis providers and patient groups • Educate patients on trial participation via physicians, patient advocacy groups, social media, and other patients with kidney disease Incorporate list of ongoing trials into patient registry and provide mechanism to determine eligibility and connect with study coordinator • Communicate trial results back to participants

CMS = Centers for Medicare and Medicaid Services; eGFR = estimated glomerular filtration; NHLBI = National Heart, Lung, and Blood Institute; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; ERA/EDTA = European Renal Association-European Dialysis and Transplant Association; HFSA = Heart Failure Society of America; KCVD = Council for the Kidney in Cardiovascular Disease; Cardio-Renal Society of America, INI-CRCT = Investigation Network Initiative-Cardiovascular and Renal Clinical Trialists; CVCT = CardioVascular Clinical Trialists Forum; KDCT = Kidney Disease Clinical Trialists; NIH = National Institutes of Health; ASN = American Society of Nephrology; NKF = National Kidney Foundation; ISN = International Society of Nephrology

FIGURE LEGEND

Figure: Strategies to Overcome the Challenges Related to Involving Patients with Kidney Disease in Cardiovascular Trials

A multi-pronged approach involving building the business case, improving study design and implementation, and changing the clinical trial culture in nephrology can foster greater participation of patients with kidney disease in cardiovascular trials.

SUPPLEMENTAL MATERIAL

In order to inform the discussion at the KHI-sponsored workshop held in September 2018, the workgroup developed and issued two anonymous polls, one directed at a broad stakeholder group of experts engaged in cardiovascular trials and one directed at patients and care-partners. Responses were collected over a 2-month period during November 2017 through January 2018. This Supplement outlines the number and key characteristics of the poll respondents and the questions that were asked.

Supplemental Table 1: Expert Stakeholder Poll Respondent Characteristics

Appendix 1: Expert Stakeholder Poll Questions

Supplemental Table 2: Patient and Care-partner Poll Respondent Characteristics

Appendix 2: Patient and Care-partner Poll Questions

Supplemental Table 1: Expert Stakeholder Poll Respondent Characteristics

Characteristic	Respondents (n=73)
Stakeholder Group (n, %)	
Academic researcher	40 (54.8)
Academic research organization	1 (1.37)
Clinician	16 (21.9)
Sponsor/Pharmaceutical/Device Company	7 (9.59)
Contract research organization	4 (5.48)
Regulatory	0 (0)
Other	5 (6.85)
Specialty/Therapeutic Area (n, %)[1]	
Cardiology	29 (39.7)
Nephrology	53 (72.6)
Endocrinology	7 (9.59)
Pediatric Cardiology	0 (0)
Pediatric Nephrology	3 (4.11)
Pediatric Endocrinology	0 (0)
Other (please specify)	7 (9.59)

[1]Multiple selections were allowed, so percentages do not sum to 100%.

Appendix 1: Expert Stakeholder Poll Questions

Introduction

Kidney disease is highly prevalent among patients with cardiovascular disease and is associated with worse cardiovascular outcomes. Thus, the management of cardiovascular disease in patients with kidney disease is a common and important clinical problem. However, the evidence on which to base the optimal management of cardiovascular disease in patients with advanced chronic kidney disease (CKD) (i.e., estimated glomerular filtration rate <30 ml/min/1.73 m^2) not requiring dialysis and end-stage renal disease (ESRD) requiring dialysis is limited by their exclusion from cardiovascular trials performed in the general population and challenges with conducting dedicated trials in these populations.

We are conducting a survey to understand the **challenges** with involving patients with advanced CKD not requiring dialysis and ESRD requiring dialysis in cardiovascular clinical trials and to generate **solutions** to overcome these challenges. We are defining cardiovascular clinical trials as studies of drugs such as (though not limited to) antiplatelet and anticoagulant agents, or heart failure treatments; procedures such as percutaneous coronary intervention; and devices such as a wearable cardioverter defibrillator.

Your responses will be anonymous. Thank you for your participation.

Stakeholder Background

1. Which stakeholder group do you represent?

☐ Academic researcher
☐ Academic research organization
☐ Clinician
☐ Sponsor/Pharmaceutical/Device Company
☐ Contract research organization
☐ Regulatory
☐ Other (please specify): _____

2. What are the specialty(ies) or therapeutic area(s) in which you work? Check all that apply.

☐ Cardiology
☐ Nephrology
☐ Endocrinology
☐ Pediatric Cardiology
☐ Pediatric Nephrology
☐ Pediatric Endocrinology
☐ Other (please specify): _____

Challenges with Involving Patients with Advanced Chronic Kidney Disease Not Requiring Dialysis and End-Stage Renal Disease Requiring Dialysis in Cardiovascular Clinical Trials

*3. What are the **challenges** with involving patients with advanced chronic kidney disease (CKD) (i.e., estimated glomerular filtration rate <30 ml/min/1.73 m^2) not requiring dialysis and/or end-stage renal disease (ESRD) requiring dialysis in cardiovascular clinical trials? Check all that apply and specify the patient population for which the challenge is relevant. If a challenge is not listed here, please elaborate in the section labeled "Other."*

Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease

	Advanced CKD (eGFR <30 ml/min/1.73 m^2) Not Requiring Dialysis		**ESRD Requiring Dialysis**	
	Yes	**No**	**Yes**	**No**
a. Low prevalence of patients with advanced CKD and/or ESRD	☐	☐	☐	☐
b. Lack of efficacy or smaller treatment effect that could weaken overall treatment effect	☐	☐	☐	☐
c. Safety concerns				
i. Concern for higher risk of adverse events	☐	☐	☐	☐
ii. Concern that intervention could worsen kidney disease	☐	☐	☐	☐
iii. Concern that intervention could worsen cardiovascular disease	☐	☐	☐	☐
d. Protocol design				
i. Standard protocols exclude patients with advanced CKD and/or ESRD	☐	☐	☐	☐
ii. Uncertainty about effect of renal impairment on drug exposure and proper drug dosing	☐	☐	☐	☐
iii. Lack of standardized cardiovascular endpoints specific to patients with advanced CKD and/or ESRD	☐	☐	☐	☐
iv. Lack of validated surrogate cardiovascular endpoints specific	☐	☐	☐	☐

to patients with advanced CKD and/or ESRD				
e. Financial concerns				
i. Need for additional funds or resources to monitor patients at high risk for adverse events	☐	☐	☐	☐
ii. Financial costs of accessing patients	☐	☐	☐	☐
iii. Risk of poor formulary placement if trial only enrolls specific populations	☐	☐	☐	☐
iv. Poor reimbursement by payers, even after drug approval	☐	☐	☐	☐
v. Reluctance of senior management to support development	☐	☐	☐	☐
f. Regulatory barriers				
i. Potential regulatory risk (e.g., safety data could impact label or approval)	☐	☐	☐	☐
ii. Lack of regulatory incentives (e.g., waiver of application fees, market exclusivity)	☐	☐	☐	☐
g. Patient recruitment				
i. Patient exclusion based on multiple comorbidities	☐	☐	☐	☐
ii. Low patient awareness of clinical trial availability	☐	☐	☐	☐
iii. Patient reluctance to participate in clinical trials	☐	☐	☐	☐
iv. Low physician awareness of clinical trial availability	☐	☐	☐	☐
v. Physician reluctance to participate in clinical trials or registries	☐	☐	☐	☐
vi. Physician reluctance to enroll patients	☐	☐	☐	☐
vii. Lack of physician experience with clinical trial conduct	☐	☐	☐	☐

h. Other: _____	☐	☐	☐	☐

4. Of the choices you selected, what is the most significant challenge? Please explain briefly.

_____

Solutions to Overcoming the Challenges with Involving Patients with Advanced Chronic Kidney Disease Not Requiring Dialysis and End-Stage Renal Disease Requiring Dialysis in Cardiovascular Clinical Trials

*5. What are potential **solutions** to overcome challenges with involving patients with advanced chronic kidney disease (CKD) (i.e., estimated glomerular filtration rate <30 ml/min/1.73 m^2) not requiring dialysis and/or end-stage renal disease (ESRD) requiring dialysis in cardiovascular clinical trials? Check all that apply and specify the patient population for which the solution is relevant. If a solution is not listed here, please elaborate in the section labeled "Other."*

Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease

	Advanced CKD (eGFR <30 ml/min/1.73 m^2) Not Requiring Dialysis		**ESRD Requiring Dialysis**	
	Yes	**No**	**Yes**	**No**
a. Trial design improvements				
i. Use of historical controls	☐	☐	☐	☐
ii. Randomized registries of patients with advanced CKD and/or ESRD running in parallel to the main trial	☐	☐	☐	☐
iii. Standardized cardiovascular endpoints specific to patients with CKD and/or ESRD	☐	☐	☐	☐
iv. Validated surrogate cardiovascular endpoints specific to patients with CKD and/or ESRD	☐	☐	☐	☐
v. Early engagement with patients in the design of the trial (e.g., including patients on steering committees)	☐	☐	☐	☐
b. Risk mitigation methods				
i. Use of predictive biomarkers for adverse events	☐	☐	☐	☐

c. Regulatory solutions				
i. Waiver of application fees as a regulatory incentive	☐	☐	☐	☐
ii. Market exclusivity to sponsors who conduct dedicated trials for patients with advanced CKD and/or ESRD as a regulatory incentive	☐	☐	☐	☐
iii. Close collaboration with regulators to better define endpoints and trial design prior to study initiation	☐	☐	☐	☐
d. Financial incentives				
i. Building of a business case such that the return-on-investment can be better appreciated	☐	☐	☐	☐
ii. Reimbursement policy changes	☐	☐	☐	☐
e. Patient recruitment improvements				
i. Investigator-run trial network for patient recruitment	☐	☐	☐	☐
ii. Acknowledgement and communication of mortality and morbidity of advanced CKD and/or ESRD to patients	☐	☐	☐	☐
iii. Cultural shift encouraging patients with advanced CKD and/or ESRD to enroll in clinical trials	☐	☐	☐	☐
iv. Communication of benefits of trial participation by other patients or kidney patient advocacy group	☐	☐	☐	☐
f. Closer collaboration with community-based researchers regarding trial design, conduct, analysis, and recruitment	☐	☐	☐	☐

g. Other: _____	☐	☐	☐	☐

6. Of the choices you selected, what do you believe will be the most effective? Please explain briefly.

_____

Follow-Up

7. Would you be willing to participate in a focus group or individual interview to discuss your perspective further?

☐ Yes

☐ No

Supplemental Table 2: Patient and Care-partner Poll Respondent Characteristics

Characteristic	Respondents (n=48)[1]
Stakeholder Group (n, %)	
Patient	42 (87.5)
Care-partner	6 (12.5)
Age (n, %)	
18-24 years	1 (3.13)
25-34 years	1 (3.13)
35-44 years	2 (6.25)
45-54 years	11 (34.4)
55-64 years	9 (28.1)
65-74 years	7 (21.9)
75 years or older	1 (3.13)
Sex (n, %)	
Male	16 (48.5)
Female	17 (51.5)
Ethnicity (n, %)	
Hispanic or Latino	0 (0)
Not Hispanic or Latino	33 (100)
Race (n, %)	
American Indian or Alaska Native	0 (0)
Asian	0 (0)
Black or African American	9 (27.3)
Native Hawaiian or Other Pacific Islander	0 (0)
White	24 (72.7)
Other	0 (0)
Comorbidities (n, %)	
Cardiovascular Disease	7 (21.2)
Diabetes	6 (19.4%)
Renal Replacement Therapy (n, %)	
Hemodialysis	14 (42.4)
Peritoneal Dialysis	1 (3.03%)
Kidney Transplant	12 (36.4%)

[1]33 respondents for sex, ethnicity, race, diagnosis of cardiovascular disease, and receipt of hemodialysis, peritoneal dialysis, and kidney transplant; 32 respondents for age; and 31 respondents for diagnosis of diabetes.

Appendix 2: Patient and Care-partner Poll Questions

Introduction
Kidney disease is common among patients with cardiovascular disease, but patients with advanced or end-stage kidney disease are often excluded from clinical trials testing treatments for cardiovascular disease. We are conducting a survey to understand your perspective regarding the challenges around participation in cardiovascular clinical trials, and hopefully learn some solutions.

Your responses will be anonymous. Thank you for your participation.

1. Are you a patient or a care-partner? If you are both, please select ONE for the purpose of filling out this survey.
☐ Patient
☐ Care-partner

Demographics Section (Patients Only)
Please answer the following questions about your demographics and medical history.

2. What is your age?
☐ 18-24 years
☐ 25-34 years
☐ 35-44 years
☐ 45-54 years
☐ 55-64 years
☐ 65-74 years
☐ 75 years or older

3. How do you identify your gender?
☐ Male
☐ Female
☐ Prefer to self-describe: _____

4. What is your ethnicity?
☐ Hispanic or Latino
☐ Not Hispanic or Latino

5. What is your race?
☐ American Indian or Alaska Native
☐ Asian
☐ Black or African American
☐ Native Hawaiian or Other Pacific Islander
☐ White
☐ Other (please specify): _____

6. What best describes the area in which you live?

☐ Urban
☐ Rural
☐ Suburban

7. Do you have a diagnosis of kidney disease that has been present for at least 3 months?
☐ Yes
☐ No

8. If yes, what is your level of kidney function (in estimated glomerular filtration rate or eGFR, ml/min/1.73 m^2)?
☐ ≥90
☐ 60-89
☐ 45-59
☐ 30-44
☐ 15-29
☐ <15
☐ Not sure

9. Are you currently receiving hemodialysis?
☐ Yes
☐ No

10. Are you currently receiving peritoneal dialysis?
☐ Yes
☐ No

11. Do you have a functioning kidney transplant?
☐ Yes
☐ No

12. How long have you been diagnosed with kidney disease?
☐ <1 year
☐ 1-5 years
☐ 6-10 years
☐ >10 years

13. Do you have a diagnosis of cardiovascular disease?
☐ Yes
☐ No

14. If so, what type of cardiovascular disease do you have? Check all that apply.
☐ Coronary artery disease (e.g., history of heart attack, stent, bypass surgery)
☐ Cerebrovascular disease or history of stroke
☐ Peripheral artery disease or history of circulation problems in arms or legs
☐ Heart failure with preserved ejection fraction
☐ Heart failure with reduced ejection fraction

☐ Heart failure but not sure of ejection fraction
☐ Abnormal heart rhythm (e.g., atrial fibrillation)
☐ Heart valve disease
☐ Other (please specify): _____

15. Do you have a diagnosis of diabetes?
☐ Yes
☐ No

Clinical Trial Participation Section (Patients Only)
16. If clinical trials are to be conducted to test if treatments for heart disease will work in patients with kidney disease, would you be willing to participate in a clinical trial?
☐ Yes
☐ No

If you answered yes, proceed with questions 17, 18, 22, 23, 24, and 33.
If you answered no, skip to questions 19, 20, 21, 22, 23, 24, and 33.

17. If yes, what are your reasons for wanting to participate in a clinical trial testing treatments for heart disease? Check all that apply.
☐ Heart disease is a leading cause of problems, even death, in patients with kidney disease, so participation in a clinical trial will help address an important issue.
☐ I want to contribute knowledge that will find better treatments for heart disease in patients with kidney disease.
☐ I want to help other patients with kidney and heart disease even if clinical trial participation may carry some risks to myself.
☐ My care team has educated me on why clinical trial participation is important.
☐ I will obtain personal health benefit and better access to care through attendance of study visits.
☐ I will receive financial compensation.
☐ Other (please specify): _____

18. Of the choices you selected, which is your most important motivation for participation in a clinical trial testing treatments for heart disease? Please type your response in the comment box below.

_____

19. If not, what would be your barriers/concerns? Check all that apply.
☐ I am not aware of the risks of heart disease that are linked to kidney disease.
☐ I am not fully aware of the potential benefits of clinical trial participation overall.
☐ I am concerned about the safety risks of trying a new treatment that is not yet approved.
☐ I am concerned that a new treatment could worsen my kidney disease.
☐ I am concerned that a new treatment could worsen my heart disease.
☐ I am concerned that a new treatment could affect my wait time on the kidney transplant list.
☐ Risk that I could receive a placebo (i.e., inactive treatment) instead of the new treatment
☐ I do not want to take another medication because I am already taking too many medications.

☐ I do not want to use a device because it is inconvenient.
☐ I do not have time to participate in a clinical trial.
☐ I do not want painful testing such as blood draws.
☐ I am concerned that I will not be fully informed of all the benefits and risks of clinical trial participation.
☐ I am concerned that my medical records will not be protected and kept private.
☐ I will not be paid enough for the time it will take to participate in a clinical trial.
☐ My physician or care team have not offered me the chance to participate in a clinical trial.
☐ Other (please specify): _____

20. Of the choices you selected, which is the most significant barrier/concern? Please explain briefly in the comment box below.

_____

21. What changes would help you to participate in a clinical trial testing treatments for heart disease? Check all that apply.
☐ More knowledge about the link between heart and kidney disease.
☐ Having my own physician offer me the chance to participate in a clinical trial and explain the benefits and risks.
☐ Having another patient with kidney disease explain the benefits and risks of participation in a clinical trial and share their experience with clinical trial participation.
☐ Have a patient advocacy group explain the benefits and risks of participation in a clinical trial.
☐ Compensation for clinical trial participation.
☐ Other (please specify): _____

22. Have you ever been turned down for participation in a clinical trial because of your kidney disease?
☐ Yes
☐ No

23. Any other thoughts you would like to share? Please type your comments in the comment box below.

_____

24. Did anyone help you to complete this form?
☐ Yes
☐ No

Clinical Trial Participation Section (Care-Partners Only)
25. If clinical trials are to be conducted to test if treatments for heart disease will work in patients with kidney disease, would the patient for whom you provide care be willing to participate in a clinical trial?
☐ Yes
☐ No
If you answered yes, proceed with questions 26, 27, 31, 32 and 33.
If you answered no, skip to questions 28, 29, 30, 31, 32, and 33.

26. If yes, what are the patient's reasons for wanting to participate in a clinical trial testing treatments for heart disease? Check all that apply.

☐ Heart disease is a leading cause of problems, even death, in patients with kidney disease, so participation in a clinical trial will help address an important issue.
☐ Desire to contribute knowledge that will find better treatments for heart disease in patients with kidney disease.
☐ Desire to help other patients with kidney and heart disease even if clinical trial participation may carry some risks.
☐ The care team has provided education on why clinical trial participation is important.
☐ Personal health benefit and better access to care through attendance of study visits.
☐ Financial compensation.
☐ Other: _____

27. Of the choices you selected, which is the patient's most important motivation for participation in a clinical trial testing treatments for heart disease? Please type your answer in the comment box below.

_____

28. If not, what would be the patient's barriers/concerns? Check all that apply.

☐ Unaware of the risks of heart disease that are linked to kidney disease.
☐ Not fully aware of the potential benefits of clinical trial participation overall.
☐ Safety risks of trying a new treatment that is not yet approved.
☐ Concern that a new treatment could worsen his/her kidney disease.
☐ Concern that a new treatment could worsen his/her heart disease.
☐ Concern that a new treatment could affect his/her wait time on the kidney transplant list.
☐ Risk of receiving a placebo (i.e., inactive treatment) instead of the new treatment.
☐ Does not want to take another medication because he/she is already taking too many medications.
☐ Does not want to use a device because it is inconvenient.
☐ Does not have time to participate in a clinical trial.
☐ Does not want painful testing such as blood draws.
☐ Concern that he/she will not be fully informed of all the benefits and risks of clinical trial participation.
☐ Concern that medical records will not be protected and kept private.
☐ Concern that he/she will not be paid enough for the time it will take to participate in a clinical trial.
☐ Physician or care team have not offered the chance to participate in a clinical trial.
☐ Other (please specify): _____

29. Of the choices you selected, which is the patient's most significant barrier/concern? Please explain briefly in the comment box below.

_____

30. What changes would help the patient participate in a clinical trial testing treatments for heart disease? Check all that apply.

☐ More knowledge about the link between heart and kidney disease.
☐ Having his/her physician offer the chance to participate in a clinical trial and explain the benefits and risks.
☐ Having another patient with kidney disease explain the benefits and risks of participation in a clinical trial and share their experience with clinical trial participation.
☐ Having a patient advocacy group explain the benefits and risks of participation in a clinical trial.
☐ Compensation for clinical trial participation.
☐ Other (please specify): _____

31. Has the patient ever been turned down for participation in a clinical trial because of his/her kidney disease?
☐ Yes
☐ No

32. Any other thoughts you would like to share? Please type your response in the comment box below.
_____

Follow-Up
33. Would you be willing to participate in a focus group or individual interview to discuss your perspective further?
☐ Yes
☐ No