

COPE-AKI Consortium Protocol

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National Clinical Trial (NCT) Identified Number:

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
5.5	Addition of clinical sites	
6.1, 6.3, 8.1	Added clarity to enrollment/baseline wording used through protocol. Enrollment refers to the first study visit. Baseline primarily refers to pre-morbid or preadmission kidney function.	
8.1.3	Added language to directly sending the survey link for the patient-reported outcomes (PROs) to study participants via text or email.	
9.4.9	Added language for sensitivity analyses to assess the value of the nadir in-hospital serum creatinine compared to the discharge serum creatinine.	

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the DSMB and IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

Principal Investigator or Clinical Site Investigator:

Signed:

Date:

Name*: Kaleab Z Abebe, PhD

Title*: Assistant Vice Chancellor for Clinical Trials, Health Sciences
Professor of Medicine & Biostatistics

Investigator Contact Information:

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For multi-site studies, the protocol should be signed by the clinical site investigator who is responsible for the day-to-day study implementation at his/her specific clinical site:

Signed:

Date:

Name: Emilio Poggio, MD

Title:

Affiliation:

Signed:

Date:

Name: Chirag Parikh, MD

Title:

Affiliation:

Signed:

Date:

Name: Edward Siew, MD

Title:

Affiliation:

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Caring for OutPatiEnts after Acute Kidney Injury (COPE-AKI) Trial
Grant Number:	1U01DK130010, 1U01DK129989, 1U01DK129980, 1U01DK129984
Study Description:	The COPE-AKI study is a phase III, randomized, pragmatic, parallel-arm trial comparing a multimodal intervention to usual care on hospital-free days through 90 days of study follow up. The primary study hypothesis is that patients randomized to the intervention will have increased odds of more hospital-free days through 90 days (primary clinical) compared to those randomized to usual care. Key secondary hypotheses will investigate the impact of the intervention on rates of major adverse kidney events, rates of recurrent AKI, and changes in patient-reported outcomes. Participants (N=2145) will be allocated 1:1 to the intervention or usual care using a web-based system to maintain allocation concealment using stratified randomization with randomly permuted blocks. Randomization will be stratified by clinical site.
Objectives*:	The primary study hypotheses for the COPE-AKI study are: compared to usual care, patients randomized to a multimodal intervention will have increased odds of more hospital-free days through 90 days (primary) and lower rates of major adverse kidney events (MAKE) at 180 days, lower rates of recurrent AKI at 180 days, and greater improvements in patient-reported outcomes over 90 days (secondary).
Endpoints*:	The primary outcome is hospital-free days through 90 days of follow up, defined as 90 minus the number of calendar days in the hospital as either an inpatient or on observation status, based on the determination made by the corresponding hospital. Key secondary outcomes include: rates of MAKE (measured at 90, 180, and 365 days), rates of recurrent AKI (90, 180, and 365 days), and 4 patient-report outcomes: global health related quality of life, AKI-specific health related quality of life, provider interactions, and social support (30, 90, 180, 365 days).
Study Population:	Study participants will include adults hospitalized with) KDIGO Stage 2/3 AKI with evidence of persistent AKI (defined as meeting Stage 2+ AKI for 2 consecutive serum creatinine concentration measurements >12 hours apart but no more than 72 hours apart).
Phase* or Stage:	Phase III

**Description of Sites/Facilities
Enrolling Participants:**

Participants will be recruited and enrolled from 9 clinical centers across the midwest, southeast, and northeast part of the United States: Cleveland Clinic, MetroHealth, Cleveland Clinic-Weston, Vanderbilt University Medical Center, University of Alabama Birmingham, Nashville VA Medical Center, The Johns Hopkins Hospital, University of Maryland Medical Center, and Yale New Haven Health.

**Description of Study
Intervention/Experimental
Manipulation:**

A multimodal process-of-care intervention that includes 1) study physician oversight and follow up care recommendations at the time of hospital discharge; 2) involvement of a nurse navigator to provide kidney-disease related education, coordinate care, and assess symptoms; and 3) pharmacist-led medication reconciliation and review. Participants in the usual care arm will be provided information about their kidney disease, nephrotoxins to be avoided, and the importance of follow up with a physician will be emphasized.

Study Duration*:

42 months

Participant Duration:

12 months

STANDARD OF CARE

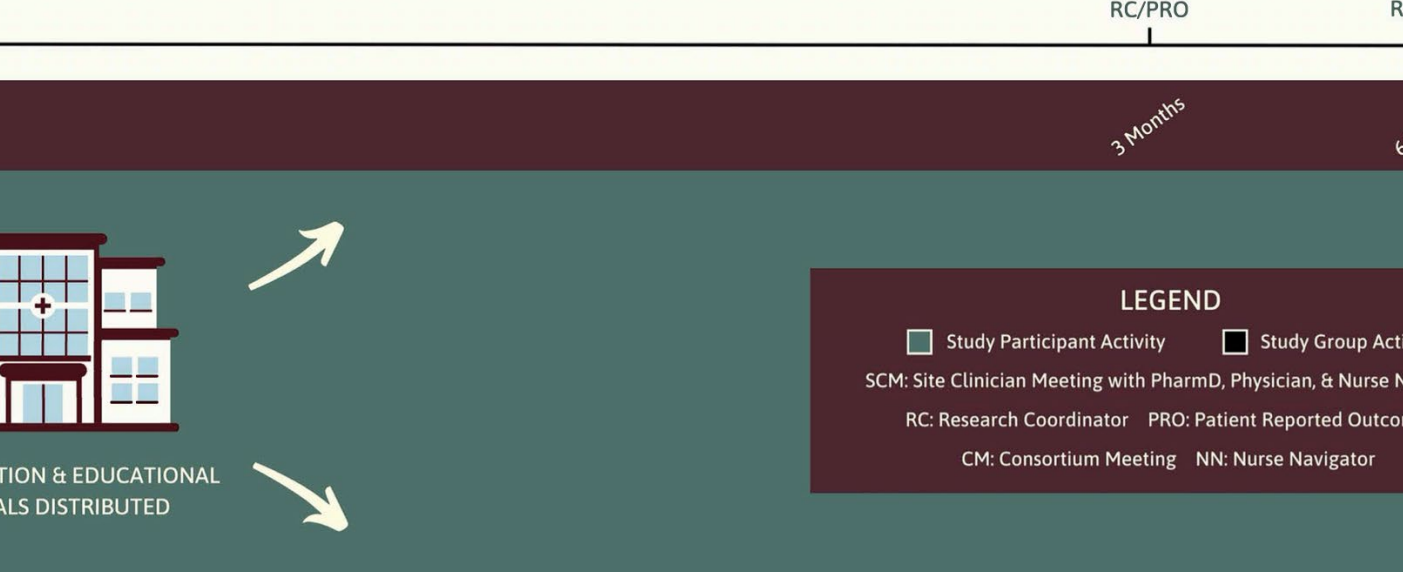
RC/PRO

Discharge

3 Months

6 Months

12 Months



The Standard of Care timeline diagram shows a horizontal timeline with a light blue background. At the top, a dark blue bar contains the text 'STANDARD OF CARE'. Below this, a horizontal line marks the timeline. Above the line, 'RC/PRO' is written at the start, and 'RC/PRO RC/PRO' is written at the end. Below the line, 'Discharge' is written at the start, and '3 Months', '6 Months', and '12 Months' are written at regular intervals. A large, light blue rectangle with a dark blue border represents the study period. Inside this rectangle, on the left, is a white icon of a hospital building with a red cross. Below the icon, the text 'RANDOMIZATION & EDUCATIONAL MATERIALS DISTRIBUTED' is written. Two white arrows point from this text towards the right. On the right side of the rectangle, there is a white box with a dark blue border. Inside this box, the text 'LEGEND' is written at the top. Below it, there are two rows of text: 'Study Participant Activity' with a light blue square icon, and 'Study Group Activity' with a dark blue square icon. Below these, there are three lines of text: 'SCM: Site Clinician Meeting with PharmD, Physician, & Nurse Navigator', 'RC: Research Coordinator PRO: Patient Reported Outcomes', and 'CM: Consortium Meeting NN: Nurse Navigator'.

RANDOMIZATION & EDUCATIONAL MATERIALS DISTRIBUTED

LEGEND

- Study Participant Activity
- Study Group Activity

SCM: Site Clinician Meeting with PharmD, Physician, & Nurse Navigator

RC: Research Coordinator PRO: Patient Reported Outcomes

CM: Consortium Meeting NN: Nurse Navigator

MULTIMODAL INTERVENTION

RC/PRO
NN & MD

SCM

SCM & CM

SCM

SCM & CM

SCM

RC/PRO
SCM & CM

RC/PRO RC/PRO

Discharge

2-3 Days

5-7 Days

7-10 Days

2 Weeks

3 Weeks

1 Month

5 Weeks

6 Weeks

7 Weeks

2 Months

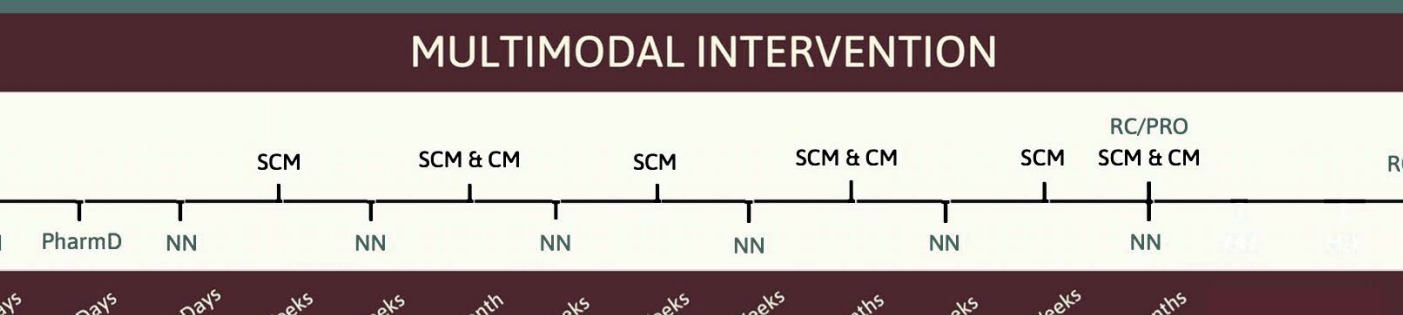
9 Weeks

10 Weeks

3 Months

6 Months

12 Months



The Multimodal Intervention timeline diagram shows a horizontal timeline with a light blue background. At the top, a dark blue bar contains the text 'MULTIMODAL INTERVENTION'. Below this, a horizontal line marks the timeline. Above the line, 'RC/PRO NN & MD' is written at the start, and 'RC/PRO RC/PRO' is written at the end. Below the line, 'Discharge' is written at the start, and '2-3 Days', '5-7 Days', '7-10 Days', '2 Weeks', '3 Weeks', '1 Month', '5 Weeks', '6 Weeks', '7 Weeks', '2 Months', '9 Weeks', '10 Weeks', '3 Months', '6 Months', and '12 Months' are written at regular intervals. A large, light blue rectangle with a dark blue border represents the study period. Inside this rectangle, on the left, is a white icon of a hospital building with a red cross. Below the icon, the text 'RANDOMIZATION & EDUCATIONAL MATERIALS DISTRIBUTED' is written. Two white arrows point from this text towards the right. On the right side of the rectangle, there is a white box with a dark blue border. Inside this box, the text 'LEGEND' is written at the top. Below it, there are two rows of text: 'Study Participant Activity' with a light blue square icon, and 'Study Group Activity' with a dark blue square icon. Below these, there are three lines of text: 'SCM: Site Clinician Meeting with PharmD, Physician, & Nurse Navigator', 'RC: Research Coordinator PRO: Patient Reported Outcomes', and 'CM: Consortium Meeting NN: Nurse Navigator'.

1.3 SCHEDULE OF ACTIVITIES

Assessment	Enrollment (Prior to Hospital Discharge)	Day 30 (±7 days)	Day 90 (±14 days)	Month 6 (±14 days)	Month 12 (±14 days)
Demographic and Clinical Data					
Demographics	X				
Brief Confusion Assessment Method (bCAM)	X				
Vital Signs (weight, height, BP, HR)	X		X	X	X
Presence of edema	X		X	X	X
Medication List (e.g., dose; OTC; supplements)	X	X	X	X	X
Vital status		X	X	X	X
Hospital admissions		X	X	X	X
Assessment of visits with PCP		X	X	X	X
Assessment of visits with nephrologist		X	X	X	X
Dialysis Dependence		X	X	X	X
Laboratory Testing					
BMP (glucose, calcium, sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine)	X		X	X	X

Assessment	Enrollment (Prior to Hospital Discharge)	Day 30 (±7 days)	Day 90 (±14 days)	Month 6 (±14 days)	Month 12 (±14 days)
Cystatin C	X		X	X	X
Urine panel (albumin, creatinine, protein)	X		X	X	X
Serum for banking	X		X	X	X
Urine for banking	X		X	X	X
Patient Reported Outcomes Instrument					
Global HRQoL	X	X	X	X	X
AKI-specific HRQoL	X	X	X	X	X
Impact of AKI (optional)	X	X	X	X	X
AKI-related symptoms (optional)	X	X	X	X	X
Functional status (optional) Physical Function Cognitive Function	X	X	X	X	X
Psychosocial status (optional) Depression Anxiety	X	X	X	X	X
Frailty (optional) Revised RAI-C	X	X	X	X	X

Assessment	Enrollment (Prior to Hospital Discharge)	Day 30 (±7 days)	Day 90 (±14 days)	Month 6 (±14 days)	Month 12 (±14 days)
AKI knowledge (optional) Objective knowledge of AKI Perceived knowledge of AKI	X	X	X	X	X
Self-efficacy (optional) Managing symptoms Managing medications	X	X	X	X	X
Social support Emotional support Instrumental support	X	X	X	X	X
Interactions with providers Patient-provider interactions Patient satisfaction	X	X	X	X	X
Healthcare utilization (optional)	X	X	X	X	X
Social determinants of health	X	X (optional)	X (optional)	X (optional)	X (optional)

2 INTRODUCTION

2.1 STUDY RATIONALE

There is a clear need for enhanced strategies that optimize the care of patients following acute kidney injury (AKI) hospitalization. The Caring for OutPatiEnts after Acute Kidney Injury (COPE-AKI) study will test a multimodal patient management intervention that will address many of these gaps in care. In the absence of specific evidence-based guidelines for post-AKI management, COPE-AKI will focus on optimizing the process of post-hospital care using enhanced patient education through multiple engagement tools, nephrologist oversight, augmented post-hospitalization follow-up through the use of a nurse-navigator, and provision of pharmacist-directed medication management using telemedicine to ensure implementation of physician-directed post-hospitalization care recommendations. This enhanced care strategy will be compared, in a randomized controlled trial, to usual post-hospital care. By enhancing patient support, we anticipate that this novel strategy for post-hospital care for individuals surviving an episode of AKI will reduce the risk of rehospitalization, assessed as hospital-free days, and improve patient-reported health-related quality of life (HRQoL). We further hypothesize that these interventions will result in more optimal management of blood pressure and volume status and better adherence to medications that are associated with decreased progression of kidney disease, thereby reducing longer-term risks of adverse events and major adverse kidney outcomes.

2.2 BACKGROUND

AKI incidence in the US is estimated to be about 6.8 per 1000, greater than that of acute myocardial infarction.¹ While AKI affects approximately 60% of all ICU patients, it has also been shown to complicate non-ICU hospitalizations with significant worsening of short- and long-term outcomes. Most clinical research related to AKI has focused on prevention of AKI and on treatment of hospitalized patients with AKI. Few intervention studies have addressed outcomes after hospital discharge, and these have predominantly been small pilot studies.^{2–5} Approximately 1 in 5 patients with AKI are readmitted within 30 days after their index hospitalization, with particular risk for admission for congestive heart failure.⁶ The development of new onset of chronic kidney disease (CKD) or worsening of pre-existing CKD occurs in approximately 30% of patients surviving an episode of AKI and is associated with increased risk of progression to kidney failure.^{1,7–9} In addition, we have found that those who recover from severe AKI have poor health related quality of life. In the VA/NIH Acute Renal Failure Network (ATN) study, 27% of AKI survivors had a health utility at 60 days considered by the general population to be equivalent to or worse than death.¹⁰

Lack of continuity of care, delayed follow-up and suboptimal medication management after AKI hospitalization exacerbate the risks of adverse outcomes. The suboptimal management includes over- or under-adjusting medications for changes in kidney function, exposure to unnecessary nephrotoxins and failure to restart medications that may have been discontinued in the acute setting, such as diuretics

and inhibitors of the renin-angiotensin system (RAS) or sodium-glucose cotransporter type 2 (SGLT2), that are needed for volume and blood pressure (BP) management which may slow progression of CKD or reduce risk of mortality. Inadequate dosing of diuretics due to concern for recurrent intravascular volume depletion may result in rehospitalization with decompensated heart failure and volume overload; excessive diuretic dosing may lead to volume depletion and rehospitalization with recurrent AKI. In addition, individuals with AKI have a higher risk of hypoglycemia and hypertension in the post-hospitalization period, leading to adverse safety events and potentially increasing the risk of rehospitalization. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend patient follow-up for monitoring of kidney function within 3 months of an AKI episode;⁷ however, follow-up with a nephrologist rarely occurs. In elderly Medicare patients, only 13% saw a nephrologist within 3 months after an AKI episode; although, 75% saw a primary care provider (PCP).^{11,12} Whether a discussion of ongoing kidney disease and CKD prevention with the PCP even occurs is uncertain since most patients do not know they had AKI in the hospital.¹³ Patients with strong risk factors for AKI, including existing CKD or diabetic nephropathy, only saw a nephrologist within 3 months of the AKI episode 23% and 29% of the time, respectively.¹² Even the majority of patients (59-88%) who required dialysis in the hospital do not see a nephrologist within 1 year of hospital discharge.^{13,14} The lack of follow-up for AKI is a missed opportunity.¹⁵ Furthermore, while nephrology follow-up within 90 days is suggested for assessment of kidney function, even earlier follow-up medical management would likely decrease the increased risk of rehospitalization, as has been demonstrated in other disease settings.¹⁵⁻²⁰

In addition to the gaps in medical management of patients after an episode of AKI, qualitative analysis of patient concerns after hospitalization for AKI include: 1) lack of awareness of their diagnosis of AKI; 2) lack of information about AKI and how to manage it at home; 3) lack of understanding about AKI; 4) a concern about the need for dialysis; and 5) a desire to know how to prevent further episodes of AKI.¹⁶ The proposed multimodal intervention is designed to address these patient-reported concerns.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There are no experimental treatments or procedures. The risks are expected to be minimal and include potential risk to confidentiality, bruising/fainting with research blood draws and a small risk of discomfort from answering survey questions.

A potential concern of the intervention is that closer monitoring might result in paradoxical increase in hospitalizations as medical problems are recognized earlier or hospitalization for less severe cause.

2.3.2 KNOWN POTENTIAL BENEFITS

A more intensified and standardized post-hospitalization care has the potential benefit of identifying medical issues prior to the need for subsequent all-cause hospitalization and for improving

communication between multiple providers and the participant. Additional benefits may include better optimization of drug therapy and avoidance of nephrotoxins. The intervention may reduce the risks of subsequent AKI, sepsis, heart failure CKD progression, and cardiovascular disease outcomes. The intervention could decrease anxiety associated with the recent illness and AKI. There may not be a direct benefit to study participants, but the study could benefit future patients with AKI.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The overall study is minimal risk. Every effort will be made to make sure that the personal information obtained from this study will be kept strictly confidential. Individuals are free not to answer any questions that make them uncomfortable.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary Clinical Outcomes			

Hypothesis: Compared to usual care, patients randomized to a multimodal intervention will have greater odds of increased hospital-free days through 90 days	Hospital-free days through day 90 defined as 90 minus the number of calendar days in the hospital as either an inpatient or on observation status.	We considered hospital-free days to day 90 as an alternative way to assess the hospitalization outcome, defined as the number of days alive and not in the hospital. Similar endpoints have been used in studies of critically ill patients and in heart failure.^{17,18} Hospital-free days integrates more data than a simple analysis of rehospitalization as it allows integration of duration of that hospitalization, data on subsequent hospitalizations and is implicitly adjusted for mortality. These benefits are particularly important in analyzing the proposed intervention in which more frequent contact with the nurse navigator could paradoxically result in earlier rehospitalization, at a point where a patient is less-symptomatic, but more readily treated, resulting in shorter rehospitalization length-if-stay. It is also possible that the intervention results in reduced numbers of secondary	By increasing medical support for patients discharged after an episode of AKI, the intervention will optimize volume, BP, and medication management leading to a decrease in hospital utilization. In addition, by providing increased knowledge about their episode of AKI and increased resources to navigate post-hospital medical care, necessary interventions will be provided to forestall rehospitalization.
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		rehospitalizations, an outcome that would not be detected by a simple analysis of first rehospitalization.		
Key Secondary Outcomes				

Compared to usual care, participants randomized to the multimodal intervention will have lower rates of major adverse kidney events (assessed by the composite of death, dialysis, and persistent kidney dysfunction) and lower rates of recurrent AKI hospitalization 180 days	MAKE-180 composite outcome of death, dialysis and assessment of kidney function defined as: • death within 180 days of index hospital discharge; • need for dialysis at 180 days after index hospital discharge; or • serum creatinine >2x baseline at 180 days after index hospital discharge MAKE-90 and MAKE-365 will be defined similarly	A putative benefit of the proposed intervention is avoidance of potential nephrotoxin exposures, prevention of ADEs and optimization of care to decrease the risk of progression of kidney disease. It is well recognized that AKI, even with initial recovery of kidney function, is associated with decline in subsequent kidney function.^{19–21} A recognized limitation to this endpoint is that a value for the pre-morbid eGFR will likely be missing for some patients resulting in a need to impute the pre-morbid baseline. In the primary analysis, if the pre-morbid	By avoidance of inappropriate nephrotoxins, optimal drug dosing, improved blood pressure control and optimization of medications that are thought to be nephroprotective (e.g., RAS blockers, SGLT2i), the study intervention will improve kidney function outcomes assessed both as glomerular filtration (with need for dialysis as a marker of severely impaired glomerular filtration rate) and as urine albumin excretion.
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		serum creatinine is not known, it will be imputed based on the hospital nadir value used for establishing the AKI stage. In a sensitivity analysis, only patients with a documented pre-morbid serum creatinine will be included.		
	Rates of recurrent AKI hospitalization at 180 days (also assessed at 90, and 365 days)			
The goal of collecting patient-reported outcomes (PROs) is to assess health-related quality-of-life (HRQoL) factors that may be directly or indirectly affected by the intervention.	Global HRQoL – assessed with 10-item PROMIS measure	These PRO endpoints were selected based on their known or hypothesized association with the experience of AKI as well as their hypothesized role as mediators or moderators of intervention effects on primary and secondary outcomes.	By increasing medical support for patients discharged after an episode of AKI, the intervention will improve patient-reported HRQoL across key domains.	
	AKI-specific HRQoL – assessed with 6-item CKD-QoL			
	Interaction with providers – assessed with 5-item PEPPI and 8-item CSQ			
	Social support – assessed with 4-item emotional support and 4 item instrumental support PROMIS measures			

Tertiary Clinical Outcomes			
Compared to usual care, participants randomized to the multimodal intervention will have lower rates of 30-day subsequent all-cause hospitalization	30-day subsequent all-cause hospitalization	Aligns with HEDIS/CMS hospital quality measure	Same as for primary outcome

Compared to usual care, participants randomized to the multimodal intervention will have lower rates of subsequent all-cause hospitalization and better kidney functional outcomes at 90, 180, and 365 days	Urine albumin to creatinine ratio at 90, 180, and 365 days	The presence of proteinuria or albuminuria is a recognized risk factor for future worsening of kidney function after an episode of AKI. ²² It is expected that there will be substantial missingness for ascertainment of baseline albuminuria and proteinuria as assessed by urine albumin to creatinine ratio (uACR) or urine protein to creatinine ratio (uPCR). We will therefore assess the effect of the intervention on uACR based on the absolute values at 90, 180, and 365 days, with an implicit assumption that baseline uACR was balanced across the treatment arms by randomization.		
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	Time to event analysis of composite of death and first rehospitalization	The time to event analysis of rehospitalization provides an alternative assessment of the primary hypothesis that the intervention will reduce the risk of subsequent all-cause hospitalization	Same as primary outcome	
	Survival through day 90, 180, and 365	Component of MAKE outcome		
	Need for dialysis at day 90, 180, and 365	Component of MAKE outcome		
	MAKE-90 eGFR Composite as composite of: - death prior to day 90 (scored as eGFR=0) - dialysis dependence at day 90 (scored as eGFR = 10) - eGFR at day 90 MAKE-180 eGFR and MAKE-365 eGFR will be defined similarly	The MAKE-90 eGFR composite provides a second approach for assessing the composite of death, need for dialysis and kidney function that does not require comparison of kidney function at day-90 to baseline kidney function. An implicit assumption for this endpoint, however, is that baseline eGFR is balanced between treatment arms.		
	eGFR at day 90, 180, and 365	Component of MAKE eGFR outcome		

	Alternative MAKE-90 composite outcome of death, dialysis, and assessment of kidney function (using pre-enrollment SCr) defined as: • death within 90 days of index hospital discharge; • need for dialysis at 90 days after index hospital discharge; or • serum creatinine >1.5x baseline at 90 days after index hospital discharge MAKE-180 and MAKE-365 will be defined similarly			
	CKD Stage at Day 90, 180, and 365 -change in CKD Stage from baseline	Combines eGFR and uACR at day 90		
Tertiary PRO Outcomes (30, 90, 180, and 365 days)				
The goal of collecting patient-reported outcomes (PROs) is to assess health-related quality-of-life (HRQoL) factors that may be directly or indirectly affected by the intervention;	Impact of AKI – assessed with 3 items from UPitt pilot study	These PRO endpoints were selected based on their known or hypothesized association with the experience of AKI as well as their hypothesized role	By increasing medical support for patients discharged after an episode of AKI, the intervention will improve patient-reported HRQoL across key domains.	

additionally, to examine factors that may mediate or moderate the effects of the intervention.	AKI-related symptoms – assessed with 10 items from UPitt pilot study Functional status – assessed with 4-item physical and 4-item cognitive PROMIS measures Psychosocial status – assessed with 4-item depressive affect and 4-item anxiety PROMIS measures AKI knowledge – assessed with 15-item objective knowledge and 6-item perceived knowledge scales from adapted KiKs Self-efficacy – assessed with 4-item symptom management and 4-item medications management PROMIS measures Healthcare utilization – assessed with 15-item Health Services Utilization Scale plus one item	as mediators or moderators of intervention effects on primary and secondary outcomes.		
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	assessing types of physicians seen generated for this study. Frailty – assessed with the 16-item RAI-C Social determinants of health – assessed with 6 selected/modified items from the ACH Health-Related Social Needs Screening Tool			
Tertiary Process of Care Measures				
The goal of collecting these process of care endpoints is to assess the implementation of the intervention (completion of visits with nurse navigator/clinical pharmacist and with PCP or nephrologist) and the effect of the intervention on clinical care (BP control, medication usage)	Completion of virtual visit with nurse navigator/clinical pharmacist within 7 days Completion of visit with PCP or nephrologist within 30 days, 6 months, 12 months Blood pressure control at 90 days, 6 months, 12 months Medication use at 30 days, 90 days, 6 months, 12 months	Completion of virtual visits with nurse navigator and clinical pharmacist will only be assessed in treatment arm to assess compliance with protocol; remainder will be assessed in both treatment arms by survey (when PROs are collected) to compare across treatment arms		

	-Diuretics -RAS blockade -SGLT2i			
Safety Endpoints (through 12 months)				
	Rate of adverse drug events			
	Rate of medication errors			



4 STUDY DESIGN

4.1 OVERALL DESIGN

The COPE-AKI study is a phase III, randomized, pragmatic, parallel-arm trial comparing a multimodal intervention to usual care on hospital-free days through 90 days of study follow up. The primary study hypothesis is that patients randomized to a multimodal intervention will have increased odds of more hospital-free days through 90 days (primary clinical) compared to those randomized to usual care. Key secondary hypotheses will investigate the impact of the intervention on rates of major adverse kidney events (180 days), rates of recurrent AKI (180 days), and changes in patient-reported outcomes (global- and AKI-specific health related quality of life, provider interactions, and social support) over 90 days. Participants will be allocated 1:1 to the intervention or usual care using a web-based system to maintain allocation concealment using stratified randomization with randomly permuted blocks. Randomization will be stratified by clinical site.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

For this trial, the control is considered usual care for patient hospitalized with AKI. Existing guidelines recommend patient follow-up for monitoring of kidney function within 3 months of an AKI episode. Known problems with the control condition include lack of physician adherence to the recommended guidelines and lack of AKI education given to patients, which can lead to increased risk for subsequent hospitalization.

As a result, the addition to usual care of the following components – involvement of a nurse navigator to provide kidney-disease related education, coordinate care, and assess symptoms; pharmacist-led medication reconciliation and review; follow up care coordination from study physician; physician oversight at the time of hospital discharge – has the potential to improve clinical patient-reported outcomes in this population.

4.3 JUSTIFICATION FOR INTERVENTION

AKI survivors are at high risk for recurrent hospitalizations, progression to CKD, and death. These patients have high levels of comorbidity and coexisting illnesses. Despite this, AKI patients have suboptimal and fragmented post-hospitalization care. Whether a systematic and coordinated post-hospitalization process of care can improve outcomes for patients with AKI is unproven. This protocol will have a multi-pronged care coordination process that will focus on improving short term outcomes while also focusing on channeling patients to evidence-based long-term pathways. The interventions will thus focus on measures that will

1. Identify and risk-stratify patients with persistent kidney dysfunction that will need ongoing nephrology care
2. Facilitate navigation of the health care system to optimize care processes and forestall need for inpatient medical care
3. Increase patient knowledge about AKI and secondary complications of AKI
4. Limit secondary insults (ex: inappropriate medication use)
5. Enable early identification of clinical deterioration to permit timely outpatient intervention.

4.4 END-OF-STUDY DEFINITION

Study participants will have reached the end-of-study when they complete the 12 month follow up visit, if they withdraw their consent for participation, or if they die.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

INCLUSION CRITERIA

- Aged ≥ 18 years
- KDIGO Stage 2/3 AKI with evidence of persistent AKI (defined as meeting Stage 2+ AKI for 2 consecutive serum creatinine concentration measurements >12 hours apart but no more than 72 hours apart)

Justification for Inclusion Criteria: We will restrict our population to patients with persistent Kidney Disease Improving Global Outcomes (KDIGO) Stage 2 or 3 AKI for 2 consecutive days who survive to discharge to enrich for patient populations that are at highest risk for poor outcomes after AKI.

Definition of Baseline Creatinine for Study Enrollment: Several approaches to estimating baseline serum creatinine concentration have been used in the literature, each with strengths and limitations. We will reduce the risk for potential misclassification through the inclusion of patients with persistent Stage 2 or 3 AKI and apply a definition of baseline serum creatinine concentration that balances accuracy with a feasible approach for real-time identification of potential study participants. For those with preadmission serum creatinine concentration values available, will use the mean of the outpatient non-emergency room preadmission serum creatinine values 7-365 days before admission (limited to the 3 most recent values). These values can include preoperative values for those admitted for elective procedures/treatments. If the above values are not available, we will use lowest of the nadir of the serum creatinine concentration values of the index hospitalization OR the most recent pre-admission (inpatient or ED) serum creatinine value.

5.2 EXCLUSION CRITERIA

EXCLUSION CRITERIA

- AKI due to primary glomerulonephritis, renal vasculitis, or thrombotic microangiopathy
- Diagnosis of end-stage kidney disease (ESKD) at the time of admission, defined as:
 - Baseline eGFR <15 mL/min/1.73m²
 - Previous kidney transplant recipient
 - On chronic dialysis
- Acute urinary obstruction with rapid kidney function improvement following relief of obstruction

- Index hospitalization involving nephrectomy
- Index hospitalization involving solid organ transplant or stem cell/bone marrow transplant
- Continued dialysis dependence at time of discharge
- Previous (within 6 months) or new referral to a nephrologist for care specifically for:
 - Previous or new diagnosis of glomerulonephritis
 - Primary electrolyte imbalance disorders unrelated to AKI (e.g., syndrome of inappropriate antidiuretic hormone secretion, Bartter syndrome)
 - Active treatment for acute interstitial nephritis
- Non-kidney end-organ failure:
 - Class IV congestive heart failure
 - Decompensated cirrhosis with MELD >30 or those with a diagnosis of hepatorenal syndrome by the clinical teams
 - End-stage pulmonary disease (advanced stage COPD, interstitial lung disease, cystic fibrosis, pulmonary hypertension)
- Active malignancy with planned or ongoing therapy requiring frequent admissions or in-person/virtual visits with an oncology provider/navigator (defined as monthly or more often)
- Primary goal of care is palliation: life expectancy <6 months
- Pregnancy
- Vulnerable populations
 - Persons incarcerated
 - Persons institutionalized
- Inability to provide informed consent
 - Impaired cognition as demonstrated by the Brief Confusion Assessment Method (bCAM)
- Concurrent enrollment in a separate greater than minimal risk interventional trial in which active intervention extends beyond hospital discharge
- Inability to participate in either in-person or remote visits

- Inability to participate as determined by the research team at time of discharge based on disposition (vs uniform decision across site about exclusion based on SNF)
- Discharge to long-term acute care facility or other hospital-based location

Justification of Exclusion Criteria: To select AKI survivors that are likely to benefit from a post-AKI care bundle, we will exclude patients who cannot experience AKI (e.g., ESRD) or in whom the diagnosis of AKI is confounded (nephrectomy). We will exclude patients in whom multidisciplinary follow-up and close monitoring of kidney function and medications are protocolized following hospitalization (transplantation). Patients with dialysis dependence at discharge or in whom ongoing nephrology care for specific indications requiring specific treatments (glomerulonephritis, nephrotic syndrome, interstitial nephritis, severe electrolyte derangements) will also be excluded. Patients with limited life expectancy (nonrenal end-organ dysfunction, advanced cancer, palliative care/hospice referral) will also be excluded. Lastly, vulnerable populations, those unable to consent, or logistically unable to participate in either in-person or remote visits will be excluded.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable for this study

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are subsequently found to be ineligible due to meeting one or more exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) occurring after consent. Individuals who are deemed screen failures may be rescreened if they again fulfill all inclusion and exclusion criteria. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Target population and accrual: we plan to enroll approximately 715 participants per primary clinical center in this study, for a total enrollment of approximately 2145 over the course of 2.5 years. We aim to enroll an equal number of men and women to this study. Representation of racial and ethnic minorities should closely match or mirror the demographic breakdown of patients at each recruitment site who develop AKI during hospitalization.

Recruitment sites: We will recruit trial participants from 3 primary clinical centers, among patients admitted to the hospital who have developed AKI and meet all inclusion criteria:

- Cleveland Clinic
 - Cleveland Clinic
 - MetroHealth
 - Cleveland Clinic-Weston
- Southeast AKI (SEAK) Alliance:
 - Vanderbilt University Medical Center
 - University of Alabama Birmingham
 - Nashville VA Medical Center
- Johns Hopkins:
 - The Johns Hopkins Hospital
 - University of Maryland Medical Center
 - Yale New Haven Health

Participant identification and recruitment: Specific processes for initial participant identification and recruitment will vary by study site. In general, we will identify patients through several means, including use of real-time algorithms that leverage data from each recruitment site's electronic health record, to identify adult inpatients who meet inclusion and exclusion criteria. A complementary approach for identification of potential research candidates involves review of patients followed by inpatient nephrology consultation teams for AKI.

All candidates who pass initial record screening will be further screened manually by research personnel. As soon as patients are confirmed to be appropriate candidates for COPE-AKI, study team members will seek permission from primary inpatient teams and approach the candidates for enrollment. All study-related activities including intervention details will be explained to study candidates in detail, with questions answered to the complete satisfaction of the candidate:

- Risks and benefits of participation in the study
- The randomization procedure will be explained in detail, including the intervention and usual care arms
- Sample collection during and after hospitalization
- Follow-up schedule both in-person and via telemedicine

- Ability to withdraw from the study at any point after consent

We will track details of enrollment including but not limited to the following:

- Demographics including race/ethnicity, age, sex/gender
- Among those who choose not to participate:
 - Reason(s) for not participating
 - Ways to improve study recruitment for future candidates

We will confirm eligibility for study participation within 24-48 hours of planned hospital discharge, and at the time of randomization to the study intervention or usual care.

Participant retention: Patients enrolled in this study will require regular study follow-up over the course of 1 year, through a combination of in-person and telemedicine visits. Research personnel will provide a clear timeline of study follow-up prior to hospital discharge. At 7 days and 1 day prior to any planned follow-up (both in-person and telemedicine), research personnel will call study participants to remind them of the upcoming visit.

To maximize participant retention, several strategies will be employed that have been successfully applied in other longitudinal kidney studies (e.g., ASSESS-AKI, CRIC). These will include preferential contact by a single project coordinator/navigator to maximize continuity. Supplemental strategies will include thank you letters and pamphlets, personalized birthday and holiday cards, and annual newsletters. For each study visit (in-person or virtual), participants will be compensated for their time and involvement with \$50 as well as parking validation for in-person visits.

To facilitate passive collection of study-outcome related data, the following will be collected at the time of enrollment at the local recruitment site:

- Social security number (SSN) to crosslink with the National Death Index (NDI) and the United States Renal Data System (USRDS)
- A release of medical information will be signed for patients' local caregivers and hospitalizations to enable supplemental EHR collection of event, hospitalization, and laboratory data to both verify patient reports on potential events as well as screen for events that the patient may not recall.

Participant withdrawal: Participants will be informed at the time of study enrollment that they are permitted to withdraw from further participation in the study at any point. At the time of study withdrawal, participants will be asked the following:

- Specific circumstances that can be addressed to allow for their continued participation

- Reasons for wanting to withdraw from the study
- Feedback to improve the study moving forward

If individuals withdraw from participation in the study, a request will be made to continue to collect medical record information.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Eligible patients will be approached by a member of the research team to obtain informed consent. Enrollment assessment of kidney disease knowledge and patient-reported outcomes will be conducted. Written information about kidney disease, nephrotoxins to be avoided and importance/need for follow up with a physician will be provided. Participants will be subsequently randomized to the multimodal intervention (see 6.1.1.1) or usual care (see 6.1.1.2).

6.1.1.1 Multimodal Intervention

COPE-AKI aims to assess a multimodal process-of-care intervention that includes 1) study physician oversight and follow up care recommendations at the time of hospital discharge; 2) involvement of a nurse navigator to provide kidney-disease related education, coordinate care, and assess symptoms; and 3) pharmacist-led medication reconciliation and review.

Study Physician/Advance Practice Provider. The nephrologist and/or nephrology-associated advanced practice provider (APP) at each site will lead the intervention team for the duration of the study. The study physicians will fulfil two main roles: (a) Provide supervision to the rest of the study team and (b) conduct a discharge assessment to triage and make recommendations for follow-up care. The study physician will provide triage (decide level of care by PCP, nephrologists or both following discharge), time to follow up (2wks is the goal to see a PCP or nephrologist and can be up to 4wks, but no longer) and patient care recommendations for kidney health (medications, laboratory) in the intervention group at the time of hospital discharge. These recommendations will be provided to the PCP and the specialist (e.g., cardiologist) providing primary follow-up for the patient, if applicable. If the study physician is unable to provide this assessment prior to discharge, they will see the patient immediately post-discharge via an in-person or telemedicine visit. Care visit summaries with any changes will be communicated with the participant and/or participants' primary care giver, PCP, and other specialists as deemed appropriate.

Nurse Navigator. The nurse navigator will be the primary contact for the participants assigned to the intervention group for the study. The navigator will obtain contact information, information about the patient's usual care providers and pharmacy, review medications, show the participant how to use the home blood pressure machine and scales and arrange for follow-up visits. The role of the nurse navigator will be to monitor the participant's medical condition; facilitate scheduling of needed medical follow-up including both routine (pre-scheduled) and ad hoc (urgent or emergency); enhance adherence with prescribed medical care and follow-up appointments; and serve as a resource to the patient to

answer questions about their AKI-related management, facilitate medical and associated care and provide enhanced psychosocial support.

The initial nurse navigator contact with the participant will be after consent is obtained but prior to hospital discharge. The purpose of the initial contact is to inform the patient of the nurse navigator role, ensure that appropriate medical care team (non-study physician names, usual pharmacies used) and contact information is exchanged, identify the preferred methods of communication, and supplement written educational materials with verbal education. In addition, the nurse navigator will obtain a list of home medications (including over the counter, herbal, and supplements) and medications prescribed at discharge ensuring the participant has a plan for obtaining discharge medications.

The second visit will occur within 2-3 days after hospital discharge. The nurse navigator will arrange for follow up visits with the patient's care providers as directed by the study physician's triage assessment at the time of hospital discharge. After the initial visits, scheduled follow-up contacts with the nurse navigator will be at 7-10 days and every two weeks for the next 2 months. Additional as needed calls/contacts can also occur, and the patient will be encouraged to consider the navigator as a resource to contact between visits or after the initial 3 months.

All interactions between the nurse navigator and patient will follow a predetermined checklist of patient care activities that will include but is not limited to the nurse navigator facilitating follow-up with the patient's non-study providers and appointments for required medical testing, assessing how the patient is feeling, providing education on kidney disease related questions, check blood pressure and weight, inquiring about medication access/adherence and ensure that the patient has appropriate follow-up with the medical care team. An AccuHealth scale and Bluetooth-enabled blood pressure cuff will be provided. After discharge and after being trained, they will be instructed to measure blood pressure and weight daily. The information will be uploaded to a central server that can be accessed by the study team to assist with management of blood pressure and volume status. This data collection will occur for 12 months. In addition, the nurse navigator will be trained on behavioral and motivational interviewing techniques that will be applied during the nurse-patient interactions. All interactions between the nurse navigator-patient will be documented including care recommendations. This information will be provided to the study physician, the non-study providers caring for the patient, and the pharmacist.

Pharmacist. The participating pharmacist will be licensed in the state of the study site and meet the study training criteria. Patient-pharmacist interactions will be scheduled within 7 days after hospital discharge or as close to this time frame as possible. The pharmacist will complete the medication reconciliation and medication regimen review per the predetermined checklist, via telemedicine if agreeable to the patient. The goal of the patient/caregiver-pharmacist interaction is to cover the following: avoidance of nephrotoxins when possible and appropriate, appropriate dosing of renally cleared drugs, review for drug-drug interactions, monitoring appropriate use of chronic medications, medication adherence, monitor for adverse drug reactions, evaluation of non-prescription medication use, medication/disease education and social support. Telemedicine will be used in order for the

pharmacist to observe the pill bottles and pills if necessary. Telephone visits will be a second choice as a method for communication if the patient does not have the technology for a telemedicine visit. Telemedicine will be the preferred method for patients admitted to SNF/LTC within state, as well. If the patient prefers communication with a family member or other caregiver instead of themselves then this is an appropriate alternative provided the patient provides consent. The pharmacist will also obtain or clarify medication information with the community pharmacy employee as directed by the patient/caregiver or clinician at the SNF/LTC facility. The pharmacist will prepare for the telemedicine in advance by obtaining the patient's medication list prior to hospitalization, medication list at discharge, information about kidney disease from the patient's medical record, most recent serum creatinine for medication dose adjustments consideration and pertinent disease monitoring parameters (weight, blood glucose, and blood pressure). The patient/caregiver-pharmacist communication session will last until the items on the checklist are complete, which is approximately 30-45 min or until the patient selects not to continue. At least 50% of the items on the checklist will need to be completed to be considered complete. Otherwise, the pharmacist will attempt to schedule another pharmacist/caregiver-patient communication. Recommendations for medication management will follow a situation, background, assessment, and recommendation (SBAR) communication format and be provided to the patient's primary care provider (PCP) for consideration and/or to the patient's personal (non-study) nephrologist, as appropriate per each patient's circumstances and preferences. The pharmacist can execute the recommendations at request of the study physician. Subsequent patient/caregiver-pharmacist interactions during 90-days following post-hospital discharge will occur at the request of the patient, nurse navigator and study physician.

6.1.1.2 Usual Care

After receiving the same written information about kidney disease, nephrotoxins to be avoided and importance/need for follow up with a physician as individuals randomized to the multimodal intervention arm, participants randomized to the control arm will receive usual care as specified by their treating providers and will not be followed by nurse navigator, pharmacist, or the study team. The only subsequent study-related activities will be the follow-up study visits for ascertainment of endpoints with the research coordinator.

6.1.2 ADMINISTRATION AND/OR DOSING

6.1.2.1 Study Physician

The study physician will meet with the patient prior to hospital discharge or if not feasible then via telemedicine as close to the time of discharge as possible. If a patient is readmitted to the hospital within the 3 months from the index admission, the study physician will attempt to meet with the patient prior to hospital discharge.

6.1.2.2 Nurse Navigator

Study visits with the nurse navigator will occur via telemedicine, telephone or in-person based on patient preference. The visits will occur at hospital discharge, again within 2-3 days after hospital

discharge, and then at 7-10 days post-discharge. After these initial visits, study visits will occur every two weeks for the next 2 months (3wks, 5 wks, 7wks and 9wks). Additional as needed calls/contacts can also occur, and patients will be encouraged to consider the navigator as a resource to contact between visits or after the initial 3 months. If a patient is readmitted to the hospital within the 3 months from the index admission, the nurse navigator will visit the participant before hospital discharge and at 2-3 days after hospital discharge, then the schedule will return to the frequency before the subsequent all-cause hospitalization and be completed at 3 months from the index admission.

6.1.2.3 Pharmacist

Patient-pharmacist interactions will be scheduled within 7 days after hospital discharge but for any reason if this time frame is not feasible for the patient, then an appointment will be scheduled at the patient's earliest convenience. Subsequent patient/caregiver-pharmacist interactions during 90-days following post-hospital discharge will occur at the request of the patient, nurse navigator and physician. If a patient is readmitted to the hospital within the 3 months from the index admission the pharmacist will visit the participant virtually within 7 days after the subsequent hospital discharge or as close to this time frame as possible.

6.1.2.4 Clinical supervision

The interdisciplinary study team (study physician, pharmacist, and nurse navigator) will meet every 2 weeks throughout study to discuss any participant concerns and the study physician will be accessible for as needed consultation for the duration of the study. Information from the local interdisciplinary study team meetings will be documented and shared during the bi-weekly meetings with the multicenter, clinician meeting. Health issues or concerning findings (whether AKI-related or not) will be discussed and acted on in conjunction with the participant's PCP if necessary. The information from the multicenter meeting will be used to guide updates in the nurse navigator-patient and pharmacist-patient checklists.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

We will follow structured clinical visits within predetermined visit windows in follow up timing to ensure homogeneity in follow-up in the intervention group. We will follow checklist-based forms to ensure adherence to study guidelines and standardize care. These may include: 1) visit logs for the nurse navigator, pharmacist, and study physician visits; 2) review of blood pressure data as well as interventions for hypertension or hypotension; and 3) review of weight data as well as interventions used. We will use formal training at study initiation and at regular intervals (refreshers) for all members of the intervention team, to ensure uniform and standardized interactions, and clinical management of participants. Newly trained personnel will be observed by designated supervisors to assess success of training.

We will review a random sample of intervention visits to assess whether a) all possible recommendations were made by the study physician as well as agreement with said recommendations; b) the study pharmacist checklist was followed; and c) nurse navigator interactions had the appropriate amount and quality of behavioral interviewing.

6.2.1.1 Nurse Navigator Training

Participating nurse navigators will be trained on the study goals, checklists, and documentation requirements for the study via zoom meetings with the SDRC. Training will include social risk assessment and how to identify support for those with social and structural challenges; behavioral and motivational interviewing and patient activation; and kidney-specific education and experience. Nurse navigators will attend sessions on training concepts and their competencies will be assessed by a lead trainer prior to study initiation. At various timepoints throughout the study, interactions between nurse navigators will be recorded and centrally reviewed by assessors to ensure that intervention fidelity is achieved.

6.2.1.2 Pharmacist Training

Participating pharmacists will be trained on the study goals, checklists, and documentation requirements for the study via zoom meetings with the SDRC. Competency based education will be used such that a case will be presented and completed by the participating pharmacists. Pharmacists will complete additional cases, if necessary, until skill is achieved. Participating pharmacists will have access to the site PIs and Co-I nephrologists at their sites for reference throughout the study.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be allocated 1:1 to the COPE-AKI intervention or usual care using a web-based system to maintain allocation concealment using stratified randomization with randomly permuted blocks. Randomization will be stratified by clinical site. Randomization will occur as close to the time of planned discharge as logistically possible and will require confirming study consent. This will minimize the loss to follow-up, which otherwise would be non-trivial. Moreover, it will ensure all participants, prior to determining treatment assignment, are capable of consent and direct interaction with a nurse navigator and other providers.

Participants and the clinical care teams (nurse navigator, pharmacist, and study physician) will not be masked due to unblinded nature of the intervention. Research coordinators who carry out screening, enrollment, and study visits at enrollment, 3, 6 and 12 months will be masked from participant group assignment. Similarly, study visits performed by research coordinator at enrollment, 3 months and 12 months will be masked. Similarly, assessment of study endpoints will be blinded to group assignment.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

We will monitor participants' adherence in the intervention group by monitoring attendance to planned appointments and laboratory assessments. Participants will be considered non-adherent if they are

unable to complete a visit with any of the study members within 2 weeks of index hospitalization discharge. The nurse navigator will be responsible for explaining the study's definition of compliance.

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

A study physician will supervise the intervention team (nurse navigator and the pharmacist) for any issues that arise within the scope of the study intervention, and oversee communications and referrals as needed. This supervision will focus on issues that are beyond the expertise of the nurse navigator and pharmacist thereby requiring escalation of care to the level of treating physician. These include (but are not limited to) the following:

- New or worsening symptoms management that is not part of the existing study protocol
- Medication discrepancies and inquiries that the pharmacist and/or nurse navigator feel requires the input of the nephrologist. These will be reviewed and addressed by the nephrologist and communicated to participants' other health care provides as appropriate.

If the recommendations by the study physician at the time of discharge to see either the patient's PCP or nephrologist do not occur, then the patient will be seen at the practice site of the study physician. This oversight by the study physician will facilitate the guidance of care and prevent any communication breakdowns. In addition, if for any reason a follow-up visit with a PCP or specialist does not occur at any point during the 3-month post-index hospitalization follow-up period when it is judged to be clinically urgent, then the practice site of the study physician will be used to provide a "rescue" clinical visit.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

In general, scenarios that would require discontinuation of the study intervention or the experimental manipulation would be rare given the study design and nature of the intervention. However, one situation that would warrant study intervention discontinuation would be if the study participant experienced a severe decline in his or her overall health status to the point that the participant's support person or the site investigator determines the burden of the intervention is no longer appropriate with the participant's goals of care. An example of this scenario would be an individual who enrolls in the study and afterward experiences a catastrophic event such as a major stroke that results in incapacitation and referral to end-of-life care, such as home hospice. In this scenario, continuation with the study intervention may no longer be commensurate with the goals of care of the participant and family, and discontinuation of therapy could be acceptable at the discretion of the site investigator and the participant's family.

Other potential scenarios that may lead to discontinuation of the study intervention is if the participant moves out of the geographic region, precluding further study visits or telehealth encounters, or if the participant is deemed end-stage kidney disease and initiates thrice-weekly dialysis following discharge. While the study intervention would be discontinued in these scenarios, patients would remain enrolled in the study to obtain study end-point measurements if feasible. This is in line with the goal of intention-to-treat.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Similar to section 7.1, scenarios in which participant discontinuation/withdrawal would be appropriate would be rare. With an intent-to-treat design study intervention, withdrawal of the study participant is generally not appropriate unless a participant requests withdrawal. With a pragmatic trial where the intervention is multi-dimensional within the context of clinical care, elements of the intervention may need to be ascertained throughout the study, but participants would not be withdrawn from their intervention arm. Nonetheless, one scenario that would be appropriate for participant withdrawal would be if there is a change in the participant's medical condition such that the patient now meets an inclusion/exclusion criterion by the time of randomization and before implementation of the intervention. An example of this would be an individual who is approached and enrolled in the study prior to discharge but experiences an event that results in initiation or resumption of dialysis at the time of discharge, which is an exclusion criterion. Another example would be an individual who is scheduled to go home but due to change in status in the hospital is discharged to a location that meets an exclusion criterion (like a long-term acute care hospital).

7.3 LOST TO FOLLOW-UP

The criteria for loss to follow-up would include inability to reach/contact the study participant beyond last protocol visit (12 months) plus 3 months (15 months). Loss to follow-up will require *active* efforts to contact participants and will be at time of last contact with participant or caregiver. Time points for attempting to contact individuals are the points in which we are capturing information related to study outcomes in both active follow-up and controls: 30 days, 90 days, 180 days, and 1 year.

Passive follow-up using registry data will be used, as needed, for ascertainment of vital status (NDI) and need for chronic kidney replacement therapy (USRDS). Passive follow-up will also include individuals re-engaging with the study on their own after being lost to follow-up for any period of time up until the end of the study. This type of follow-up could still provide valuable information that updates the study about participant outcomes.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

8.1.1 Primary Endpoint

The primary endpoint will be hospital free days through day 90. Ascertainment will require collection of vital status through day 90 and data on hospitalizations. We will use combination of active and passive follow up to capture hospitalization information in a consistent manner. Active follow-up will include calling patients and/or their surrogates at frequent intervals to identify hospitalizations. Records will be obtained including discharge summaries, progress/consultation notes, laboratory values, and discharge medication lists. To facilitate this data collection, we will ask patients and/or their surrogates to provide a list of local hospitals and outpatient clinics (including PCPs) in their local region in which they have previously or are most likely to be hospitalized or receive outpatient care. Passive follow-up will include examining the local electronic medical records for hospital encounters during follow-up occurring at clinical sites and their affiliates. These will include gradually integrated links within our EHRs via platforms such as 'Care Everywhere' and other regional health information exchanges (HIE) as well as scanned media files.

Hospital-free days will be calculated as 90 minus the number of calendar days in the hospital as either an inpatient or on observation status, based on the determination made by the corresponding hospital. Any hospital stay that crosses midnight will count as 2 hospital days. Days in an acute-care hospital or long-term acute care hospital (LTACH) will be counted as inpatient days. Days spent in an emergency department, skilled nursing facility, acute rehabilitation facility, or hospice will not be counted as hospital stays. For patients who die, withdraw, or are lost to follow up prior to day 90, days out of the hospital prior to day of death, withdrawal, or lost-to-follow up will be counted as hospital-free days.

8.1.2 Secondary Clinical Endpoints

A. Hospitalization data at 30, 90, 180, and 365 days

Hospitalization data at 30, 90, 180, and 365 days will be ascertained as for the primary endpoint. Additionally, the primary and secondary diagnosis codes will be used to determine cause of hospitalization (e.g., sepsis, congestive heart failure, etc.).

B. Vital status at 30, 90, 180, and 365 days

Vital status will be determined based on whether follow-up visits can be completed at specified time points. Secondary/emergency contact information will be obtained at enrollment and if participants are unable to be reached for follow-up visits, status will be determined by contacting their secondary/emergency contacts. If the secondary/emergency contacts cannot be reached, online searches to assess vital status will be conducted. Death certificates will be requested for individuals who are deceased. Vital status will ultimately be verified against the National Death Index (NDI).

C. Kidney Function outcomes

The assessment of kidney function at 90, 180, and 365 days will differ from kidney function at baseline. Kidney function at 90, 180, and 365 days will be assessed based on blood and urine laboratory testing. Serum creatinine and cystatin C will be measured at each time point and estimated glomerular filtration rate (eGFR) will be calculated using the 2021 CKD-EPI equations.²³ Urine albumin excretion will be calculated as the ratio of urine albumin (mg/dL) and urine creatinine (mg/dL) and reported as mg/g creatinine. Need for dialysis will be determined based on patient interview and confirmed from medical records and/or registry data from the United States Renal Data System (USRDS).

We will use an iterative approach to define baseline kidney function as follows:

1. For those with preadmission creatinine available, we will use the mean outpatient non-emergency room baseline creatinine 7-365 days prior to admission.
2. For those undergoing elective surgery/procedures, preoperative serum creatinine values may be used if occurring within 30 days of or at index hospitalization.

If no preadmission baseline creatinine is available, we will use the nadir inpatient serum creatinine to anchor the definition of AKI. While the latter has been shown to potentially overestimate the incidence of AKI (e.g., possibly due to decreased creatinine generation/hemodilution in some patients), we will reduce this risk through our inclusion of participants with persistent Stage 2 or 3 injury. We will also limit the use of nadir creatinine to that available within the first 7 days of hospitalization to reduce further misclassification due to muscle loss from prolonged hospitalization.^{24,25}

C.1. MAKE-90/MAKE-180/MAKE-365

The composite MAKE outcome at 90, 180, and 365 days will be determined based on vital status at the specified time point, dialysis dependence at the specified time point, or serum creatinine at the specified time point exceeding twice the value of the baseline (pre-morbid) serum creatinine prior to the index hospitalization.

As a sensitivity analysis, this endpoint will be determined including only participants with an outpatient serum creatinine 7 to 365 days prior to the index hospitalization and a second sensitivity analysis including all participants in whom an adjudicated baseline could be determined without imputation

In an additional analysis, the MAKE endpoint will be assessed as a semi-continuous variable (MAKE-eGFR) based on vital status, dialysis-dependence and eGFR at 90, 180, and 365 days, using the following definitions:

MAKE-eGFR = 0 if the patient is deceased at the specified timepoint

MAKE-eGFR = 10 if the patient is dialysis-dependent at the specified timepoint

MAKE-eGFR = the calculated 2021 CKD-EPI creatinine-cystatin C eGFR for all other patients

Patient Status at specified timepoint	MAKE-eGFR value
Deceased	0
Dialysis-dependent	10
Alive and dialysis-independent	2021 CKD-EPI creatinine-cystatin C eGFR

C.2 Albuminuria

Urine albumin excretion will be assessed at 90, 180 and 365 days as the ratio of albumin and creatinine in a random voided urine sample and reported as mg albumin per gram creatinine.

C.3 CKD Stage

CKD stage will be calculated at each timepoint using the KDIGO CKD classification with eGFR calculated using the 2021 CKD-EPI creatinine-cystatin C eGFR equation.²³

	uACR (mg/g creatinine)		
eGFR (mL/min/1.73 m ²)	<30	30-300	>300
>90	G1A1	G1A2	G1A3
60-89	G2A1	G2A2	G2A3
45-59	G3aA1	G3aA2	G3aA3
30-44	G3bA1	G3bA2	G3bA3
15-29	G4A1	G4A2	G4A3
<15	G5A1	G5A2	G5A3

C.4 Recurrent AKI Hospitalizations

Episodes of recurrent AKI during subsequent all-cause hospitalizations will be adjudicated based on hospitalization data, defining recurrent episodes of AKI based on an increase in serum creatinine of >50% relative to the lowest-known value preceding or including the rehospitalization.²⁶

8.1.3 Administration of patient-reported outcomes (PRO) assessments.

PRO assessments, which are summarized in Table 1, will be conducted at enrollment, 30, 90, 180, and 365 days. The PROs are standardized, previously validated instruments that provide coverage of key AKI-related domains agreed upon by the COPE-AKI Consortium. The key secondary outcome PROs (AKI-specific and global QoL, social support, and provider interactions) will be administered first with all other PROs as optional. Exceptions to above include the REALM-SF, which measures health literacy only at enrollment, and the social determinants of health measures, which are believed to modify the effect of the intervention and will also be administered at enrollment.

The estimated time to complete all 138 PRO (required and optional) items is approximately 40 minutes. Required PROs will take approximately 10 minutes to complete. Note that not all PROs will be collected at all time points (e.g., demographics at enrollment only).

Table 1. Domains and measures			
Domain	Instrument	Source	# of Items
Global HRQoL	PROMIS HRQoL ²⁷	PROMIS – Cella, et al., 2007	10
AKI-specific HRQoL	CKD-QoL ²⁸	Ware et al., 2019	6
Impact of AKI (optional)	Developed from pilot survey ²⁹	Switzer et al., 2021	3
AKI-related symptoms (optional)	Developed from pilot survey ²⁹	Switzer et al., 2021	10
Functional status (optional) Physical function Cognitive function	PROMIS Physical Function SF v2.0 4a ²⁷	PROMIS – Cella, et al., 2007	4
	PROMIS Cognitive Function SF v2.0 4a ²⁷	PROMIS – Cella, et al., 2007	4
Psychosocial status (optional) Depression Anxiety	PROMIS Depression v1.0 4a ²⁷	PROMIS – Cella, et al., 2007	4
	PROMIS Anxiety SF v1.0 4a ²⁷	PROMIS – Cella, et al., 2007	4
Frailty (optional)	RAI-C ³⁰	JAMA Network Open Shinall, 2020	16
AKI Knowledge (optional) Objective knowledge of AKI Perceived knowledge of AKI	KiKS adapted for AKI ³¹	Siew et al., 2019	15
	Perceived KiKS ³¹	Siew et al., 2019	5
Self-efficacy (optional) Managing symptoms Managing medications	PROMIS ²⁷	PROMIS – Cella, et al., 2007	
	Managing Symptoms SF v1.0 4a Managing Meds SF v1.0 4a		4 4
Social support Emotional support Instrumental support	PROMIS Emotional Support SF v2.0 4a ²⁷	PROMIS – Cella, et al., 2007	4
	PROMIS Instrumental Support SF v2.0 4a ²⁷	PROMIS – Cella, et al., 2007	4
Interaction with providers Patient-provider interactions Patient satisfaction	PEPPI ³²	Maly et al., 1998	5
	Client Satisfaction Questionnaire – 8 ³³	Attkisson et al., 2007	8
Healthcare utilization (optional)	Health Services Utilization Scale ³⁴	Health & Retirement Study	16

Social determinants of health (enrollment only; all other timepoints optional)	ACH Health-Related Social Needs Screening Tool (selected/modified items) ³⁵	Centers for Medicare and Medicaid Services, 2017	6
Medical Literacy (enrollment only)	Rapid Estimate of Adult Literacy in Medicine Short Form (REALM-SF) ³⁶	Arozullah et al., 2007	7
Demographic characteristics	Standard Items	Standard Items	6
Total Items			138
Total Completion Duration			40 min

At enrollment, the PROs will be administered by the research coordinators at the clinical sites. At subsequent 30, 60, 180, and 365 day follow up assessment dates, PRO assessments across sites will be conducted using a centralized Computer-Assisted Telephone Interviewing (CATI) facility – the Survey Research Program (SRP) at the University Center for Social and Urban Research (UCSUR) at the University of Pittsburgh. Interviewers read questions as they appear on the screen and enter the respondents’ answers directly into the computer. CATI allows for complex question contingencies, sample management, and call scheduling to be handled automatically. Site personnel will transfer patient contact information and date of enrollment, which will trigger target assessment dates (30, 90, 180, and 365 days). As the project evolves, SRP simultaneously conducts assessments at all time points, based on continuous patient enrollment across sites. SRP uses standard multiple call attempt protocols (different days of week or times of day) and relies on stated best times to call by participants to maximize response rates. SRP also has the capability for participants to call in to schedule assessments. An approximate ± 2 -week window is allowed around each assessment to allow multiple attempts to contact – for all assessments other than enrollment, this window can extend to 4 weeks post-target assessment date. In cases where a participant cannot be reached within the window, the assessment time point will be counted as “missed” but attempts will continue to conduct all remaining scheduled interviews. Interviewers are continuously monitored during data collection for quality assurance, and periodic re-training sessions occur as necessary. During the field period, data are exported and examined by programmer/data management specialists on a regular basis for additional quality control purposes.

We will also provide flexibility such a) that the site coordinator has the ability to administer the PROs if the participant allows it; and b) the participant can receive the PROs via text message, email, or postal mail to complete.

8.1.4: Study Procedures

All participants will be evaluated by a research coordinator for the enrollment visit, and at 90-, 180-, and 365-days following discharge of index hospitalization. The enrollment visit will occur immediately after informed consent, but prior to discharge from the hospital. The enrollment and follow up visits will include (1) assessment of interval clinical events (also at 30d), (2) medications (also at 30d), (3) physical exam, (4) laboratory (chemistry profile, urine albumin/creatinine, and biobank samples), and (5) assessment of patient-reported outcomes (at enrollment only).

Vital signs: Weight, height, blood pressure, and heart rate will be collected from the medical record at discharge. For all study participants, height, weight, blood pressure, and heart rate will be measured at the time of visits for blood draws: 90, 180, and 365 days. This will be done either in person or by a home-visiting nurse.

Laboratory tests: Blood and urine will be collected at enrollment (time of hospital discharge) and then by home visiting nurse at 90, 180, and 365 days. The participant will have the option of having the urine and blood collected at the study site. In some cases, it may be possible to have a study visit at the participant's home, rather than at the study site to collect blood and urine and vital signs. These services will be offered to patients who are at a significant distance from the study site or are otherwise unable to make the visits in person. These home visits will be done by a third-party company called ExamOne which is a subsidiary of Quest Diagnostics.

The tests for serum creatinine concentration and urine albumin excretion will be analyzed at a central laboratory at ADRL in Minnesota.

Samples for future analysis will be spun, aliquoted, and stored at the local sites for batch shipment to the University of Minnesota for processing and freezing. At the end of the study, a subset of samples will be sent to the NIDDK biorepository for future use by other investigators.

A basic metabolic panel (BMP) will be run on blood samples (glucose, calcium, sodium, potassium, bicarbonate, chloride, blood urea nitrogen, and creatinine) and cystatin C. Microalbumin and creatinine will be assessed from urine samples.

Medication information: The study coordinator will collect a list and dosages of medications that the participant is taking, including over the counter medications and supplements at 90, 180, and 365 days.

Medical record data collection: The medical record will be queried for hospitalizations, urgent care/emergency room visits and provider visits. Laboratory data on chemistry values, kidney function and urine tests will be collected. If there is a hospitalization at an outside hospital, where the data is not available in the electronic record, a signed HIPAA authorization will be sent to obtain information from the hospitalization

8.2 SAFETY ASSESSMENTS

As a process of care intervention study, the intervention is not expected to lead to serious adverse events. There may be events of interest related to clinical care.

Hyperkalemia: defined as a potassium greater than 5.5 meq/L or requiring intervention. Events will be collected from a review of the medical record including emergency room or urgent care visits.

Adverse drug events: defined as harmful effects from medication requiring intervention. This will be collected from a review of hospital admissions, emergency room visits, or urgent care visits

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are a subset of adverse events. An SAE is defined as any untoward medical occurrence that meets any of the following criteria:

- results in death
- is life-threatening (The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect in a child of a study participant.

In addition, an important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Death and hospitalization are expected as part of the natural history of individuals after an episode of acute kidney injury and are therefore expected events during the study. Although these events will be categorized as SAEs for regulatory purposes, they will only be evaluable at interim timepoints, and study completion based on differential rates between treatment arms.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Except as outlined in sections 8.1 and 8.2, non-serious adverse events will not be collected. Events will not otherwise be characterized by severity

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All serious adverse events will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinicians based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The SAE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the SAE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the SAE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

This is a minimal risk study. Death and hospitalization are expected as part of the natural history after an episode of AKI and are therefore anticipated to occur during the study. It is not anticipated that there will be any SAEs potentially related to the study intervention. However, if there is an SAE where there is a concern that it might be potentially related to the study intervention, a clinician with appropriate expertise in nephrology will review the event to determine whether the serious adverse event is expected or unexpected based on the participant's medical status and treatments provided.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Serious adverse events such as hospital admissions, will be ascertained at time of PRO collection. If the study team becomes aware of an admission or death at other times, information will be collected.

8.3.5 ADVERSE EVENT REPORTING

Except as outlined in section 8.1 and 8.2, non-serious adverse events will not be collected.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event to determine if it is potentially related to the study intervention. Potentially related SAEs shall be reported to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 5 working days after the investigator

first learns of the event. As death and hospitalization are anticipated study endpoints, these SAEs will not be reported in an expedited fashion unless determined to be related to the study interventions.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable, except as described in 8.2

8.3.9 REPORTING OF PREGNANCY

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

An unanticipated problem is any incident, experience, or outcome that meets **all** of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

Fatal unanticipated problems will be reported to the IRB and the NIH within 24 hours of becoming aware of the problem. Nonfatal unanticipated problems will be reported to the IRB, NIH, and DSMB within 10 business days of becoming aware of the UAP.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

If the unanticipated problem involves new risks to participants, they will be informed. The timing of reporting (e.g., next study visit or more expeditiously) will be determined by the IRB, DSMB and NIH.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary study hypothesis is that patients randomized to a multimodal intervention will have increased odds of more hospital-free days through 90 days (primary clinical) compared to those randomized to usual care. Secondly, compared to usual care, patients randomized to a multimodal intervention will have lower rates of major adverse kidney events at 180 days, lower rates of recurrent AKI hospitalizations at 180 days, and greater improvements in patient-reported outcomes (global health related quality of life, AKI-specific health related quality of life, provider interactions, and social support) over 90 days.

9.2 SAMPLE SIZE DETERMINATION

Power and sample size calculations were based on Monte Carlo simulation studies performed in R. Data was generated based on the following assumptions for usual care participants: 1) subsequent all-cause hospitalizations were considered to be a recurrent event with rates over 90 days ranging from 25-50%; 2) length-of-stay for each simulated subsequent all-cause hospitalization was assumed to be 7 days; and 3) 90-day mortality rates were assumed to be 15% and death was considered a competing event. We also assumed the intervention had varying, separate effects on subsequent all-cause hospitalization (hazard ratio of 0.75 or 0.80) and mortality (hazard ratio of 0.9 or 1). Lastly, we assumed that the intervention would reduce the subsequent all-cause hospitalization length-of-stay for those participants anywhere from 0 days to 4 days.

We then simulated 1000 datasets, each with samples sizes of N=1050, 1200, and 1500. Within each simulated dataset, a proportional-odds model was fit for the ordinal outcome of hospital-free days (HFD) over 90 days, and the null hypothesis was that the coefficient for the intervention was no different than 0. The number of times this hypothesis was rejected out of 1000 was an indication of power. We also considered 2 other primary outcomes: 1) a composite outcome of time until the first subsequent all-cause hospitalization or death, using a Cox proportional hazards model (COMP); and 2) time until the first subsequent all-cause hospitalization with a competing risk of mortality, using a cause-specific Cox proportional hazards model (CR).

Assuming 25% subsequent all-cause hospitalization and 15% mortality rates through 90 days of follow up in the usual care arm, 1500 participants completing 90-day follow up would provide at least 92% power to detect an odds ratio (OR) of 1.42, corresponding to a mean difference as small as 1.38 hospital-free days between arms. If the impact of the intervention on mortality is null (HR=1), this results in at least 82% power to detect an OR of 1.35, corresponding to a mean difference as small as 0.78 hospital-free days between arms. The below table displays power and detectable ORs across varying hospitalization rates in the usual care arm as well as varying assumed hazard ratios for mortality and hospitalization.

90d Hospital Free Day Outcome								
% Hosp	LOS Red	HR Death	HR Hosp	OR	Ctl Mean HFDs	Tx Mean HFDs	Δ (days)	power
25	-1	0.9	0.75	1.44	80.16	81.54	1.38	0.93
25	-2	1.0	0.75	1.35	80.18	80.96	0.78	0.82
25	-4	0.9	0.80	1.43	80.16	81.96	1.8	0.92
30	-1	1.0	0.75	1.42	79.38	80.2	0.82	0.93
30	-4	1.0	0.80	1.40	79.36	80.67	1.31	0.92
35	0	0.9	0.75	1.32	78.59	80.05	1.46	0.82
50	0	0.9	0.80	1.31	75.57	77.29	1.72	0.81

The overall target is to enroll and randomize N=2145 participants to have at least N=1500 complete 90 days of follow up (approximately 30% attrition).

9.3 POPULATIONS FOR ANALYSES

The primary and secondary analyses will be performed according to an intention-to-treat (ITT) principle and will comprise all participants who have been randomized to either study, regardless of discharge status or engagement in either study arm. As a sensitivity analysis, we will repeat our primary analysis in a modified ITT population, defined as all participants in the ITT population who have been discharged.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Demographic and baseline characteristics will be presented as mean and standard deviations for continuous variables and sample proportions for categorical variables, presented overall and by treatment group according to the CONSORT guidelines. Effect sizes and corresponding 95% confidence intervals will be calculated for all primary and secondary analyses.

Missing Data. As a preventive measure, we will make every attempt to document all reasons for missing data. In addition, baseline characteristics will be compared between participants who do and do not withdraw from the study to assess the impact of missing information and attrition. We will also compare the rates of lost-to-follow-up (LTF) between study arms. An important consideration for our longitudinal secondary outcomes will be whether there is any informative censoring. As a result, we will utilize shared parameter models to jointly estimate the change over time as well as the time-to-censoring.³⁷ For missingness associated with observed and pre-dropout responses, we will assess the plausibility of missing-at-random (MAR) assumption and employ multiple imputation by chained equation (MICE) to

impute missing data. To determine HFD for our primary outcome, the total number of hospital days will be the sum of observed (pre-dropout) and imputed (post-dropout) number of hospital days.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary outcome of hospital-free days (HFDs) at 90-days will be described as using means and standard deviations; however, HFDs will be analyzed using a multivariable proportional-odds model given the ordinal nature of the outcome. In the event of a preponderance of zeros, we will use a zero-inflated Poisson model to simultaneously model the rate of hospitalizations and the length of stay. Key covariates in the model will be study arm (intervention vs usual care) and our design variable (clinical site). The intervention effect will be presented as an adjusted odds ratio (OR) along with a 95% confidence interval (CI).

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The key secondary outcomes of MAKE-180 and recurrent AKI at 180d will be analyzed using multivariable Cox proportional hazards models. If the assumption of proportional hazards is violated for either of these outcomes, we will use a time-varying coefficient Cox model as an alternative. Key covariates in the models will be study arm (intervention vs usual care) and clinical site. The intervention effects for the above models will be presented as adjusted hazard ratios or beta coefficients along with corresponding 95% CIs. The key secondary patient-reported outcomes (global health related quality of life, AKI-specific health related quality of life, provider interactions, and social support) will be assessed using generalized linear mixed models. For each PRO, we will compare the 3-month trajectory as a function of time, study arm, time-by-arm interaction, and the design variables. If the relationship between a particular PRO and time is non-linear, we may treat time as a categorical predictor. Random effects for subject as well as slope will be included to account for correlated observations as well as heterogeneity in the rate of change. The intervention effect will be based on the significance of the time-by-arm interaction and presented as mean difference in slopes (or 3-month changes) along with 95% CIs.

9.4.4 SAFETY ANALYSES

Adverse events will be reported and compared between the multimodal intervention and usual care. The proportion of patients with at least one event and event rate per person-year of follow up will be calculated. Logistic and Poisson regression models will be used to compare differences in proportions and rates, respectively, adjusting for our design variables (presence of CKD and clinical site).

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographic and baseline characteristics will be presented as mean and standard deviations for continuous variables and sample proportions for categorical variables, presented overall and by treatment group according to the CONSORT guidelines.

9.4.6 PLANNED INTERIM ANALYSES

Interim study reports will be delivered to the DSMB every 6 months or at the DSMB discretion. Planned interim analyses for efficacy, futility, and safety are as follows:

Operational inadequacy. There is no pre-specified stopping rule for operational inadequacy, but the COPE-AKI DSMB can recommend study termination due to failure in the implementation of the trial such as slow recruitment, poor retention, improper data handling or data loss, inability to implement the protocol, etc.

Efficacy. There will be one planned interim analysis that allows stopping for efficacy for the primary outcome of hospital-free days; this will be reported at the first DSMB meeting that occurs after we have reached 50% of the anticipated information fraction on the primary outcome (n=750 patients completing 3 months of follow up). The stopping rule will use the Haybittle-Peto boundary, recommending an efficacy stoppage if $p < 0.001$ favoring benefit of the intervention; otherwise, the trial will continue enrollment to the planned sample size target of n=1500 participants completing 3 months of follow up. The DSMB may request additional interim analyses.

Futility. There will be no formal stopping rules for futility on the primary outcome of hospital-free days. However, the DSMB will have the ability to suggest calculating conditional power for the study. In other words, the probability of seeing a significant result, conditional on the data observed data and future trends.

Safety. While there is no pre-specified stopping rule for safety, the COPE-AKI DSMB will have access to closed report data on all safety outcomes reported every 6 months for the duration of the trial and may ask for additional analyses to inform any decisions to stop the study over concerns related to safety.

The final analyses will be conducted once study follow-up is complete, after all data are cleaned, and once the study database is locked.

9.4.7 SUB-GROUP ANALYSES

Subgroup analyses on the primary outcome of 3-month HFDs will be operationalized in the model by including the main effect of the subgroup and the two-way interaction with study arm, with the significance of the interaction term denoting a subgroup effect. A priori subgroup analyses will be based on the following measures assessed at enrollment or earlier:

- clinical site
- race
- ethnicity
- gender
- age > 65 years
- presence of pre-morbid CKD (defined by eGFR < 60)

- history of diabetes
- history of congestive heart failure
- ICU hospitalization (vs non-ICU)
- sepsis during hospitalization
- Charlson comorbidity index
- AKI stage (stage 2 vs Stage 3 vs kidney replacement therapy requiring AKI)
- history of AKI within 1 year
- prior hospitalization within 1 year
- social determinants of health measures

All other subgroup analyses will be considered exploratory regardless of result.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Any individual participant data will be examined and presented in such a way as to fully protect privacy and anonymity.

9.4.9 EXPLORATORY ANALYSES

All other outcomes will be considered tertiary or exploratory and will follow similar analytic approaches as described above. Subsequent all-cause hospitalization (30-, 90-, 180-, and 365-day), MAKE (90-, 180-, and 365-day), and the composite outcome of hospitalization and mortality (90-, 180-, and 365-day) will be analyzed using a multivariable Cox proportional hazards model. If the assumption of proportional hazards is violated for either of these outcomes, we will use a time-varying coefficient Cox model as an alternative. Additionally, we will assess the impact of the intervention on each of the individual components of each composite outcome (e.g., hospitalization, mortality, dialysis dependency, doubling of serum creatinine) in separate regression models. Key covariates in the models will be study arm (intervention vs usual care) and clinical site. Linear mixed models will be used for uACR with month, study arm, the interaction between month and study arm, and design variables as fixed covariates. Random effects for subject as well as slope will be included to account for correlated observations as well as heterogeneity in the rate of change. The intervention effects for the above models will be presented as adjusted hazard ratios or beta coefficients along with corresponding 95% CIs.

The remaining PROs will be assessed using generalized linear mixed models. For each PRO, we will compare the trajectory as a function of time, study arm, time-by-arm interaction, and the design variables. If the relationship between a particular PRO and time is non-linear, we may treat time as a categorical predictor. Random effects for subject as well as slope will be included to account for correlated observations as well as heterogeneity in the rate of change. The intervention effect will be based on the significance of the time-by-arm interaction and presented as mean difference in slopes along with 95% CIs.

Other analyses will include assessing the impact of the intervention on 3-, 6-, and 12-month changes in eGFR, uACR, and CKD stage. Linear mixed models will be used for eGFR and uACR with month, study arm, the interaction between month and study arm, and design variables as fixed covariates. Random

effects for subject as well as slope will be included to account for correlated observations as well as heterogeneity in the rate of change. Change in CKD stage will be modelled using a multinomial proportional odds model. Key covariates in all models will be study arm (intervention vs usual care) and clinical site.

We will compare the intervention with usual care on several process-of-care outcomes, including 30- and 90-day rates of PCP/nephrologist visit completion, blood pressure control, and medication use.

While between-arm differences on baseline covariates are not indicative of problems with randomization, we will assess whether any clinically meaningful differences exist. For those that are present, we will conduct sensitivity analyses in which the primary analytic model is augmented to include the measure as an additional baseline covariate. An example of this would be CKD status at enrollment.

Lastly, the primary analysis strategy for secondary outcomes would be to anchor these based on the baseline serum creatinine value, which will be the pre-admission value for the majority of study participants and the nadir in-hospital value for a minority of participants (see section 5.1). However, we acknowledge that the serum creatinine value closest to hospital discharge may be lower than the recorded nadir value. As a sensitivity analysis, we could use the lower of the nadir in-hospital SCr or the discharge SCr to anchor secondary outcomes.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol [\[insert list\]](#).

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, the funding agency, the sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility (operational or statistical)

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study sites will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Pittsburgh Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NIDDK Central Repository.

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see <https://grants.nih.gov/policy/sharing.htm>). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see <https://humansubjects.nih.gov/coc/index>). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g.,

policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of Pittsburgh SDRC. Six months after publication of the primary manuscript or 18 months after study completion, whichever occurs first, the de-identified, archived data will be transmitted to and stored at the NIDDK Central Repository, for use by other researchers including those outside of the study. Permission to transmit data to the NIDDK Central Repository will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the NIDDK Central Repository with the same goal as the sharing of data. These samples could be used for research regarding the causes of AKI, its complications, and other conditions for which individuals with AKI are at increased risk, and to improve treatment. The NIDDK Central Repository will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the NIDDK Central Repository.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor or Independent Safety Monitor

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including acute kidney injury, clinical trials, ethics, and biostatistics. DSMB members will be appointed by the NIDDK. Members of the DSMB should be

independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the NIDDK.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Monitoring activities will be as follows:

The SDRC at the University of Pittsburgh will develop and implement a remote risk-based monitoring plan for the COPE-AKI study which will include specifics for site initiation visits, interim monitoring visits, for-cause visits (if necessary), and a close-out visit. Our risk-based monitoring plan^{38–40} will focus on:

- Consent monitoring: Participants at clinical sites will be able to electronically sign informed consent documents. If paper versions are signed, there will be the ability to upload signed consents to a secure repository (which has been used in previous studies), which the SDRC data coordinator will be able to monitor in real time.
- Eligibility confirmation: Sites will be able to upload source documents to a secure serve for review by a SDRC data coordinator in real time. Additionally, CC PIs will be able to review and electronically sign all screening-related CRFs prior to study enrollment. This process will prevent participants from being enrolled in error.
- Complete ascertainment of primary and key secondary outcomes: The SDRC data coordinator will be notified in real time if there are instances of potentially missing data (i.e., expected visit complete, yet primary outcome information not entered within a span of time), which will allow the coordinator to query the clinical site and resolve the issue. Additionally, eCRFs that are related to primary and key secondary outcomes will be developed with a level of rigor and stringency to prevent form submission with missing information.
- Serious adverse events and protocol violations: The SDRC data coordinator will be notified via email of all SAEs and protocol violations as they occur. They will notify the appropriate entities (i.e., NIDDK, DSMB) regarding all study-related SAEs within reporting guidelines (see Section 8.3). SAEs will be categorized according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE). On a monthly basis, SAEs will be reviewed by the steering committee or relevant safety sub-committee. In addition, a comprehensive annual report detailing all study-wide SAEs—both related and unrelated to study participation—will be provided for the NIDDK and DSMB.
- Virtual Site Audits: During the development of the Consortium DSMP, source documents will be identified if the electronic data entry is not the source (i.e., lab results). Site coordinators will be able to upload source documents to the study website, where SDRC data coordinators will be able to complete a full source data verification of critical elements in real time as well as regulatory documents that include DSMB minutes; IRB submissions, correspondence, approvals

and renewals; and participant informed consents. At the conclusion of the audit, a summary of the site visit findings will be discussed with the site PI and study personnel. A detailed summary report will document the audit findings and will be supplied to the DSMB Chair, NIDDK program staff, site PI, and site personnel. This information will also be kept in the electronic regulatory management system.

- **Audits of COPE-AKI Core Facilities:** Our monitoring process will be extended to the COPE-AKI core facilities. We will establish a frequency of monitoring visits with the core facility and assess how each core facility adheres to the protocol as well as their SOPs. Additionally, we will collect essential documents specific to each core facility within our electronic Master Regulatory File (eMRF), such as contact information, certification and licensures, and investigator CVs.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will work with the SDRC to perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. All sites will follow a common quality management plan.

Quality control (QC) procedures will be implemented as follows:

Informed consent – Clinical site personnel will review both the documentation of the consenting process as well as completed consent documents that are completed on paper. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the SDRC to ensure proper consenting procedures are followed.

Source documents and the electronic data – Study data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy SDRC may ask clinical site personnel to upload paper-based source document into the web-based data entry system in order to compare a representative sample of source data against what has been entered, targeting key data points in that review.

Intervention Fidelity - Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations - The SDRC will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern. Should independent monitoring become necessary, the clinical site PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into SDRC's electronic System for Data Management (eSYSDM), a 21 CFR Part 11-compliant data capture system provided by the Center for Clinical Trials & Data Coordination. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Council on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigators to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the NIDDK Program Official and the University of Pittsburgh SDRC. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested by other researchers 6 months after publication of the primary manuscript or 18 months after study completion, whichever comes first, by contacting [the NIDDK Central Repository](#). Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIDDK has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities

10.4 PROTOCOL AMENDMENT HISTORY

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11 REFERENCES

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