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