

# **Expanding and Promoting Alternative Care and Knowledge in Decision-Making: The ExPAND Study (Improving Shared Decision- Making and Access to Non-Dialytic Treatment for People with Kidney Disease)**

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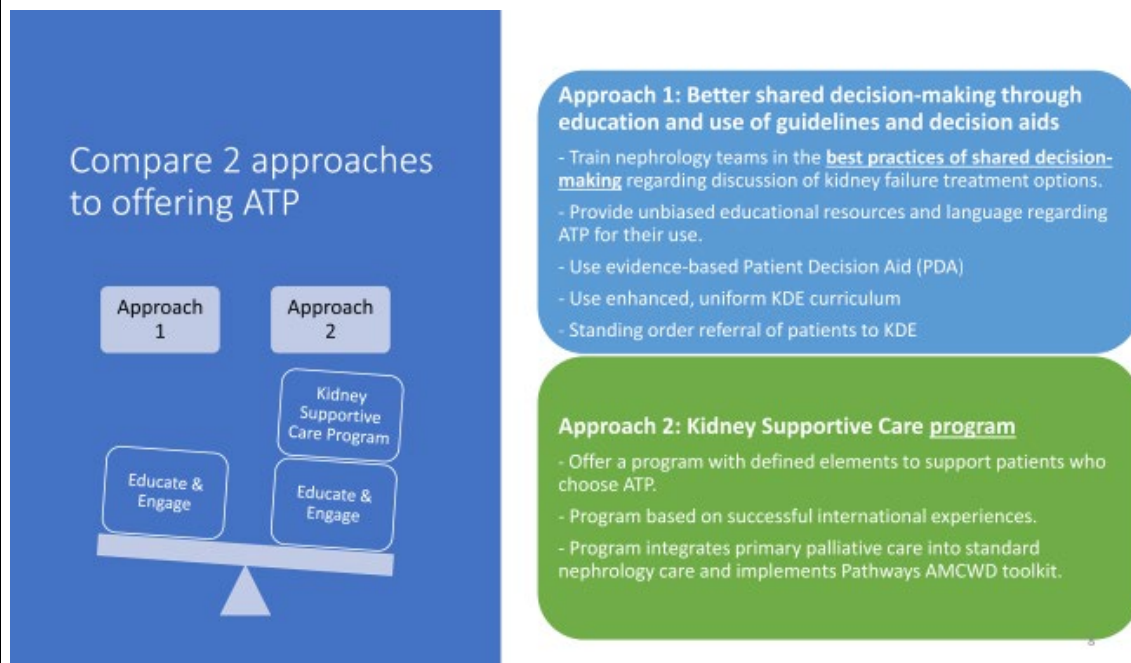
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## SYNOPSIS

### Primary Objective

The primary objective of this study is to compare two health system-based approaches for offering kidney failure treatment options to older patients with kidney failure, to ensure they are actively involved in a shared decision-making (SDM) process covering a full range of choices and have meaningful access to that full range of choices, including standard in-center or home dialysis (SIHD) and alternative treatment plans (ATPs): active medical care without dialysis (AMCWD), time-limited trial of dialysis (TLT), and palliative dialysis.



**Aim 1:** Compare the effectiveness of two approaches: 1) improved kidney disease education (KDE) and SDM or 2) improved KDE and SDM plus the creation of a kidney supportive care program in increasing proportion of patients choosing ATP and explore comparative effectiveness on patient reported outcomes of decisional conflict and shared decision-making as well as health care utilization and advance care planning.

### Secondary Objectives (if applicable)

**Aim 2:** Compare the patient and family experience of an ATP between Approach 1 and Approach 2, with particular emphasis on TLT and AMCWD in terms of quality of life, services used, and end-of-life (EOL) experience through medical record review and interviews with a

sample of bereaved family members. Aim 2a will focus on experience while patients are receiving an ATP (several months to several years). Aim 2b will describe the EOL experience.

**Aim 3:** In order to evaluate implementation of each intervention (Approaches 1 and 2), the EXPAND research team will cooperate with a separate tandem evaluation conducted by an independent evaluation team based at NORC. The implementation evaluation is a mixed-methods design based on the expanded Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework. The implementation evaluation will consist of staff surveys, interviews, and site visits conducted by the NORC evaluation team. Regulatory oversight of AIM 3 will be handled by the NORC IRB.

### General Design Description

This will be a repeated, cross-sectional stepped wedge cluster randomized trial (SW-CRT) with randomization at the nephrology clinic level. Clinics are randomly assigned to one of three sequences. Each sequence consists of four 10-month time periods during which patients are accrued and followed for study outcomes. To minimize contamination in the primary analysis, we will exclude patients recruited during the 4 months before each sequence moves to Approach 2 (see white squares in the table below). These patients will be included in a sensitivity analysis. In the 4<sup>th</sup> study period, accrual of new patients will stop during a 4-month follow-up period (to collect primary outcomes) at the end of the study. All practice sites begin by implementing Approach 1 (Educate and Engage). Practice sites then add Approach 2 (Kidney Supportive Care Program) at the assigned period based on their sequence.

**Periods of patient accrual and follow-up for 14 CKD clinics randomized to 3 sequences\***

Sequence	Period 1 Mar-Dec 2025		Period 2 Jan-Oct 2026		Period 3 Nov 2026-Aug 2027		Period 4 Sep 2027-Jun 2028	
S1 (5 clinics)								
S2 (4 clinics)								
S3 (5 clinics)								

Approach 1
  Approach 2
  4-month follow-up – no recruitment

\* Excludes 9 clinics at one organization that withdrew after randomization.

Patients will receive the intervention based on the approach (condition) in which the site is enrolled at the time of accrual. When a practice site begins implementation of Approach 2,

referral to the kidney supportive care program for patients considering ATPs will become standard care at that site. All patients still alive who chose ATPs in prior periods will be offered the option of receiving care from the newly organized supportive care program.

There are several advantages to a SW-CRT design vs. standard cluster-randomized trial. First, SW-CRT gives every practice the opportunity to implement both approaches, which is something that the physician practice leaders have told us they value. Second, SW-CRT means that from the patient perspective, they will be receiving the standard care delivered by the practice site at any given time, and there is no need for patients to opt in or out of a trial to receive this improved access to best practice care.

In addition to the primary SW-CRT comparing the two intervention approaches, we will do a pre-post comparison of primary outcomes, comparing clinic practices at baseline with each of the interventions.

#### **Primary Outcome Variable**

- Proportion of patients 65 years and older who choose alternative treatment plans (ATP)

#### **Secondary and Exploratory Outcome Variables (if applicable)**

- Decisional conflict score 4 months after decision initiated
- Know-CKD score: assessment of patient knowledge about chronic kidney disease (CKD) and treatments 4 months after decision initiated
- Patient experience of shared decision-making as on SDM Q-9 and COLLABORATE scales 4 months after decision initiated
- Patient reported decision regret 9 months after decision initiated
- Advance care planning documentation in chart 4 months after index visit
- End of life intensity of treatment (ATP patients)
- Unplanned start of dialysis in last 30 days of life (ATP patients)
- Advance care planning at end of life for patients who die

Additional secondary and exploratory outcomes detailed further in section 5.2.2

#### **Number of Participants**

##### **Table 6.1.1 Number of Participants**

Population	Description	N
1. Patients of the nephrology practices (Aims 1 and 2)	Patients 65+ years old with eGFR less than 30. Within this population, patients are grouped according to their treatment choice (within first 10 months).	1,655 <ul style="list-style-type: none"> <li>Choose dialysis: 897</li> <li>Choose ATP: 345</li> <li>No decision: 414</li> </ul>
2. Family/care partners of ATP patients (Aim 2)	Sample of family members and care partners of patients who choose an ATP	35 <ul style="list-style-type: none"> <li>Longitudinal Interviews: 15</li> <li>Bereavement interviews: 20</li> </ul>
3. Employees of the nephrology practices (Aim 3)	Administrators/leaders (n = 50), other clinicians and staff (including doctors, advanced practice provider (APP)s, nurses, social workers, dieticians, palliative care specialists, and staff, n = 90)	140 <ul style="list-style-type: none"> <li>Administrators: 50</li> <li>Other employees: 90</li> </ul>

**Visit Schedule Table (Optional)****Synopsis Table 1. Schedule of Study Activities**

Time	Activity	Population

Screening (approx. weekly)	Research coordinator (RC) reviews upcoming appointments to identify eligible patients.	All	
Post-screening	RC notifies treating nephrologist/APP of plans to enroll patient at upcoming visit.	All eligible	
Time 0 / Index visit	Eligible patients enrolled in study for chart monitoring.	All eligible	
Time 0 / Index visit	Under a practice protocol for ExPAND including a provider standing order, patient is referred to kidney disease education (KDE). Provider introduces topic of treatment decision.	All eligible	
Time 0 / Index visit	RC consents patient for surveys and administers first Decisional Conflict Survey: DCS-1	Survey eligible (Has decision-making capacity and speaks English or Spanish.)	
4 months after Time 0	RC administers DCS-2	Survey eligible	
4 months after Time 0	Chart audit of advance care planning documentation	All eligible	

4 months after Time 0	RC reviews chart, records current treatment preference and other outcomes	All eligible	
9 months after Time 0	RC administers DCS-3	Survey eligible	
9 months after Time 0	RC reviews chart for missing outcomes, records current treatment preference, and enters Aim 1 completion status for patient (completed all study activities; followed for 9 months but did not complete all activities; died, lost to follow-up)	All eligible	
After treatment decision	RC begins quarterly chart audit of ATP patient.	ATP patients	
After treatment decision	RC requests permission from ATP patient and/or care partner to share contact information with external research team.	ATP patients who participated in DCS surveys and their family/care partners	
Every 4 months after treatment decision	ExPAND Research Team interviewers conduct longitudinal interviews	Sample of ATP patients and family/care partners	
	RC conducts end-of-life chart audit		

3 Months after ATP patient death		ATP patients who died during study	
4 Months after ATP patient death	ExPAND Research Team interviewers conduct bereavement interviews	Sample of family/care partners of ATP patients who died during study	
<b>Study Flow Chart (Optional)</b> See <i>Flowchart of Study Activities and Outcomes</i> (Appendix) for schematic flow of Aim 1 and Aim 2 activities and outcomes.			

## ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
AMCWD	active medical care without dialysis
APP	advanced practice provider
ATP	alternative treatment plan
DCS	Decisional Conflict Scale
DND	deciding not to decide (about treatment for kidney failure)
DSMB	Data Safety Monitoring Board
ED	emergency department
EOL	end-of-life
ICC	intraclass correlation
IRB	Institutional Review Board
NKF	National Kidney Foundation
NP	nurse practitioner
PDA	patient decision aid
RC	research coordinator
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance

REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SIHD	standard in-center or home dialysis
SW	stepped wedge
SW-CRT	stepped wedge cluster randomized trial
TLT	time-limited trial of dialysis

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## **1. Statement of Compliance**

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to the Common Rule at 45CFR46 (human subjects) and other applicable government regulations and Institutional research policies and procedures.

## 2. Background

Why this project is needed:

Over 130,000 patients with kidney failure start dialysis annually (1). Older patients constitute the fastest growing segment (1). Those who are frail or have other serious medical conditions may not live any longer with dialysis than without it (2). US healthcare policy has created a powerful "dialysis default," where virtually all patients with kidney failure who do not receive a transplant are treated with a standard dialysis regimen in a dialysis center regardless of whether it will help them live any longer or better. About 20% of patients regret the decision to start dialysis, yet non-dialysis alternatives are rarely offered to them (3). Most report they were unaware they had a choice about kidney failure treatment. Many older patients with kidney disease value independence over staying alive longer. Not aware of their patients' values, most nephrologists do not offer alternatives to standard dialysis such as active medical care without dialysis (AMCWD), a time-limited trial of dialysis (TLT), palliative dialysis, or deciding not to decide (DND) until a later date.



Similarly, these options, which we have collectively labeled alternative treatment plan (ATP)s, are rarely included in kidney disease education (KDE) sessions for patients funded by Medicare. Other countries—notably Australia, Canada, and the United Kingdom—have found that about 15% of older patients with kidney failure prefer AMCWD (4). They have created programs within their healthcare systems that integrate primary palliative care into care for patients who choose an ATP. These programs report excellent outcomes in terms of patient quality of life, care according to patient's wishes, and patient survival on average for over a year. They have shown

it is possible to avoid complications at the end of life such as patients who wanted AMCWD being started on dialysis because their symptoms were not well managed. These programs provide an extra layer of support and prepare patients and families for when the patient's kidney failure worsens.

Shared decision-making is recognized as the preferred approach to implementing patient-centered care and assuring that patients receive treatment that matches their goals. For over a decade, shared decision-making (SDM) has been recommended by nephrology professional societies before initiating dialysis (5). Despite the recommendation and preference for SDM (6) (7) of people with advanced chronic kidney disease (CKD), it remains poorly implemented, and observers have noted a "powerful [dialysis] default option with few perceived alternatives." (8) There is an urgent need for strategies to increase adoption and implementation of SDM in nephrology practices and elsewhere in healthcare systems where CKD patients receive care.

### 3. Rationale/Significance

#### 3.1 Problem Statement

For older patients with advanced CKD and comorbidities, frailty, and/or dementia, dialysis may not provide a survival advantage for them once they have reached end-stage kidney failure. In the United States in contrast to other countries including Australia, Canada, and the United Kingdom, there are **not** well-established programs to care for these patients if they choose NOT to start dialysis. The problem to be addressed in this project is how best to implement a kidney supportive care program that will 1) fully inform patients of all their treatment options including in-center and home dialysis, kidney transplantation, a time-limited trial of dialysis, palliative dialysis, deciding not to decide about dialysis till a later date, and AMCWD; and 2) provide an infrastructure to support patients who choose an alternative to in-center or home dialysis and kidney transplantation that will manage their symptoms, conduct advance care planning with them, refer them to hospice as appropriate, and support them in a symptom crisis so that they have the options to stay at home or be treated in an inpatient hospice as an alternative to going to a hospital emergency department (ED).

#### 3.2 Purpose of Study/Potential Impact

Using a *comparative effectiveness* approach, the purpose of this study is to determine, in real-world nephrology practices, whether 1) KDE using a shared decision-making approach and patient decision aids alone OR 2) improved KDE plus the creation of a kidney supportive care program is the most feasible and effective way to educate and provide alternative treatment plans to older patients with kidney failure, including those who do NOT want standard in-center or home dialysis. Although we hope to see a shift from in-center hemodialysis to home dialysis consistent with recently implemented federal value-based care initiatives, and although we expect that the intervention may contribute to such a shift, this study will evaluate change in the proportion of the less commonly offered alternate treatments (AMCWD, TLT, and palliative dialysis). The choice of this outcome reflects the specific goals of the project as well as the need to avoid confounding by secular trends in the take-up of home dialysis.

The potential impact of this study is immense. Patients with advanced chronic kidney disease 75 years of age and older are the age group with the highest incidence and prevalence of patients on dialysis. Dialysis is a labor-intensive and expensive life-prolonging intervention. Once fully informed, approximately 15-20% of older patients with advanced chronic kidney disease in other countries choose a non-dialysis option for their kidney failure treatment. There is a paucity of data on the number of such patients who make this decision in this country, but it is thought that it is only about 1-3%. If one of the approaches in this study proves effective and acceptable to patients and the number in this country increases to a number comparable to other countries, 15,000 or more patients each year in the US could benefit from a non-dialysis treatment approach according to their wishes.

It is important to note that we are NOT trying to compare the experience or outcomes of ATP to the experience or outcomes of hemodialysis. Such descriptive comparisons already exist in the evidence base, especially for AMCWD. (9) (10) (11) (12) (13) These cited comparison studies provide evidence for the rationale for making ATP more widely available to the subset of patients who might not do well with dialysis and who might want and benefit from AMCWD, since the quality and quantity of life outcomes are non-inferior for older, frail patients. This evidence base has been criticized because few of the studies involved randomization, but such a randomized trial comparing patients who choose to prepare for dialysis to those who prepare for AMCWD is currently underway in the United Kingdom (14). We have designed a trial whose primary aim is to test HOW best to increase SDM and access to ATP's. A second aim is to provide a comprehensive description of patient and family experience during ATP.

### **3.3 Potential Risks and Benefits**

#### **3.3.1 Potential Risks**

*Patients:* Because this study is implementing recommended best practices in the care of older patients with advanced chronic kidney disease, there are no anticipated major risks associated with it. Clinicians will employ recommended communication approaches and ask for permission to provide information about the patient's kidney disease and possible treatment options before doing so. Nonetheless, some patients might experience distress once informed that they have advanced chronic kidney disease if they were not previously aware of it. This distress is comparable to that experienced by patients in routine clinical practice who receive bad news. This study may differ from standard care in that patients might become better informed and more aware of the range of treatment options they have. Also, in taking the Decisional Conflict Scale and other surveys, they might realize more clearly that they don't know 1) what are the benefits of treatment that matter most to them, 2) what risks and side effects are most troublesome to them, and 3) overall, what treatment option is best for them. Interviewers will be trained to watch for indications of emotional distress and will be trained in how to respond calmly and empathetically. If the situation persists or worsens, the interview will be terminated, and the incident will be reported within 24 hours to the patient's treating clinician, who will develop a plan for supporting the patient including referral for further mental health services, as indicated.

*Care partners and clinic employees:* The main risk to these participants is loss of confidentiality of research data. Specific steps to minimize these risks are described in section 8.3.

Before data collection starts, all research personnel will be required to undertake appropriate training in the conduct of human subjects research, such as Collaborative Institutional Training Initiative (CITI) or Association of Clinical Research Professionals (ACRP) coursework. All staff will complete a training program developed by the study PIs. This training will include modules covering: 1) study overview, 2) recruitment procedures, 3) study arm procedures, 4) collection and management of study data, and 5) adverse event reporting and managing emergencies. The trial will be registered on ClinicalTrials.gov and Advarra will be the Central IRB (IRB of

record). Participant recruitment will begin at each site only after that site's clinical trials office (or equivalent) has approved the study materials containing IRB-approved protocol, surveys, and data collection instruments.

### **3.3.2 Potential Benefits**

Because this study mirrors recommended best clinical practices such as the use of shared decision-making, patient decision aids, and kidney supportive care to address unmet palliative care needs in the population of older patients with advanced chronic kidney disease, the investigators believe that there will be significant benefits for the participants. These include being aware that they have a choice about treatment to make, being fully informed of all treatment options, participating as co-equals in treatment decisions and in the development of a treatment plan, being offered the opportunity to participate in advance care planning, being routinely assessed for symptoms and being treated for them, and being referred to palliative care and/or hospice in a timely manner as appropriate.

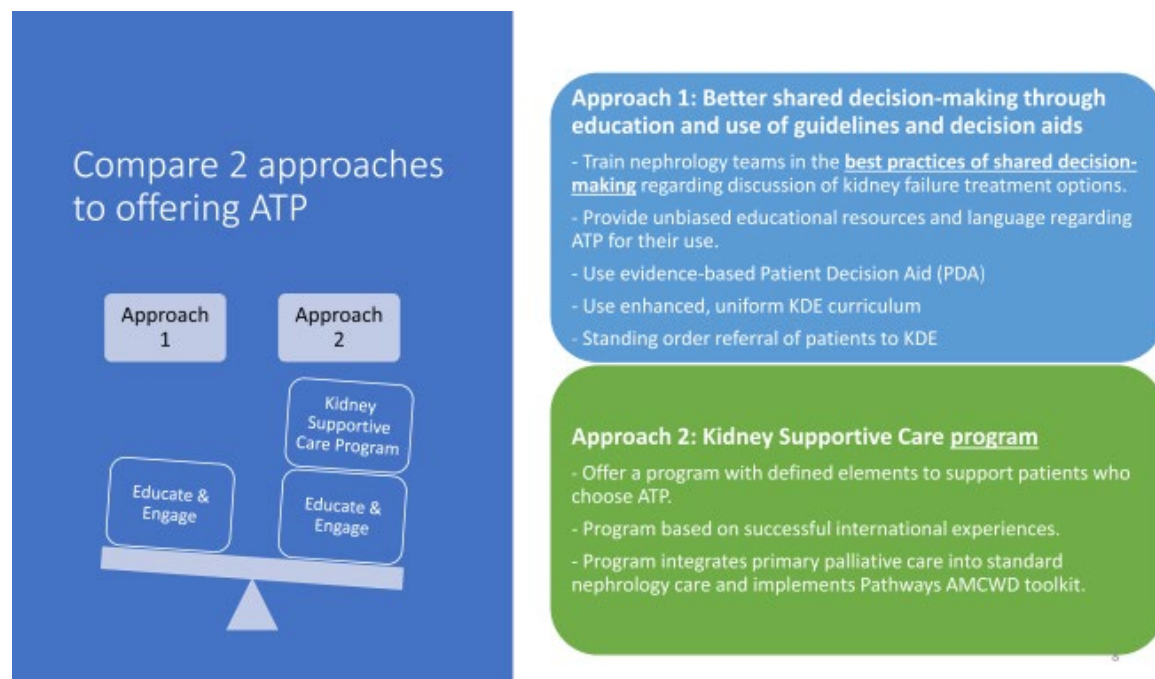
## 4. Study Objectives

### 4.1 Hypothesis

**Primary hypothesis:** Approach 1 (Educate and Engage) will be less effective than Approach 2 (Provide Primary Palliative Care) in increasing proportion of patients choosing ATP. **Subgroup hypothesis:** The difference in the primary outcome, selection of ATP, will be more pronounced for older/frailer patients and for patients with heart disease.

### 4.2 Primary Objective

The primary objective of this study is to compare two health system-based approaches for offering kidney failure treatment options to older patients with kidney failure, to ensure they are actively involved in a shared decision making (SDM) process covering a full range of choices and have meaningful access to that full range of choices, including standard in-center or home dialysis (SIHD) and alternative treatment plans (ATPs): active medical care without dialysis (AMCWD), time-limited trial of dialysis (TLT), and palliative dialysis.



**Aim 1:** Compare the effectiveness of two approaches: 1) improved kidney disease education (KDE) and SDM or 2) improved KDE and SDM plus the creation of a kidney supportive care program in increasing proportion of patients choosing ATP and explore comparative effectiveness on patient reported outcomes of decisional conflict and shared decision-making as well as health care utilization and advance care planning.

#### **4.3 Secondary Objectives (if applicable)**

**Aim 2:** Compare the patient and family experience of an ATP between Approach 1 and Approach 2, with particular emphasis on TLT and AMCWD in terms of quality of life, services used, and end-of-life (EOL) experience through medical record review and interviews with a sample of bereaved family members. Aim 2a will focus on experience while patients are receiving an ATP (several months to several years). Aim 2b will describe the EOL experience.

**Aim 3:** In order to evaluate implementation of each intervention (Approaches 1 and 2), the ExPAND research team will cooperate with a separate tandem evaluation conducted by an independent evaluation team based at NORC. The implementation evaluation is a mixed-methods design based on the expanded Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework. The implementation evaluation will consist of staff surveys, interviews, and site visits conducted by the NORC evaluation team. Regulatory oversight of AIM 3 will be handled by the NORC IRB.

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S1 (5 clinics)								
S2 (4 clinics)								
S3 (5 clinics)								
<div> <div></div> Approach 1           <div></div> Approach 2           <div></div> 4-month follow-up – no recruitment         </div>								
* Excludes 9 clinics at one organization that withdrew after randomization.								

Patients will receive the intervention based on the approach (condition) in which the site is enrolled at the time of accrual. When a practice site begins implementation of Approach 2, referral to the kidney supportive care program for patients considering ATPs will become standard care at that site. All patients still alive who chose ATPs in prior periods will be offered the option of receiving care from the newly organized supportive care program.

There are several advantages to a SW-CRT design vs. standard cluster-randomized trial. First, SW-CRT gives every practice the opportunity to implement both approaches, which is something that the physician practice leaders have told us they value. Second, SW-CRT means that from the patient perspective, they will be receiving the standard care delivered by the practice site at any given time, and there is no need for patients to opt in or out of a trial to receive this improved access to best practice care.

In addition to the primary SW-CRT comparing the two intervention approaches, we will do a pre-post comparison of primary outcomes, comparing clinic practices at baseline with each of the interventions.

## 5.2 Outcome Variables

### 5.2.1 Primary Outcome Variable

**Table 5.2.1 Primary Outcome**

Primary Outcome				
Name of outcome	Specific measure	Timepoints	Power (effect size)	N
<b>Aim 1: Effectiveness - compare 2 approaches to offering ATP</b>				
Proportion of patients choosing ATP*	<i>Patients choosing</i> <i>All enrolled patients</i>	Month 4 (return nephrology visit)	.87 (medium)	1,655

\* ATP: alternative treatment plan, including active medical care without dialysis (AMCWD), time-limited trial of dialysis (TLT), and palliative dialysis.

### 5.2.2 Secondary and Exploratory Outcome Variables (if applicable)

**Table 5.2.2.A Secondary Outcomes for Aim 1**

<b>Secondary Outcomes</b>
---------------------------

Name of outcome	Specific measure to be used	Timepoints	Power (effect size)	N
<b>Aim 1: Effectiveness - compare 2 approaches to offering ATP</b>				
Decisional conflict score at return nephrology visit	Decisional Conflict Scale (Month 4 score, adjusted for baseline score)	Month 0 (covariate) <b>Month 4 (return nephrology visit; outcome)</b> Month 9 (exploratory)	.71 (medium)	439
Knowledge about CKD and treatments at return nephrology visit	Know-CKD (Month 4 score, adjusted for baseline score)	Month 0 (covariate) <b>Month 4 (return nephrology visit; outcome)</b> Month 9 (exploratory)	.71 (medium)	439
Patient-reported experience of SDM	SDM-Q-9	Month 4	.87 (medium)	439
	CollaboRATE	Month 4	.87	439

Patient-reported experience of SDM			(medium)	
Advance care planning (ACP) documentation	Complete ACP measure (Three elements present in chart: a surrogate, a goals of care discussion, and either an accessible advance directive or medical order such as POLST or DNR.)	Month 4	.99 (medium)	1,655

Table 5.2.2.C Exploratory Outcomes			
Name of Outcome	Specific measure to be used	Timepoints	N
<b>Aim 1: Effectiveness - compare 2 approaches to offering ATP</b>			
Decisional conflict scale subscale scores	Decisional Conflict Scale	Month 0 (covariate)	439

	(Month 4 score, adjusted for baseline score)	<b>Month 4 (return nephrology visit; outcome)</b> Month 9 (exploratory)	
Patient reported decision regret	Modification of dialysis decision regret: Do you regret your decision to start (treatment selected)	Month 9	122
<b>Aim 2a: Descriptive - experience during ATP</b>			
Proportion of <b>AMCWD</b> patients who change to dialysis at any time ( <i>Primary for Aim 2</i> )	Proportion of patients who initially choose AMCWD who subsequently switch to dialysis (standard in-center hemodialysis, home dialysis, TLT, or palliative).	At study end or patient death	$n_1 = 76$ $n_2 = 179$
Proportion of ATP patients who “crash” into dialysis	Proportion of patients who initially chose an ATP who have unplanned dialysis start: defined as starting dialysis urgently in the hospital during an unscheduled admission. (See	At study end or patient death	$n_1 = 76$ $n_2 = 269$

	examples in notes below table.)		
Patient reports of their experience of an ATP	Open-ended qualitative questions about their experience  One item (Part A) from the McGill Quality of Life Questionnaire	Reported by sample of patients in longitudinal cohort every 4 months	40
Care partner reports of their experience caring for patients who have selected an ATP	Open-ended qualitative questions about their experience =  One item (Part A) from the McGill Quality of Life Questionnaire	Reported by sample of care partners in longitudinal cohort every 4 months	15
<b>Aim 2b: EOL experience</b>			
EOL intensity scale	Measure based on hospitalization, ICU admission, intensive procedures during last 30 days of life and death in hospital.	Chart review 3 months after death	$n_1 = 19$ $n_2 = 67$

AMCWD patients who initiate dialysis in the last month of life	Proportion of AMCWD patients who die who used dialysis in last 30 days of life.  Sensitivity analysis – also examine change to dialysis 60 days and 90 days before death.	Chart review 3 months after death	$n_1 = 19$ $n_2 = 45$
Advance care planning (ACP) documentation for ATP patients who die.	Complete ACP (same measure as in Aim 1, but performed over different time period.)	Chart review 3 months after death	$n_1 = 19$ $n_2 = 67$
Hospice Use	Proportion of deaths with hospice care, length of use of hospice	Chart review after death	$n_1 = 19$ $n_2 = 67$
Care partner reports of their experience of end-of-life care	Open-ended qualitative questions about their experience	Family members/care partners approached 4 months after patient death	20

**Notes.** Where unequal n's are expected under the 2 approaches,  $n_1$  and  $n_2$  are number of patients expected under Approach 1 and 2, respectively; otherwise, the n's are expected to be equal. **Planned Admission for Dialysis Start Example:** Patient with congestive heart failure (or other condition such as hypotension that could increase the risk of dialysis) and ESKD who is admitted as a precaution to monitor cardiac status during the first or several sessions of hemodialysis. Because dialysis is planned, the patient has a “permanent” access, an arteriovenous fistula, an arteriovenous graft, or a tunneled cuffed catheter. **Unplanned Admission for Dialysis Start Example:** Patient with advanced CKD who does routine lab work for next nephrology appointment and labs reveal one or more of the following: life-threateningly high potassium, very low CO<sub>2</sub>, and/or BUN is very high (>75 mg/dL), OR patient has symptomatic uremia or volume overload with dyspnea/hypoxia. Patient is requested to go to the Emergency

Department or is a direct admit to the hospital. Patient will need a temporary (non-tunneled) dialysis catheter for urgent start hemodialysis.

## 6. Study Population

### 6.1 Study Population

#### Study Population 1: Patients at participating clinics

Patients at participating CKD clinics who are 65+ years old and have eGFRs < 30. These patients are at the point in their disease course when they should make a decision about treatment for kidney failure.

#### Study Population 2: Family and care partners of patients who choose ATPs

To learn about family/care partner perceptions of the healthcare received by patients who choose an ATP, we will survey/interview a sample of family members and care partners a) throughout care and b) after patient's death.

#### Study Population 3: Employees of participating clinics

Employees who participate in the training to deliver the interventions will be asked to complete surveys measuring the impact of the training.

#### 6.1.1 Number of Participants

**Table 6.1.1 Number of Participants**

Population	Description	N
1. Patients of the nephrology practices (Aims 1 and 2)	Patients 65+ years old with eGFR less than 30. Within this population, patients are grouped according to their treatment preference at month 4.	1,655* <ul style="list-style-type: none"> <li>Choose dialysis: 896</li> <li>Choose ATP: 345</li> <li>No decision: 414</li> </ul>
2. Family/care partners of ATP patients (Aim 2)	Sample of family members and care partners of patients who choose an ATP	35 <ul style="list-style-type: none"> <li>Longitudinal Interviews: 15</li> <li>Bereavement interviews: 20</li> </ul>

3. Employees of the nephrology practices (Aim 3)	Administrators/leaders (n = 50), other clinicians and staff (including doctors, advanced practice provider (APP)s, nurses, social workers, dietitians, palliative care specialists, and staff, n = 90)	140 <ul style="list-style-type: none"> <li>• Administrators: 50</li> <li>• Other employees: 90</li> </ul>
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\*This sample size will give us 87% power for the primary outcome; however, we will enroll up to 3,000 patients, if possible, to provide better power for secondary outcomes.

### 6.1.2 Eligibility Criteria/Vulnerable Populations

#### Study Population 1: Person with CKD, cared for at participating clinic

##### Inclusion Criteria:

- Age 65 years or older
- Most recent eGFR <30 at time of screening AND meets practice site criteria for KDE referral
- Treatment naïve (no dialysis or kidney transplant prior to enrollment)

##### Exclusion Criteria:

- The current decrease in eGFR is thought to be due to an acute event.
- Education and initiation of shared decision-making process are not yet indicated for the patient, (per practice protocol and/or provider's judgment).
  - The patient will continue to be screened to see if their kidney function falls to the point where education and shared-decision making are indicated.
  - Note that patients who lack decision-making capacity should be enrolled when they would otherwise be eligible.

All patients who meet the criteria above should be enrolled in the study. Additional exclusions apply for patients recruited for surveys and interviews:

- Insufficient decision-making capacity
- Non-English and non-Spanish speaking
- Treating nephrologist/APP opts patient out (for example, if contraindicated for patient's health)

Study Population 2: Family member or care partner of patient in Study Population 1

## Inclusion Criteria:

- Family member or care partner of Population 1 patient who has a) chosen an alternative treatment plan and b) consented to the decisional conflict surveys.
- 18+ years old
- English or Spanish speaking
- Cognitively able to participate in surveys/interviews

Study Population 3: Administrator, clinical provider, or staff at participating chronic kidney disease clinic

## Inclusion Criteria:

- Currently practicing or employed at participating clinic

*Employees are a vulnerable population.* The intervention is at the clinic level, and supervisors at each site will decide which employees will be asked to participate in training and implementation. Participation in the *evaluation* of the training and interventions is voluntary, as described below.

In order to evaluate effectiveness of the training to implement the interventions and for quality improvement purposes, we will survey staff before and after the training. Participation in surveys will be voluntary, and employees will not be subject to firing or any other punitive action if they do not participate. We will not disclose which employees participate. In reporting aggregate results to the clinic sites, we will exclude results that would make it easy to identify participants (e.g., results for dieticians at Clinic A (n=1)); however, it may be possible in some cases for other staff members to infer participation.

## 7. Methods

### 7.1 Intervention

#### 7.1.1 Description of Intervention

**Intervention Approach 1 — Educate & Engage:** This is a bundle of three components to improve SDM. Other than these activities aimed at decision-making, patients receive standard CKD care, which rarely offers what is provided under Approach 2 (care coordination, case management, active symptom management, and advance care planning). The components of Approach 1 are:

1. Practice sites encourage patients to engage with a formal KDE program using the National Kidney Foundation (NKF) Council of Advanced Practice Providers curriculum enriched by the investigators to include an expanded and balanced presentation of TLT, palliative dialysis, and AMCWd. The project will train the educators providing the KDE in best practices for engaging patients and families and for culturally sensitive and inclusive delivery of KDE. Under a practice protocol for ExPAND including a provider standing order, all eligible patients will be referred to KDE unless opted out by provider.
2. Practice sites use evidence-based decision aids that include unbiased presentations of ATP options. These will be vetted by the project with input from advisory group to assure cultural inclusivity.
3. Current CKD teams (nephrologists, APPs, nurses, social workers, and kidney educators) receive training in communication skills using the Ask-Tell-Ask approach and the 9 elements of SDM. SDM best practices include using unbiased language to describe all options and using decision aids.

**Intervention Approach 2 — Provide primary palliative care to patients choosing ATP:** In this comparator, practice sites implement a new systematic kidney supportive care program to manage and coordinate additional services for patients choosing ATP. In addition to the Approach 1 bundle of education and engagement activities, practice sites set up and offer a systematic program integrating primary palliative care to support patients and their families who choose any ATP regimen. This program closely follows patients on ATP treatment regimens and implements care coordination, symptom management, advance care planning, and psychosocial support. The project team will assist the CKD practice site in building a program based on the Pathways Project AMMWD toolkit (<https://go.gwu.edu/ammwd>), which integrates palliative care into routine CKD patient care. The original toolkit will be expanded to include support for other ATPs. Practice sites will designate a lead clinician (usually a nurse practitioner) and will be encouraged to expand the staff of the primary palliative care program to include social worker and dietician. Practices will forge a relationship with at least one community palliative care and hospice organization so that these services can help to support patients and families in their ATP care. Services provided via the primary palliative care

program include regular care coordination, frequent patient contact not normally deployed in CKD practices (such as biweekly to monthly symptom check calls), systematic advance care planning, care management, symptom assessment and management, attention to psychosocial and family concerns, early involvement of specialty palliative care/hospice, and anticipatory guidance with a plan in advance of a symptom crisis. Patients considering ATP are referred to this team for initial consultation. If they choose an ATP, they are followed by the team in addition to usual services provided by their nephrologist.

### 7.1.2 Method of Assignment/Randomization

Randomization will be performed at the clinic (practice site) level. The statistician will use (constrained) stratified randomization to assign each clinic to one of the three sequences. The assigned sequence determines when the clinic moves from Approach 1 to Approach 2. Stratification will be based on projected enrollment ( $< 150$  vs.  $\geq 150$ ) and affiliation with an academic institution (yes/no).

Patients will receive the intervention based on the approach (condition) in which the site is enrolled at the time of accrual. When a practice site begins implementation of Approach 2, referral of patients who choose ATP to the supportive care clinic will become standard care at that site. All patients still alive who chose ATP during prior periods will be offered the option of receiving care from the newly organized supportive care program. Ethics require offering existing ATP patients the new care option once it is implemented.

### 7.1.3 Selection of Instruments/Outcome Measures

**Table 7.1.3 Instruments and Surveys**

<b>Instrument</b>	<b>Measures</b>	<b>Items</b>	<b>Completed by</b>
Decisional Conflict Scale (DCS) — Statement Format: 16 item 5 response (15)	Decisional conflict	16	All
Know-CKD (16)	Knowledge about kidney failure	12	All

Stage of Decision Making: 1 item (17)	Readiness	1	All
The 9-item Shared Decision Making Questionnaire (SDM-Q-9) (18)	SDM	9	All
CollaboRATE (19)	SDM	3	All
Dialysis decision regret (modified): "Do you regret your treatment decision?" (5 point Likert scale from 1 to 5, with 1 being "no regret at all" and 5 being "a lot of regret") (3)	Decision regret	1	Patients who have started treatment by month 9
McGill Quality of Life Questionnaire – Part A (20)	Quality of life	16	ATP patients and care partners in longitudinal qualitative interviews
Staff Training Evaluation Surveys (One per training session)	Self-Reported Confidence in Learning Objectives	Varies 10-15	Employees

**ExPAND End of Life Intensity Score for People with CKD (Adapted from Wong, O'Hare, 2012 (22) ):**

<b>Intensity of Care During the Final Month (30 days) of Life</b>		
<b>Measure</b>	<b>Points</b>	<b>Notes</b>
Any hospital admission	1	
Total days hospitalized > 14 days	1	Cut-off from Earle, 2004 (23)
Any intensive care unit admission	1	
Total days in ICU >= 4	1	Wong mean was 3.5 for dialysis patients
Any intensive procedure	1	Mechanical ventilation, CPR, or feeding tube
Death in hospital	1	
<b>Total</b>	<b>6</b>	

**Complete advance care planning measure:** This multi-component measure was successfully used in the Pathways Project (24). Trained auditors use a checklist to ascertain the presence and quality of documentation for each of the following elements: designated surrogate decision-maker, narrative discussion of goals of care, an accessible advance directive, and a medical order such as a do-not-resuscitate (DNR) or orders for life-sustaining treatment (e.g. POLST or MOLST). Complete ACP documentation requires three elements: a surrogate, a goals of care discussion, and either an accessible advance directive or medical order.

#### **7.1.4 Intervention Administration**

The intervention will be administered by clinicians (nephrologists, APPs, nurses, social workers, and kidney disease educators) at the participating nephrology centers according to the schedule specified by the stepped wedge design. At each clinic, all eligible patients will receive the intervention being used by the clinic at the time of treatment.

#### **Training and support**

Approach 1: Clinicians administering the intervention receive training in communication skills using the Ask-Tell-Ask approach and the 9 elements of SDM. SDM best practices include using unbiased language to describe all options and using decision aids. Training will use learning methodologies including small group case discussion, recorded role plays with standardized patients, and video observation of SDM and critique. Our goal is to train at least 50% of existing CKD practice staff (including nephrologists).

Approach 2: The project team will assist the CKD practice sites in building a kidney supportive care program based on the EXPAND ACTIVE program toolkit (these materials will be approved by the central IRB), which integrates palliative care into routine CKD patient care. Access to the Active Toolkit materials is given to the sites at the time that they begin Approach 2 implementation training in order to preclude contamination of sites still in Approach 1. Practice sites will designate a lead clinician (usually a nurse practitioner (NP)) and will be encouraged to expand the staff of the primary palliative care program to include social worker and dietician. Practices will forge a relationship with at least one community palliative care and hospice organization so that these services can help to support patients and families in their ATP care.

There can be considerable turnover of staff in nephrology practices for reasons beyond the influence of the research project. If there is staff turnover at clinical sites, especially the champion nephrologist, nurse practitioner or research coordinator, we will orient and train their successor. If staff such as research coordinator changes, we will re-train the replacement staff in study processes. If key clinical staff, such as champion nephrologist or NP leaves, we will attempt to orient a new champion at the site. We will provide the new champion with one-to-one orientation and training in the intervention and the study processes. The most critical problem will be if the lead staff person running the ATP program leaves, it may take time for the site to recruit a replacement ATP clinician. If this were to happen, we might have to pause accrual at

that site until the ATP clinic and approach 2 could be restarted with sufficient staffing resources at the clinic.

### **Core Functions/Form**

To accommodate local adaptations, we will be using an implementation science framework called Core Functions and Forms. This format allows flexibility in the "forms" (specific methods) sites may use in order to fulfill the core "functions" of the intervention. The central research team (including patient advisors), together with key collaborators at the clinic sites, will finalize and develop a document describing the core (required) functions of the intervention, including functions for 1) provider discussions with patients that incorporate shared decision-making and an ask-tell-ask approach, 2) patient kidney disease education (KDE), 3) patient decision aid (PDA)s, and 4) the palliative care program of Approach 2.

### **7.1.5 Reaction Management**

#### **Patient reactions**

Because of the nature of this minimal risk study, no physical harms are expected. It is possible that patients might suffer psychological distress. Some patients may become emotionally upset when thinking about their disease progression or the decisions they are making about their treatment. In standard CKD patient care, patients also need to make decisions about what treatment they want. This study may differ from standard care in that patients might become better informed and more aware of the range of treatment options they have. Also, in taking the Decisional Conflict Scale (DCS) and other surveys, they might realize more clearly that they don't know 1) what are the benefits of treatment that matter most to them, 2) what risks and side effects are most troublesome to them, and 3) overall, what treatment option is best for them.

Interviewers will be trained to watch for indications of emotional distress and will be trained in how to respond calmly and empathetically. If the situation persists or worsens, the interview will be terminated, and the incident will be reported within 24 hours to the patient's treating clinician, who will develop a plan for supporting the patient including referral for further mental health services, as indicated.

#### **Nephrology practice-level reactions:**

As the intervention occurs at an organizational level, it is possible, although highly unlikely, that the intervention could create undesirable impacts for the staff. The most plausible would be higher than usual staff turnover due to changes in work processes due to the intervention. If an organization experiences staff turnover that the organizational leadership judges is related to the study intervention, the organizational leadership will report this to the Co-PI's. This will be discussed with the Clinical Site Council and the Data Safety Monitoring Board (DSMB) for potential adjustments to the intervention implementation.

## 7.2 Assessments

### 7.2.1 Efficacy

The efficacy of the two intervention approaches will be compared using the measures below. See 7.1.3 for more information about survey instruments.

#### **Aim 1 - All Patients**

##### Primary

- Chart review: Proportion of patients who choose an ATP, as reported in the medical record.

##### Secondary

- Survey: Decisional Conflict Scale
- Survey: Know-CKD
- Survey: SDM-Q-9
- Survey: CollaboRATE
- Chart review: Proportion of patients with advance care planning documented in the medical record.

### 7.2.2 Safety/Pregnancy-related Procedure

NA

### 7.2.3 Adverse Events Definition and Reporting

No serious adverse events related to this minimal risk study are anticipated. However, to be comprehensive in our monitoring of adverse events, we have developed detailed policies and processes for monitoring and reporting adverse events. The key feature is distinguishing between adverse events that may be related to the study interventions from adverse events that are likely to happen in the study population but are unrelated to the study interventions. Local site PI's will assess all serious events and all unexpected events to determine whether or not they are related to study participation. Specific reporting timetables for reporting events are detailed in the appendix.

#### **Definitions**

*Adverse Event (AE):* Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, 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 (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice). AEs encompass both

physical and psychological harms. AEs are assessed in terms of seriousness, expectedness, and relatedness.

*Serious adverse event (SAE):* An AE that meets any of the following conditions:

- results in death
- is life-threatening (actually, not hypothetically)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- Other 'important medical events' may also be considered serious if they jeopardize the participant or require an intervention to prevent one of the above consequences.

*Unexpected Adverse Event:* An AE is "unexpected" when its nature, severity or frequency is inconsistent with risk information previously reviewed and approved by the IRB in the context of the study population.

*Related Adverse Event:* An AE is "possibly related" to the research procedures if, in the opinion of the investigator, the research procedures may have caused the harm.

### **ExPAND study expected AEs**

*Unrelated AEs:* Due to the nature of advanced CKD and its treatment, especially in multi-morbid frail older people, SAEs would be expected to occur frequently throughout the course of the disease. These expected SAEs include:

- Abnormal electrolyte and hematological laboratory results that can be explained directly or indirectly by their advanced CKD or comorbidities
- Hospital admissions — elective and emergency — that can be explained directly or indirectly by their advanced CKD or comorbidities
- Hospice admissions — planned and emergency — that can be explained directly or indirectly by their advanced CKD or comorbidities
- Infections and cardiovascular events, including fluid overload and swelling, that can be explained directly or indirectly by their advanced CKD or comorbidities
- Commencement of dialysis
- Death that can be explained directly or indirectly by their advanced CKD or comorbidities

*Study-related AEs:* Because of the nature of this minimal risk study, no physical harms are expected. It is possible that patients might suffer psychological distress. Some patients may become emotionally upset when thinking about their disease progression or the decisions they are making about their treatment. In standard CKD patient care, patients also need to make

decisions about what treatment they want. This study may differ from standard care in that patients might become better informed and more aware of the range of treatment options they have. Also, in taking the DCS and other surveys, they might realize more clearly that they don't know 1) what are the benefits of treatment that matter most to them, 2) what risks and side effects are most troublesome to them, and 3) overall, what treatment option is best for them. Interviewers will be trained to watch for indications of emotional distress and will be trained in how to respond, (see 7.1.5).

More details can be found in the document *ExPAND Adverse Event Reporting Guidelines* (Appendix).

### **AE Reporting**

The Site Principal Investigator will assess the severity, expectedness, and relatedness of the AE, which will be reported accordingly.

*Prompt reporting:* The Site Principal Investigator will report the following events to the study Principal Investigator within 24 hours of becoming aware of the event. The study Principal Investigator will report the AE to the Institutional Review Board (IRB) within 48 hours of becoming aware of the event.

- SAEs, that are **study-related** (related to the research procedures)
- AEs (whether serious or not) that are both **unexpected and study-related**

*Other reporting:* All **study-related** adverse events will be recorded in Research Electronic Data Capture (REDCap ) by the research coordinator (RC)(date, description, severity, expectedness, relatedness, and management/remediation of AE). The central data management team will assemble a list and summary of AEs, which will be reported to the IRB, DSMB, study sponsor, and site principal investigators as part of periodic reporting.

### **7.2.4 Pharmacokinetics (if applicable)**

NA

### **7.2.5 Biomarkers (if applicable)**

NA

## **7.3 Study Procedures**

### **7.3.1 Study Schedule**

#### **Baseline chart audit:**

Prior to the beginning of the intervention (Approach 1), or as soon as possible thereafter, local RC will conduct a retrospective chart audit to assess key outcomes at baseline. Section 8.5 describes the methodology and data to be collected.

**Intervention (Approaches 1 and 2) - All eligible patients:**

1. Local RC screens patients with upcoming appointments for eligibility and identifies candidates.
2. RC notifies treating nephrologist/APP. They plan for research activities at patient visit, potentially including discussion about treatment options, referral to KDE and/or recruitment for decisional conflict surveys (DCS).
3. **Enrollment Visit = Time 0.**
  - When an eligible patient attends initial visit, the patient is enrolled. With HIPAA waiver of authorization and a waiver of consent, RC will monitor chart outcomes for all enrolled patients.
  - Clinician assesses patient frailty and decision-making capacity. (These assessments are not required for enrollment but will be used for assessing heterogeneity of treatment effect.)
  - Clinician initiates discussion about treatment decision and/or refers patient to KDE.
  - RC approaches survey-eligible patients (English/Spanish speaking with decision-making capacity). For patients who provide informed consent, administer first survey (DCS-1). (May be administered up to 2 months later but not after post-enrollment KDE, if attended. May be administered in person or remotely.)
4. Four months after Time 0, RC administers DCS-2 in person or remotely. (May be up to 2 months early or 2 months late, preferably after 2<sup>nd</sup> visit with provider).
5. Four months after Time 0, RC reviews chart, records current treatment preference and other outcomes. (May be up to 2 months late, preferably after 2<sup>nd</sup> visit with provider).
6. Four months after Time 0, RC completes chart audit of advance care planning. (May be up to 2 months late, preferably after 2<sup>nd</sup> visit with provider).
9. Nine months after Time 0, RC administers DCS-3 in person or remotely. (May be up to 2 months early or 2 months late.)
7. Nine months after Time 0, RC reviews chart for missing outcomes (e.g. treatment decision) and enters Aim 1 completion status for patient (completed all study activities; followed for 9 months but did not complete all activities; died, lost to follow-up).

**Patients who choose ATP:**

1. After patient chooses an ATP, RC submits quarterly report for each patient via REDCap. This report includes clinic visits, change in treatment plans, dialysis, hospitalizations, and death.

2. RC approaches patients who consented to DCS and, where available, care partners. Requests permission to share contact information with ExPAND research team interviewers for longitudinal and bereavement interviews. For patients and care partners who assent, RC adds addendum to ICF, and enters contact information into REDCap.
3. Purposeful sample of ATP patients and care partners selected to participate in longitudinal series of interviews. ExPAND research team interviewers contact selected subjects, provide information about the interviews, and invite them to participate. For participants who agree, they schedule and administer the interviews, starting with verbal consent. The interviewer will send thank-you cards upon completion of each longitudinal interview. Follow-up interviews are conducted every 4 months until study end or patient death.
4. If an ATP patient dies, RC reports data on end-of-life service intensity and ACP documentation at end of life.

**Bereaved family members or care partners:**

If an ATP patient dies, and family/care partner has previously assented to be contacted, an ExPAND research team interviewer sends a bereavement card to family/care partner. Four months after patient death, interviewer follows up with family/care partner and invites them to participate in a bereavement interview.

**Clinic staff:**

1. Clinic staff who participate in training activities complete pre-and post-test survey at beginning and end of training.

See *Flowchart of Study Activities and Outcomes (Appendix)* for schematic flow of Aim 1 and Aim 2 activities.

**7.3.2 Informed Consent**

Multiple consent processes will be employed, depending on subject population and study activity. In general,

- for chart reviews, we will ask the IRB to approve a HIPAA waiver of authorization and waiver of consent
- for surveys conducted by the local RC, we will obtain verbal or written informed consent or eConsent (decision by participating nephrology practices)
- for surveys/interviews conducted remotely by the central research team (external to the site), we will obtain verbal consent and ask the IRB to approve a HIPAA waiver of documentation of consent

**Patients:**

*Chart audits:* We will ask the IRB to approve a HIPAA waiver of consent in order to conduct chart audits to gather data on treatment choice, health service utilization, and advance care planning for all patients meeting inclusion/exclusion criteria.

*Decisional conflict surveys (administered by site RC):* the site RC will approach eligible patients, explain the study, and obtain informed consent to participate in the three DCS surveys. Ideally, the initial approach and consent will be in person but if needed, the RC may conduct these activities by phone, email, or US mail.

Given that this is a minimal risk study and that participation in the surveys involves no procedures for which written consent is normally required outside of the research context, we will ask the central IRB to approve a waiver of documentation of consent. We will provide an information sheet to each patient, allow time for the patient to read it, answer any questions the patient has about participation, and obtain verbal consent. The research coordinator will document the verbal consent in the study records and will use an IRB-approved agreement form to obtain and share the personal information required by the payment vendor to provide payments to the patient after each survey. See *Patient Information Sheet for DCS Survey, Recruitment Letter/Email to Patients for DCS Survey, Payment Agreement Form for DCS Survey*.

Alternatively, where local IRBs require documentation of consent, research coordinators may use the IRB-approved informed consent form or may obtain eConsent by any of several mechanisms: 1) we have implemented an eConsent process in REDCap; 2) patients may sign a paper copy of the consent form, scan it, and email it to the RC; 3) sites may use their own Advarra-approved eConsent mechanisms. See *Informed Consent Form for Patient DCS Survey, eConsent REDCap Script*.

**ATP Patients, family members, and care partners:**

*Longitudinal and bereavement interviews (conducted by ExPAND Research Team interviewers; waiver of documentation of consent):* After patients choose an alternative treatment plan (ATP), the RC will approach those patients who have previously consented to the DCS surveys at a clinic visit, along with their care partners, where available. The RC will provide a patient/care partner information sheet about the interviews and ask for permission to share contact information (for the patient and/or family/care partners) with the external research team for this purpose. If the patient and/or care partner assents, the RC will collect the contact information and share it with the central research team. Permission to share contact information will be documented in an IRB-approved agreement form. (Alternatively, where required by local IRBs, consent to have their contact information shared will be documented as an addendum to the ICF for the DCS surveys.) The patient/care partner will be reminded that only a sample of patients/care partners who provide contact information will be contacted. See *Patient and Care Partner Information Sheet for Aim 2 Interviews, Permission to Share Contact Information for Aim 2 Interviews, Addendum to Patient ICF — Contact Info*.

Subsequently, if the patient or care partner is selected for longitudinal interviews or bereavement interview, ExPAND Team interviewers will notify the local RC and then contact the participant (patient or family/care partner) to invite them to participate. The process and interview content will be described, and any participant questions will be answered. An information sheet and consent statement document will also be shared with the participant by email or by U.S. mail if they provide their street address or email. For willing participants, an interview will be scheduled. At the beginning of the telephone or video call, the consent language will be read by the interviewer over the phone and verbal consent will be obtained both before and after the interview recording starts. A copy of the consent will be mailed to the participant if they wish to provide their street address or email. A thank-you card will be sent to the interview participant upon completion of the interview either via email or U.S. mail. Payment for participating will be provided upon completion of the interview and will be based on the participant's preferred payment method.

### **7.3.3 Screening**

On a regular (e.g., weekly or biweekly) basis, an RC at each clinic will review the medical record of patients with upcoming clinic visits to identify eligible candidates. For eligible patients, the RC will notify the treating nephrologist/APP. They will plan for research activities at the upcoming patient visit, potentially including discussion about treatment options, referral to KDE and/or recruitment for decisional conflict surveys.

Patients who meet the eligibility criteria and attend the planned visit will be automatically enrolled for EHR data collection. We will seek a HIPAA waiver of authorization and a waiver of consent for this. EHR data will be collected for all patients who meet the primary eligibility criteria, including patients who lack decision-making capacity or do not speak English or Spanish.

### **7.3.4 Recruitment, Enrollment and Retention**

#### **Patients, family members and care partners**

*Intervention:* Trial enrollment and randomization are at the site level. All patients at each site receive the intervention based on the approach in which the site is enrolled at the time.

*Chart review:* With a HIPAA waiver of authorization and a waiver of consent, the utilization outcomes will be collected on all eligible patients, with little missing data expected.

*Participant level recruitment* is applicable to patient and care partner reported outcomes collected via surveys and interviews as described below.

*Decisional conflict surveys (DCS):* The site RC will approach survey-eligible patients for the DCS at the enrollment visit or shortly thereafter. (May be up to 2 months later but not after post-enrollment KDE, if attended.) All eligible patients should be invited to take the surveys, including

those who make a treatment decision at the enrollment visit and regardless of KDE referral status. For this outcome, we believe that the administration of the short (10-20 minute) survey on site during clinic visits will maximize participation rates. Ideally, the RC will approach eligible patients, explain the study, obtain consent, and then immediately administer the survey. If needed, the RC may approach the patients by phone or email to obtain consent and administer the survey. We will pay an incentive for completion of DCS on the following schedule: \$50 on completion of the first survey, \$50 on completion of the second survey, \$25 on completion of 3rd survey. We estimate that 35% of eligible patients will consent and 26% will complete the survey at all three time points. If the response rate is higher than expected, we will introduce random sampling to determine which patients are invited to participate.

*Longitudinal and bereavement interviews (ATP patients/family/care partners):* After patients choose an ATP, the RC will approach those patients who have previously consented to the DCS surveys at a clinic visit, along with their care partners, where available. The RC will provide a patient/care partner information sheet about the interviews and ask for permission to share contact information (for the patient and/or family/care partners) with the external research team for this purpose. A patient may provide permission for his or her own contact information even if the care partner chooses not to, and vice versa. If the patient and/or care partner agrees, the RC will collect the contact information and share it with the central research team. The patient/care partner will be reminded that only a sample of patients/care partners who provide contact information will be contacted. See *Patient and Care Partner Information Sheet for Aim 2 Interviews*.

Subsequently, if the patient or family/care partner is selected for longitudinal interviews, or if the patient dies, the ExPAND Team interviewers will contact the participant (patient or family/care partner) to invite them to participate. The process and interview content will be described, and any participant questions will be answered. An information sheet and consent statement document will also be shared with the participant by email or by U.S. mail if they provide their street address or email. For willing participants, an interview will be scheduled. At the beginning of the telephone or video call, the consent language will be read by the interviewer over the phone and verbal consent will be obtained both before and after the interview recording starts. A copy of the consent will be mailed to the participant if they wish to provide their street address or email. Participants will be paid \$50 for each interview. We expect some drop out for the longitudinal interviews. Bereavement interviews are given only once.

### Response rates

Although we will strive for higher response rates, we based our power calculations for the patient-reported outcomes on conservative projections of response rates. This conservative estimate aligns with our prior experience seeking to survey dialysis patients during the Pathways Project. This estimate is also consistent with the national response rate for the Consumer Assessment of Healthcare Providers and Systems In-Center Hemodialysis Survey (ICH CAHPS). The ICH CAHPS survey response rate, based on average response rates for all

survey periods that have been completed as of Feb 2020, showed an expected response rate of 28% for mail only responses, 24% for telephone only responses, and 33% for mixed mode (mail and telephone).

To strengthen our response rate, we will incorporate evidence-based best practices for patient surveys, especially for vulnerable patients. Three key components that will be integrated into the survey instruments are brevity, clarity, and consistency. Keeping surveys short helps reduce burden and increase participation. An additional best practice we will employ is to offer multiple modality options such as in person, telephone, online. We will provide information about the study in multiple formats such as posters, flyers, and postcards. Finally, we will offer the surveys in English and Spanish.

The key to recruitment of patients will be at least one committed RC at each clinical site. The RC will be research personnel employed by the site who will have responsibility for 1) screening medical records and appointment lists to identify persons who meet the eligibility criteria for the study, 2) approaching eligible patients to explain the study and obtain their consent to participate in the survey portion of the study, 3) administer the DCS surveys, 4) approach ATP patients and care partners to obtain permission to share contact information with the central research team, and 5) facilitate payment of incentives to participating patients.

We will pre-test these processes at one site. We expect to refine the recruitment process based on the pre-test experience and on input from the site planning group and National Advisory Council.

### **Clinical sites**

*Study Site Selection:* The organizations providing the study sites were selected because their organizational leadership is invested in improving kidney supportive care, is willing to deliver the interventions, has sufficient research infrastructure, and has sufficient number of CKD patients. These organizations manage over 70,000 patients with kidney disease at more than 70 offices and satellite practice sites. They are "real world" settings operating under the regulatory and financial conditions and constraints typical for nephrology clinical practice, which will bolster generalizability of the results. The patient population served across all sites includes rural, suburban, and urban populations, patients from diverse races and ethnicities, and a wide range of economic circumstances. The organizations identified the specific participating sites based on size (at least 1,000 CKD patients), staffing levels, presence of a nephrologist or NP "champion" to be lead at the site, and availability of research infrastructure.

One of the key ways we will retain clinical sites is to meaningfully engage their leadership in the project. One mechanism for engagement will be a Clinical Site Council of the participating practices. Each practice site will designate a representative to serve on the council, which will provide input especially into questions around adaptation of the interventions for implementation based on local conditions. The council will consult with the investigators on barriers and

problems that arise during the project as well as identify innovations in practice that facilitated implementation through incorporation in routine workflows.

We prepared for 15% site dropout over the course of the study. However, as of September 2025, 10 of the original 24 sites had dropped out. Nine were with a single organization which chose to exit the study, after randomization of sites, for financial reasons at the corporate level. The other site was dropped before randomization, by mutual agreement between the organization and ExPAND, because the site was too small and did not have enough eligible patients. Because the dropout experienced was more than planned for, we changed from two co-primary outcomes to a single primary outcome, which enabled us to power the study with the lower enrollment that would result from fewer remaining sites. This version of the protocol (v9 and later) is based on the new number of sites (23 sites from 8 organizations randomized, 14 sites from 7 organizations continuing).

### **Clinical staff participants**

The intervention is at the clinic level, and supervisors at each clinic will decide which employees will be asked to participate in training and implementation. Recruitment applies to feedback provided by employees to the research team via surveys. Members from the ExPAND team will provide an online link for the training evaluation survey, and reminders including the survey link will be emailed to participants.

### **Avoiding undue influence or coercion in recruitment:**

*Patients:* Patients, family members, and care partners will be informed that participation is voluntary and that all patients, regardless of their participation status, will continue to receive standard care. They will be informed that they may stop participating at any time without penalty. Research staff will not provide final lists of participants to the nephrology center providers or staff. In some cases, research staff may include nurses who have had human subjects research training. Otherwise, in general, the people delivering patient care will not be aware of whether an individual patient participated.

*Staff:* The intervention is at the clinic level, and supervisors at each clinic will decide which employees will be asked to attend training and participate in implementation. Participation in the evaluation of the training is voluntary. Participants will be informed that their employment will not be affected in any way by their participation status and that they may stop participating at any time without penalty. In summary reports to sites, we will not identify study participants; however, due to the small sample sizes, it is possible that participant identities may be inferred in some cases.

### **7.3.5 Study Visits**

See section 7.3.1 for study schedule.

### **7.3.6 End of Study and Follow Up**

Enrollment of patients into the study will stop on February 29, 2028.

Follow-up of patients, including bereavement interviews of family members/care partners will stop on June 30, 2028.

### **7.3.7 Removal of Subjects**

No subjects will be removed from the EHR data collection (with HIPAA waiver) unless it is determined that they were added in error, i.e., they did not meet the eligibility criteria.

Consented participants who request to be withdrawn from the study in writing will be removed for purposes of further data collection, but data already collected may be used. We will not publish any quotations or individual-level data for these participants.

Consented participants who drop out or are lost to follow-up will not be removed from the study and data collected may be used.

## **7.4 Statistical Method**

### **7.4.1 Statistical Design**

#### **Effectiveness (Aim 1)**

To compare which mode of improving SDM and access to ATP is more effective, we will use a repeated cross-sectional stepped wedge (SW) design with randomization at the practice site level. Each clinic will be randomly assigned to one of three sequences. Each sequence consists of four 10-month time periods during which patients are accrued and followed for study outcomes. To minimize contamination in the primary analysis, we will exclude patients recruited during the 4 months before each sequence moves to Approach 2 (see white squares in Figure 5.1). These patients will be included in a sensitivity analysis. In the 4<sup>th</sup> study period, accrual of new patients will stop at 6 months, allowing a closing 4-month follow-up period to collect primary outcomes at the end of the study, (see Figure 5.1). All practice sites begin by implementing Approach 1 (Educate and Engage). Practice sites then add Approach 2 (Kidney Supportive Care Program) at the assigned period based on their sequence. Patients will receive the intervention based on the approach (condition) in which the site is enrolled at the time of accrual. When a practice site begins implementation of Approach 2, referral to the supportive care clinic will become standard care at that site. All patients still alive who chose ATP in the prior period will be offered the option of receiving care from the newly organized supportive care program. Ethics require offering existing ATP patients the new care option once it is implemented, even though this may greatly reduce the number of patients who die during Approach 1 care, thereby limiting our ability to compare Approach 1 and Approach 2 on EOL outcomes (Aim 2b).

There are several advantages to a cluster randomized stepped wedge (SW) design vs. standard cluster randomized trial. First, SW gives every practice the opportunity to implement both approaches, which is something that the physician practice leaders have told us they value.

Second, SW means that from the patient perspective, they will be receiving the standard care delivered by the practice site at that time, and there is no need for patients to opt in or out of a trial to receive this improved access to best practice care.

Prior to implementation of Approach 1, we will measure the proportion of patients who choose each treatment option. We will also retroactively assess hospital EOL utilization and proportion of ATP patients who begin dialysis within 30 days of death.

### **Patient and family/care partner experience using ATP (Aim 2)**

To describe the patient/family experience of ATP care through the end of life, we will monitor utilization patterns for all ATP patients and conduct chart audits at end of life, survey a subset of ATP patients periodically throughout the course of care, and interview bereaved family members. A panel of patients who have chosen an ATP and family members/care partners will be interviewed every 4 months to develop a description of experience over time. A sample of bereaved family members/care partners will be interviewed 4 months after a patient's death. Mixed methods, including thematic analysis, will be used to explore themes about quality of life during receipt of ATP, concordance of end-of-life experience with patient goals, family/care partner experience of caregiving and at EOL, and utilization patterns, especially change to other treatment modes and hospitalizations.

Exploratory comparison of patients who receive EOL care in Approach 1 vs Approach 2 will be conducted, especially through qualitative themes emerging during interviews. The study may not have sufficient power to detect differences in the quantitative measures because the number of patients receiving Approach 1 who are projected to die is expected to be small. Nevertheless, the qualitative interviews will reveal themes that illuminate the effects of the two approaches. We expect that Approach 2, which provides more care management and more advance care planning, will lead to lower EOL intensity scores, fewer initiations of standard dialysis within 30 days of death, and care more concordant with known patient wishes as reported by family. (See *Flowchart of Study Activities and Outcomes* (Appendix) for schematic flow of Aim 2 clinical processes and data collection points.)

### **7.4.2 Sample Size Considerations**

#### **Update November 2025**

We prepared for 15% site dropout over the course of the study. However, as of September 2025, 10 of the original 24 sites had dropped out, one before randomization and nine after randomization. Because the dropout experienced was more than planned for, we changed from two co-primary outcomes to a single primary outcome, which enabled us to power the study with the lower enrollment that would result from fewer remaining sites. This version of the protocol (v9 and later) is based on the new number of sites (23 sites from 8 organizations randomized, 14 sites from 7 organizations continuing).

### **Sample Size and Power (Aims 1 and 2)**

Detailed assumptions for sample size targets are shown in the table below. Sample sizes will vary by outcome, e.g., medical record derived outcomes should be available for all eligible patients, while survey-based outcomes will need to exclude patients who do not consent to complete the surveys. Aim 2 outcomes are only relevant to patients choosing ATP.

**Table 7.4.2.A Assumptions for Sample Size and Power Projections**

Assumption	Rationale/Data Source/Calculation	Resulting N
<b>AIM 1: Impact of approaches on patient treatment decisions</b>		
14 practices; 11 clusters	Current enrollment projections.	1,655 patients <ul style="list-style-type: none"> <li>• Approach 1: 759 pts</li> <li>• Approach 2: 896 pts</li> </ul>
<ul style="list-style-type: none"> <li>- 89% of patients have decision-making capacity (DMC)</li> <li>- 35% of patients with DMC consent to Decisional Conflict survey offered <u>onsite</u> at 1st practice visit.</li> <li>- 85% of these complete 2nd survey at 2nd practice visit.</li> </ul>	<p>Prior experience of team, including My Way project (40% response rate of patients approached for participation)</p> <p>759*.89 with decision-making capacity*.35 consent to survey*.85 complete 2<sup>nd</sup> survey = 201 in Approach 1.</p> <p>896*.89 with decision-making capacity*.35 consent to survey*.85 complete 2<sup>nd</sup> survey = 238 in Approach 2.</p>	<p>439 for Aim 1 Decisional Conflict survey</p> <ul style="list-style-type: none"> <li>• Approach 1: 201 pts</li> <li>• Approach 2: 238 pts</li> </ul>
<b>AIM 2: Patient and family experience during ATP care and at end of life</b>		
<p># patients who will choose ATP:</p> <p>Approach 1: 10% AMCWD, 0% TLT or palliative dialysis= 10% ATP. (SIHD = 10% home dialysis, 80% in center dialysis)</p> <p>Approach 2: 20% AMCWD, 5% TLT, 5% palliative dialysis=30% ATP. (SIHD= 15% home dialysis, 55% in center dialysis)</p>	<p>Approach 1: Expert opinion</p> <p>Approach 2: Canadian, Australian, UK experience: 20% of older patients choose AMCWD. We have assumed lower rate as the Approach 2 programs may need time to get established and gain the trust of providers and patients.</p> <p>759*0.10 = 76 patients added in Approach 1</p> <p>896*0.30 = 269 patients added in Approach 2</p>	<p>345 patients choose <b>ATP</b> (AMCWD, TLT, palliative dialysis)</p> <ul style="list-style-type: none"> <li>• Approach 1: 76 pts</li> <li>• Approach 2: 269 pts</li> </ul> <p>255 (of 345) choose <b>AMCWD</b></p> <ul style="list-style-type: none"> <li>• Approach 1: 76 pts</li> <li>• Approach 2: 179 pts</li> </ul>
# patients who switch back to dialysis	Expert opinion. Canadian, Australian, UK experience – very few AMCWD patients switch to dialysis.	345 for denominator (all ATP)
Randomly sample ATP patients to invite for qualitative interviews. 25% will agree to interview.	Prior experience of team, including My Way project and Pathways project. Difficult to reach patients for phone interview; many patients too tired or sick for phone interview.	10-15 interviews, until thematic saturation
25% of ATP patients anticipated will die yearly (.02 person/month)	This is more conservative than actual experience in Australian and Canadian programs to allow for possibility that patients will be choosing ATP earlier in disease progression and thus living longer	<p>86 <b>ATP</b> deaths</p> <ul style="list-style-type: none"> <li>• Approach 1: 19</li> <li>• Approach 2: 67</li> </ul> <p>64 <b>AMCWD</b> deaths</p> <ul style="list-style-type: none"> <li>• Approach 1: 19</li> <li>• Approach 2: 45</li> </ul>

Contact family member for all patients who die. Will not have contact information for some proportion.	Survey data will be examined for missing items, and any patterns will be reported qualitatively and be used to qualify the interpretation of findings, e.g., "families under more apparent stress were less likely to complete certain of the quality-of-life items.	About 30 family members may be reachable and agree to interview. Complete 10-15 interviews, until thematic saturation.
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\* The number of deaths was calculated for each period using a 25% annual mortality rate and the number of ATP patients alive (under each approach) at the beginning of the period. Note that some patients accrued under Approach 1 will die under Approach 2.

**Table 7.4.2.B Power for Comparing Approach 1 and Approach 2 Outcomes**

#	Outcome	N	Effect Size, Power		
			Smaller Effect	Medium Effect	Larger Effect
Aim 1 (all patients making treatment decision)					
1	Proportion of patients choosing ATP	1,655	P <sub>1</sub> =.10, P <sub>2</sub> =.15 Power = .38	P <sub>1</sub> =.10, P <sub>2</sub> =.20 Power = .87	P <sub>1</sub> =.10, P <sub>2</sub> =.25 Power = .99
2	Decisional conflict score at return nephrology visit	439	d=.20 Power = .28	d=.36 Power = .71	d=.50 Power = .93
3, 4	Patient-reported experience of SDM (SDM-Q-9, CollaboRATE)	439	d=.40 Power = .69	d=.50 Power = .87	d=.60 Power = .96
5	Patient reported decision regret (proportion regretting decision)	122	P <sub>1</sub> =.25, P <sub>2</sub> =.15 Power = .15	P <sub>1</sub> =.25, P <sub>2</sub> =.10 Power = .29	P <sub>1</sub> =.25, P <sub>2</sub> =.05 Power = .52
6	Advance care planning documentation	1,655	P <sub>1</sub> =10., P <sub>2</sub> =.15 Power = .38	P <sub>1</sub> =10, P <sub>2</sub> =.25 Power = .99	P <sub>1</sub> =.10, P <sub>2</sub> =.35 Power = .99
Aim 2a (only includes patients initially choosing ATP)					
7	Proportion of AMCW patients who change to dialysis at any time.	n <sub>1</sub> =76, n <sub>2</sub> =179	P <sub>1</sub> =.40, P <sub>2</sub> =.30 Power = .16	P <sub>1</sub> =.40, P <sub>2</sub> =.25 Power = .30	P <sub>1</sub> =.40, P <sub>2</sub> =.20 Power = .50

Notes.  $P_1$ ,  $P_2$  are proportions choosing the outcome for Approach 1 and 2, respectively. Where unequal n's are expected under the 2 approaches,  $n_1$  and  $n_2$  are number of patients expected under Approach 1 and 2, respectively; otherwise, the n's are expected to be equal.  $d$  is Cohen's  $d$  (standardized effect size). Yellow highlight=good power  $>.80$  to  $<.90$ . Green highlight = excellent power  $>.90$ .

Table 7.4.2.B summarizes minimum sample size expectations and power estimates for key outcomes. The survey-based sample size (Outcomes 2-5) is much lower because patient consent and availability is required. Power calculations used R package swCRTdesign version 3.3. (28) ICCs currently listed in the CLOUD Bank (29) for SW studies in health care settings average about .03, and therefore a slightly more conservative ICC=.05 was incorporated into calculations. Alpha (two-sided) is set at .05 for all outcomes.

For Outcome 1, an increase from 10% choosing an ATP under Approach 1 to 20% under Approach 2 would be substantial enough to be considered important (30) (31) and we believe an increase to 25% or 30% is highly plausible. This is based on personal communication with US nephrologists regarding the present number of CKD patients wanting AMCWD and on reports from AMCWD programs in the UK, Australia, and Canada. (32) (33) (34) The moderate effect (change from 10% to 20% choosing ATP) is detectable with .87 power.

For Outcomes 2, 3, and 4, the standardized effect sizes detectable with .80 or higher power range from .50 to .60 in magnitude. Power calculations for those outcomes assume a conservative pre-post outcome correlation of  $r=.50$ . Larger correlations will result in increased power. (35) Power for Outcome 5 (decision regret) will be weak. For Outcome 6 (ACP documentation) power should be excellent (.99) for detecting plausible differences based on experience from the My Way study, where the rates were 4% at baseline, 18% in the enhanced control and 33% among CKD patients who received ACP coaching. (36)

For the Aim2a Outcome 7, although we expect a large effect of Approach 2 in reducing change to dialysis, we will have weak power to detect it. Therefore, a non-significant result would need to be interpreted cautiously, with an emphasis on descriptive statistics and confidence intervals.

### **7.4.3 Planned Analyses**

#### **7.4.3.1 Primary Analyses**

##### **Aim 1 and 2**

For all primary outcomes as well as most secondary quantitative outcomes, statistical hypotheses concern the contrast between patients accrued under Approach 1 and 2. The intent-to-treat (ITT) principle will be followed for all primary outcomes. Treatment choice, unless otherwise defined, refers to the 4-month treatment preference (recorded 4-6 months after enrollment). Differences between the two approaches will be tested through a generalized linear mixed effect model, which can accommodate the random cluster effects inherent to the SW design and handle outcomes that are binary, normally distributed, etc. Analyses will include age, gender, race, cluster size (high/low), whether the cluster is affiliated with an academic medical center, and period (time) as fixed effect covariates, and cluster as a random effect. For each survey-based outcome, the baseline value for that outcome assessed at the first nephrology visit will also be included as a covariate.

*Sensitivity Analysis:* We have not included deciding not to decide (DND) as an alternative treatment choice because we will not be able to reliably distinguish between a conscious shared decision to postpone deciding and simply not deciding. Patients who have not identified a treatment preference after 4-6 months of follow-up will be included in the denominator and not in the numerator, i.e., they will not be counted as having chosen an ATP. To measure the impact

of this population, we will conduct a sensitivity analysis including them in the numerator (as patients who have chosen an ATP).

*Heterogeneity of Treatment Effects:* It is hypothesized that for Outcomes 1 and 2, there will be a more pronounced effect for patients who are over age 80, frail, or have heart disease. Although pre-specified tests are described here, they will be interpreted as secondary analyses because of uncertainties regarding power. As a pre-specified analysis, this will be tested by adding Approach x Age Group, Approach x Frailty Group, and Approach x Heart Disease Group terms to the regression model, which would also include the main effect variables (age group, frail group, and heart disease group as indicator variables). Because these subgroups are likely to have considerable overlap leading to possibly high multicollinearity of variables, the 3 interaction terms will first be tested together as a set with an omnibus test. A significant p-value result ( $< .05$ ) would be followed by testing the regression coefficients for each of the separate terms (with significance at  $p < .05$ ), which would determine, say, whether the heart disease group was more affected by Approach 2 after controlling for the other interaction effects. For Outcome 1, as an exploratory analysis, heterogeneity in approach effect across clinics will be tested through inclusion of a Site x Approach interaction random effect. Practice site differences in Approach effects will also be examined through descriptive and graphical methods. Any strong patterns observed will then be compared with known characteristics of each practice site to gather plausible explanations of any important Approach effect differences among the clinics. Currently, this is the only exploratory interaction test planned. If any later heterogeneity tests are conducted, these will be tested through an interaction term added to the model; however, any publication describing those results will state clearly that these are exploratory and therefore those results are highly tentative.

*Preliminary analyses:* Internal consistency reliability will be assessed for scale scores. Because the SW design partly confounds treatment and time, we will examine de-identified patient demographic and diagnostic trends across the study period to identify any that may confound or limit study interpretation. For example, shifts in outcomes under either study condition may occur due to secular external trends, new legislation or rules, etc., as well as changes due to greater staff experience. As an indicator of secular trends, we will monitor the proportion of older adults (80+ years) starting dialysis in the national data reported annually by the USRDS and include this information in the interpretation of results.

*Exploratory analyses:* Although a primary outcome is choosing any ATP, the range of specific ATPs or standard dialysis options chosen will be examined descriptively. For example, one of the approaches may lead to greater or less use of home dialysis as a sub-type of SIHD. Other analyses will examine practice site characteristics as predictors of outcomes as a multi-level model e.g., stronger Approach 2 effects for clinics with higher staff/patient ratios.

#### **7.4.3.2 Analysis of Subject Characteristics**

Subject characteristics (e.g., age, gender, race, etc.) will be collected, summarized, and regularly reported (overall and by site) at DSMB meetings. Subject characteristics will be reported in all publications.

#### **7.4.3.3 Interim Analysis (if applicable)**

No interim analysis of outcomes is planned as the interventions pose minimal risk.

#### **7.4.3.4 Health economic evaluation, if applicable**

NA

#### **7.4.3.5 Other**

NA

#### **7.4.4 Subsets and Covariates**

Subgroups of patient population (older patients ( $\geq 65$  years) with stage 4 or 5 CKD (eGFR  $< 30$ ) being cared for at a participating practice site):

- Patients who are frail ( $\geq 5$  on the Clinical Frailty Scale (39))
- Patients who are 80+ years old
- Patients with heart disease: ICD-10 I20-I52
- (Exploratory only) Patients with diabetes
- (Exploratory only) Black patients
- (Exploratory only) Hispanic patients
- (Exploratory only) socioeconomic status, based on zip code

The following covariates will be included in models for the outcomes specified:

- Age (in models for all Outcomes)
- Gender (in models for all Outcomes)
- Race (in models for all Outcomes)
- Baseline scale scores (Outcomes 2-4)

#### **7.4.5 Handling of Missing Data**

Missing data. For the outcome of choosing ATP, data will be available for all participants via chart audit. Survey-based outcomes will only be available for participants who consent and complete the survey. This may introduce a selection bias, e.g., if participants under Approach 2 feel more motivated to complete the survey. A preliminary analysis will therefore examine whether there is a difference in study participation rate between the 2 study conditions. If there

is an important difference, then the survey-based results will be subjected to sensitivity analyses to identify whether the conclusions would differ under various reasonable missing data scenarios.

Practice site dropout. If any practice sites drop out of study participation after randomization, the primary ITT analyses will include data from subjects at the dropped sites that have any outcome data available. Sensitivity analyses in which data from these subjects is dropped will also be carried out.

## 8. Trial Administration

### 8.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

This is benign behavioral intervention and a minimal risk study.

#### HIPAA waiver of authorization and waiver of consent

To answer the research questions (effect of interventions on number of patients who attend kidney disease education, choose alternative treatment plans, have advance care planning documentations in the chart), we need to have the information for all eligible patients. Obtaining informed consent would introduce selection bias and reduce power to evaluate the effects of the intervention. It might also undermine our ability to evaluate the effect of the intervention on subgroups (race, comorbidities, etc.). With a HIPAA waiver of authorization and waiver of consent, we will collect data from the medical record that are protected (PHI), but not highly sensitive. Most of the information we will collect will be completely deidentified, but we need to collect dates of services to reliably keep track of time intervals and of which services take place under each intervention approach. Because some patients will be followed as the clinic moves from Approach 1 to Approach 2, we need to measure the duration of exposure to each approach, and to know whether certain activities occurred during the baseline period, Approach 1, or Approach 2. We will not collect date of birth but will collect year of age to be able to evaluate whether effects differ by age. We will also collect provider name (to evaluate reach of intervention), zip code as a means to assess the impact of social determinants of health and whether we see disparities by zip code. Non-PHI to be collected include demographic information, clinical information (e.g., comorbidities), kidney failure treatment decision, and healthcare utilization (clinic visits, hospital visits, etc.)

We expect that the waiver will not directly affect the participants in any way. No research data will be added to the patients' permanent medical records. The data collected will be used only for the purposes of the research, and we will take appropriate measures to minimize the potential for a breach of confidentiality (8.3, 8.9). We will destroy the identifiable information and code link when this research and any approved follow-up research are complete, as described in section 8.10.

#### Information collected with consent

After providing informed consent, some patients will participate in surveys and interviews. Recruiting and consenting procedures, including measures taken to avoid coercion, are described in sections 7.3.2 and 7.3.4. When describing the study to patients, we will use general language without specific descriptions of the differences between the two intervention approaches. The reason is to avoid introducing bias by influencing treatment decisions or perceptions about care that are reported in patient-reported outcomes (surveys and interviews). For example, a patient in Approach 1 who might otherwise consider AMCWd, who learned that other clinics were providing a kidney supportive care program while their own clinic was not,

might conclude that they would not receive adequate support and decide to choose dialysis after all; or the same patient might have negative perceptions about the care they received if they imagined that patients in the other approach were receiving better care.

#### HIPAA waiver of documentation of consent

Because of the strict timing window for the first DCS survey, and because research coordinators cannot always be present at the enrollment visit, we have allowed for recruitment, consenting, and survey administration to be conducted remotely. In this context, obtaining written informed consent can be a barrier to recruitment. Since this is a minimal risk study and the survey procedures would not normally require written consent outside of the research context, we will request a waiver of documentation of consent for the DCS surveys.

To reduce the burden on site RCs, some surveys and interviews will be administered remotely by EXPAND Team interviewers. For these interviews, the site RC will obtain permission from patients and/or family members/care partners to share their contact information with the research team outside the local clinic. With patient/care partner permission, this contact information will be stored in REDCap and made available to the remote interviewers. The remote interviewers will be responsible for describing the research procedures and verbally consenting the patients, as described in sections 7.3.2 and 7.3.4. We will request a HIPAA waiver of documentation of consent for these activities. The reason we ask for waiver of documentation of consent is to reduce the burden on the local RC (to obtain consent) or on the participant (to return a signed consent form in the mail). It will also facilitate maximal participation, which will provide more statistical power and reduce selection bias.

#### Payments to participants

Participants (patients and family members/care partners) will receive the following payments for participation in surveys and interviews:

- Decisional conflict survey (\$50 after first and second surveys, \$25 after third survey)
- Longitudinal interviews (\$50 per interview)
- Bereavement interviews (\$50 per interview)

As part of consent, patients may choose to receive the payment in the form of a debit card, electronic wire transfer, or paper check delivered via US mail. We believe these amounts will express our appreciation and provide an incentive to participate while not being so significant as to be coercive.

Family members/care partners who participate in a longitudinal or bereavement interview will receive a gift card upon completion. During the interview, the family member/care partner may choose to receive the gift card either via email or US mail.

## 8.2 Institutional Review Board (IRB) Review

### Central IRB / IRB of Record

Advarra will serve as the Central IRB (also known as the IRB of Record).

The protocol will be submitted to the Central IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any modification to the protocol will be approved by the Central IRB before implementation.

Continuing review requests will be submitted to the Central IRB annually, and a study closure report will be submitted after all research activities have been completed.

Other study events (e.g., data breaches, protocol deviations) will be reported as described in this protocol and per the Central IRB's policies.

### Relying Institutions

Each participating practice will formally cede their IRB review to the Central IRB using a fully executed reliance agreement (known as an IRB authorization agreement or IAA).

Study documents approved by the Central IRB, including initial and modified protocols, consent forms, and others, will be sent to the relying institutions per Central IRB protocol. Reports and other communications with the Central IRB will be reported to relying institutions, if relevant.

## 8.3 Subject Privacy, Confidentiality & Data Management

### Protection of data confidentiality:

We will maintain all standard processes for maintaining data in a secure manner:

- Identifiable data will be stored only in secure REDCap research database at GWU or other secure platform approved for regulated data (e.g., GW Box). (A copy of site-specific study data may be housed securely at each participating site.)
- Access to the secure database will be limited to specified research staff.
- All enrolled patients will be assigned a unique study identification number. All data collected will be identified only by these study identification numbers. Where it is necessary to collect direct identifiers (e.g., for contact and payment of survey participants), these will be kept in separate databases from other data collected. A site-specific link between each study identification number and participant name will be kept in a password-protected file on a password protected computer at each participating site.
- Research personnel at the clinical sites may temporarily use paper documents for participant tracking and data collection. Data will be transcribed to REDCap in a timely

manner. Paper documents will be secured in a locked cabinet at the clinical site until they are no longer needed. Then they will be shredded.

- Only completely de-identified data will be provided to others outside the study team as needed for data analysis.
- No medical records or protected health information (collected for the patient participants only) shall be re-disclosed, unless required by law.
- Data and code links will be destroyed after the period for maintaining data has elapsed, in accordance with this protocol and Central IRB's policies, (see section 8.10).

#### Oversight of research personnel to maintain research participant protection and rights:

For GWU and all subaward organizations, all research personnel will have up to date training in the conduct of human subjects research, such as Collaborative Institutional Training Initiative (CITI) or Association of Clinical Research Professionals (ACRP) coursework. Research personnel will meet either the GW IRB requirements for training, or the requirements of their home institution.

At clinical sites (participating nephrology practices), RCs (aka "study coordinators") employed by the sites will have responsibility for 1) screening medical records to identify persons who meet the eligibility criteria for the study, 2) conducting chart reviews to obtain data on treatment decision, advance care planning and service utilization (e.g. hospitalizations at end of life), 3) entering study data into REDCap, 4) maintaining a code link, 5) approaching eligible patients to explain the study and obtain their consent to participate in the survey portion of the study, 6) administering the DCS surveys, 7) providing contact information to ExPAND Team interviewers of patients who give permission, and 8) facilitating incentive payments to participating patients. We will also provide project specific videoconference training for the site research personnel on the study protocol, best practices for involving patients from diverse backgrounds, and best practices for maintaining privacy, confidentiality and protection of research participants and data collected.

For personnel involved in the study in roles *other than research* (for instance, nurse practitioners who lead the kidney supportive care clinics) but do not obtain data from the chart or from patients for research purposes, we will provide an overview of research ethics and procedures as part of the orientation to the overall project. Clinical personnel who provide information to patients about the clinical services being studied under each approach are not considered to be engaging in research and will not be tracked as to whether they have appropriate training in the conduct of human research. We will also clearly delineate between patient *assent* processes (giving assent to provide contact information to the research team) — for which research training is not required — and *consent* processes (being informed about risks and benefits, asking questions, and providing consent to use data). Consent will only be obtained by personnel who have appropriate research training.

## 8.4 Deviations/Unanticipated Problems

### Protocol Deviations

This is a minimal risk study, and we do not expect protocol deviations to impact participant safety. In the unlikely event that a protocol deviation occurs that may impact participant safety, it will be reported to the IRB and the DSMB within 48 hours of the Principal Investigator becoming aware of the event. Other protocol deviations will be logged and reported to the IRB and DSMB as part of periodic reports and continuing review requests. The log will be maintained by the Project Manager and will include date, description of deviation, impact on participants, and remediation actions. Examples of protocol deviations that could occur in this study are:

- Enrollment of an ineligible participant
- Failure to obtain informed consent
- Data collection outside study windows
- Mishandled data

### Unanticipated problems

Unanticipated problems are defined as any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
- Related or possibly related to participation in the research. 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
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Unanticipated problems will be reported to the IRB and the DSMB within 48 hours of the Principal Investigator becoming aware of the problem. They will be logged by the Project Manager, as for protocol deviations, and included in periodic reporting to the IRB, DSMB, and PCORI.

## 8.5 Data Collection

### Code link and separate storage of data

To better ensure confidentiality, patient research data will be stored in several separate secure REDCap databases:

1. The first database will contain patient PHI and other information collected from the medical record under a HIPAA waiver of authorization and a waiver of consent. This database will include indirect identifiers, as described in section 8.1.
2. The second database will contain patient survey data. No identifying information will be stored in this database.
3. The third database will contain information needed by the Advarra payment system to pay participant incentives. This includes direct identifiers.
4. The fourth database will contain patient/family/care partner contact information for use in administration of remote surveys and interviews.
5. The fifth database will contain data from the ExPAND Research Team interviewers. This includes interview completion status, interviewer/interviewee information, and date of the interview.

All enrolled patients will be assigned a unique study identification number. All data collected will be identified only by these study identification numbers, which will be used to link patient and care partner data between the REDCap databases. A site-specific link between each study identification number and participant name will be kept in a password-protected file on a password protected computer at each participating site. (More information about secure management of the code link and data can be found in sections 8.3, 8.9, and 8.10.)

#### Collection of patient and care-partner information

See section 7.3 for study procedures including schedule of study activities.

- Chart audit and participant tracking data (with indirect patient identifiers, mainly dates) will be entered by site RC directly into REDCap database 1.
- DCS survey data (completely deidentified) will be entered into a REDCap database 2 by the RC or directly by the patient (for patients who choose to take the survey electronically).
- Information needed for payment of patient incentives (including direct identifiers) will be entered by site RC directly into REDCap database 3.
- Patient/family/care partner contact information will be entered by the RC into REDCap database 4, to keep identifying information separate from deidentified survey responses and partially deidentified medical record data.
- For the ATP patient and family/care partner telephone interviews, the ExPAND Team interviewers will enter information pertaining to interview completion status into REDCap database 5.

- All recordings and transcripts of the longitudinal and bereavement interviews will be kept in the GW Box.
- De-identified interview transcripts will be imported to GWU's NVivo for thematic analysis.

Alternatively, the RC may use paper documents temporarily for participant tracking and data collection. In that case, data will be transcribed to GW Box in a timely manner. Paper documents will be secured in a locked cabinet at the clinical site until they are no longer needed and then shredded.

#### Collection of clinic employee information

- Employee survey data will be stored on GW Box or other platform approved for regulated data by GWU.

#### Collection of baseline chart audit data

Prior to the beginning of the intervention (Approach 1), or as soon as possible thereafter, local RC will conduct a retrospective chart audit to assess key outcomes at baseline (prior to intervention Approach 1). Patients seen in the clinic between 1/1/2023 and 1/31/2024 will be retrospectively screened for study eligibility using the same criteria as for the main study. The charts of eligible patients will be reviewed from the date of eligibility to six months later. The following outcomes will be recorded: referral to KDE (y/n, eGFR at referral), attendance at KDE (y/n), advance care planning documentation (y/n), treatment decision (choice), start of treatment, if applicable (y/n, treatment, number of days after eligibility), death or loss to follow-up (number of days after eligibility). For patients who chose an alternative treatment plan, the follow-up period will be through July 31, 2024 for the following additional outcomes: death (number of days after eligibility), place of death, dialysis start (number of days after eligibility, setting). In addition to the outcomes data, the RC will record the patient's age, gender, race, ethnicity, whether the patient has decision-making capacity, and the most recent eGFR at the time of eligibility. All data will be completely deidentified: ages > 90 years will be recorded as 90, and all dates will be reported as the number of days from becoming eligible. Deidentified data will be entered into REDCap.

### **8.6 Data Quality Assurance**

With the use of video-conferencing and instructional documents, site RCs will be trained in study protocol and data collection procedures. In addition, the data management team will correspond regularly with site RCs to answer questions and solve problems.

Data will be entered into REDCap, which has built-in mechanisms to minimize typos, encourage data entry in the correct format, flag missing data, and apply customized data quality checking in real time. Data will be regularly monitored by the data management team using human assessment as well as customized software to check for missing, improperly formed, or implausible data in the context of the study. Data quality reports will be sent regularly to the data

collection personnel at the clinical sites, who will work with the data management team to correct missing and erroneous data.

### **8.7 Study Records**

The following study records will be maintained by the ExPAND Project Manager

- Regulatory documents (IRB applications and approvals, approved documents)
- Reports to the funder (PCORI)
- Reports to and from the DSMB
- Study protocol

The following study records will be maintained by the RC at each clinical site

- Consent forms
- Code link

The following study records will be maintained in REDCap or on GW Box by the ExPAND data management team

- Case report forms
- Patient data collected from the medical record
- Patient contact and payment information (with permission)
- Survey responses (with written or verbal consent)
- Interview completion status (REDCap)
- Interview recordings and transcripts (GW Box)

### **8.8 Access to Source**

Data will be collected from four sources:

1. Patient medical record: collected by site RC and entered into REDCap
2. Patient surveys
  - a. DCS survey responses collected by RC and entered into REDCap, or entered directly by participant (if taking the survey electronically)
3. Employee surveys
  - a. Surveys: responses entered directly into REDCap or U.S. mailed to central data management team

4. Semi-structured interviews: recorded by interviewers, transcribed, and stored securely on GW Box or another GWU-approved platform approved for regulated data

### **8.9 Data or Specimen Storage/Security**

Most study data will be stored on a GWU-approved REDCap server. REDCap (Research Electronic Data CAPture) is a mature, secure, web-based application for building and managing online surveys and databases. Security measures include both electronic (encryption) and physical (monitored, restricted access) measures. It is the database platform of choice for all NIH Clinical and Translational Science Award (CTSA) awarded institutions and for other institutions who want to collect and store health-related research data securely. REDCap is HIPAA compliant.

Some study data, including semi-structured interview data, may be stored on another platform that has been approved by GWU for regulated data, such as the password-protected GW Box.

See section 8.3 for other information on how we will maintain data security and confidentiality.

### **8.10 Retention of Records**

After this study, we would like to do a follow-up study to see what happens with patients' health for up to 5 years after the end of the current study. If we obtain funding and approval for the follow-up study, we will retain the study records (listed in 8.7) until the completion of the follow-up study, including data analysis and dissemination of results.

At the completion of the follow-up study, or sooner if no follow-up study is done, we will completely deidentify the study patient data and add the deidentified data to a shared data repository, as required by PCORI. The code links at each participating nephrology practice site will then be destroyed (electronic records deleted). At the completion of the follow-up study, the clinic staff data will not be shared to the data repository and will be destroyed.

After completion of the studies, deidentified data, consent forms, and research records will be maintained for the period required by the Central IRB. Consents documents will then be shredded.

### **8.11 Study Monitoring**

Ongoing study progress is reported at least annually to the ExPAND Clinical Site Council, ExPAND National Advisory Council, ExPAND Data Safety and Monitoring Board, the Central IRB, and PCORI.

Mandatory reporting to PCORI occurs at least quarterly for pre-specified study milestones. Enrollment reports are submitted to PCORI monthly.

### **8.12 Data Safety Monitoring Plan**

The study will empanel a Data and Safety Monitoring Board (DSMB) to act in an advisory capacity to the PIs and to evaluate the progress of the study, including periodic assessments of

data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcomes. The DSMB will make recommendations to the PIs concerning the continuation, modification, or conclusion of the trial.

The DSMB will have multidisciplinary representation, including physicians from relevant medical specialties, biostatisticians, ethicists, clinical trialists, patients, and a person expert in racial and ethnic inequities in healthcare. The DSMB members shall be free of significant conflicts of interest (i.e., financial, intellectual, professional, or regulatory). A DSMB Charter for the study will be developed by the study team and approved by the DSMB members. Further details are in the attached *DSMB Charter* and *Data Safety Monitoring Plan* (Appendix).

The DSMB will meet in person or by Zoom:

- prior to recruitment to review and approve the study protocol
- every 12 months, at a minimum, to review study progress
- after the end of data collection

The Principal Investigators will attend these meetings, and minutes and any recommendations will be documented. The DSMB will review enrollment and attrition rates and advise the PIs on any potential risks as well as on any risk mitigation plans. The DSMB recommendations will be discussed with the PIs. All data will be reviewed for protocol adherence, including a data verification check that the appropriate outcome measures are given at the appropriate time points.

### **8.13 Study Modification**

Any modification to the protocol will be approved by the Central IRB before implementation. The IRB-approved revised protocol and other revised documents will be sent to the relying institutions per Central IRB protocol.

Modifications that increase risk for participants (not anticipated) will be brought to the Data Safety Monitoring Board for review.

Any major changes in overall research plan (as contrasted to changes in procedures) will be submitted to PCORI for approval.

### **8.14 Study Discontinuation**

Any decision about study discontinuation will be made in conjunction with the DSMB.

### **8.15 Study Completion**

After the last patient is enrolled for EHR data collection (with HIPAA waiver), chart data will be collected for up to six months. During this time, final surveys and interviews will be collected.

The data will then be analyzed, and the results reported to participants (unless they opted out during consent), stakeholders, and the public, via conferences and peer-reviewed journals. We have found that dissemination can take up to two years or more.

Study data, including data stored at GWU and code links maintained at each site, will be retained, shared (deidentified data only), and eventually destroyed as described in section 8.10.

At this point, final reports will be made to the IRB and DSMB, and the study will be closed.

#### **8.16 Conflict of Interest Management Plan**

The independence of this study from any actual or perceived influence, such as by the dialysis industry, 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 trial. The study leadership in conjunction with the appropriate conflict of interest review committee 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.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed following the procedure outlined in the George Washington University Conflict of Interest Policies. A conflict management plan will be established according to GW policy and reviewed by appropriate Dean and approved by the study sponsor prior to participation in this study. All investigators will follow the applicable conflict of interest policies. As needed, the PI's will consult with the GW Office of Ethics, Compliance, and Risk for guidance on any conflict of interest issues.

#### **8.17 Funding Source**

This study is funded through a contract from the Patient Centered Outcomes Research Institute (PCORI).

Contract title: Expanding Patient Choice in Kidney Failure Treatment, Contract #: IHS-2022C2-27678

#### **8.18 Publication Plan**

Abstracts for Scientific Meetings of Professional Societies

1. Abstracts will be submitted to annual scientific meeting of the American Society of Nephrology and the spring clinical meeting of the National Kidney Foundation
2. Abstracts with palliative medicine outcomes will be submitted to the annual assembly of the American Academy of Hospice and Palliative Medicine

3. Abstracts will be submitted to the annual American Nephrology Nurses Association National Symposium

Papers submitted to peer-reviewed journals will have authorship pre-specified by the ExPAND publication committee. The plan for peer reviewed publications include, but is not limited to the following:

#### Trial background:

- 1) Background paper (see for example from PREPARE trial:  
<https://pubmed.ncbi.nlm.nih.gov/32940683/>)
- 2) Protocol paper (see for example from PREPARE trial:  
<https://pubmed.ncbi.nlm.nih.gov/39420412/>) (submit towards end so have final protocol--- but must publish before end of trial)
- 3) Development of Approach 1 - KDE intervention material, training of nephrology clinicians
- 4) Paper on adapting training and materials (handouts, slides, and video) to patients-results from focus groups and national patient advisory group-what does it mean to be culturally tailored and patient-centered from the patients' perspective
- 5) Development of Approach 2 – how to launch an ACTIVE KSC program

#### Results

- 6) Aim 1 – results – primary outcomes – impact of approach 1 vs approach 2 on treatment choice and on decisional conflict
- 7) Aim 1 – results – Additional secondary and exploratory outcomes that didn't fit in main results paper
- 8) Aim 2- results – descriptive Aim 2 outcomes – especially EOL outcomes – do they differ between approaches
- 9) Aim 2 – qualitative results – description of patient experience during AMC (some comparison between approach1 vs approach 2 – but mostly describe longitudinal experience)
- 10) Aim 2 – qualitative results of bereaved family interviews –
- 11) Aim 3- evaluation of implementation of interventions (NORC takes lead on this paper).

#### Implementation

- 12) “lessons learned” from all the site PI's on what it takes to change SDM, implement KSC in real world
- 13) Implementation models paper – if different types of implementation models emerge, we could write about variations – like NP-led vs nephrologist led KSC or other different workflows that emerge
- 14) NORC paper on application of implementation science to real-world nephrology practices

Other manuscripts as topics of interest to publication committee are identified.

Lay press dissemination plan to be developed in conjunction with advisory groups and publication committee.

Final Report to PCORI

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Table 5.2.2.B Secondary Outcomes for Aims 2 and 3	5.2.2 Secondary and Exploratory Outcome Variables (if applicable)
Table 6.1.1 Number of Participants	6.1.1 Number of Participants
Table 7.1.3 Validated Instruments	7.1.3 Selection of Instruments/Outcome Measures
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## LIST OF CHARTS

Title	Section
Stepped Wedge Design	5.1 General Design Description
Alternative Treatment Plans	2 Background
Two Approaches to Offering ATP	4.2 Primary Objective

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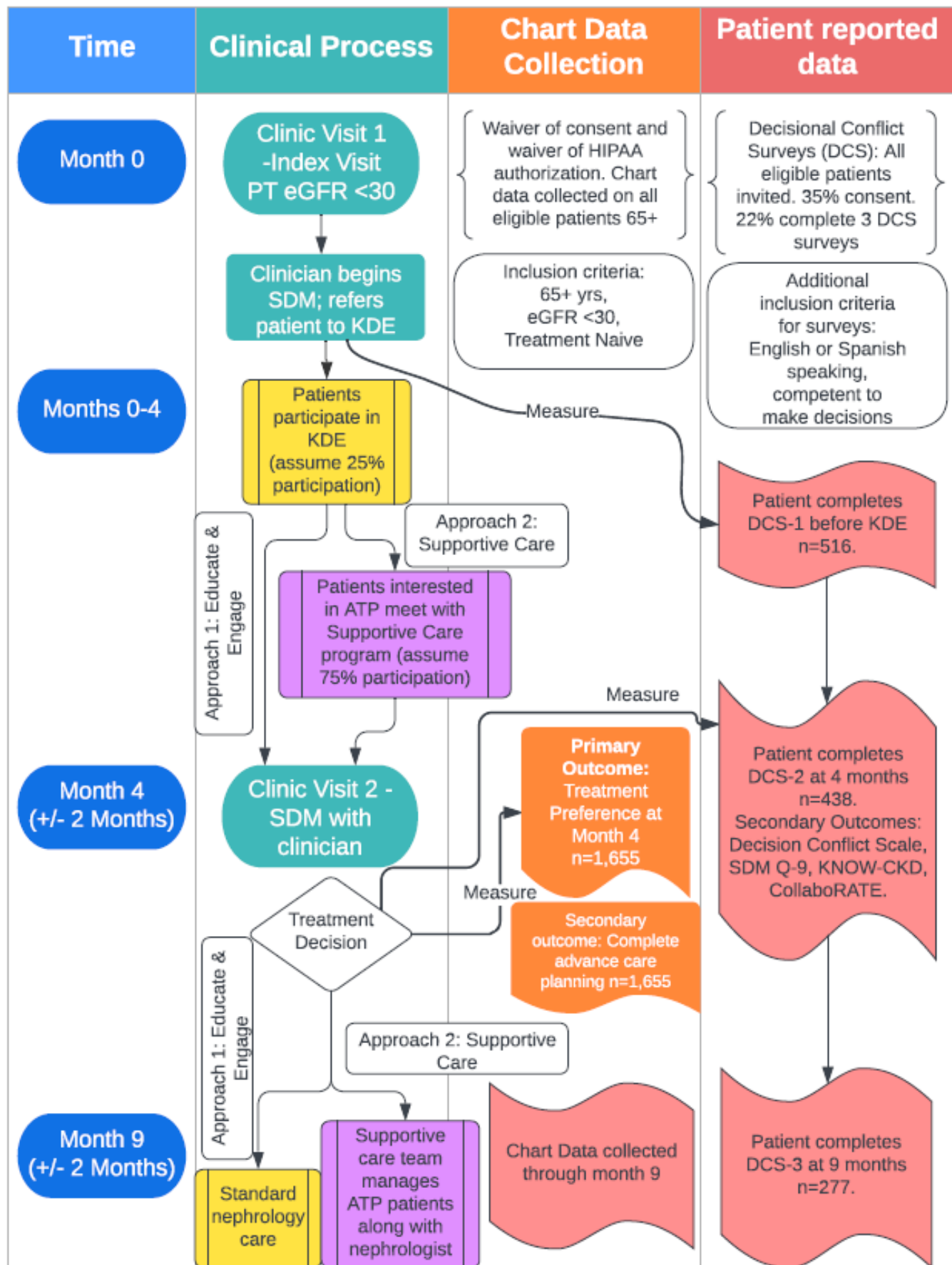
**APPENDICES**

#	Title	Section	Topic
1	Flowchart of Study Activities and Outcomes	Synopsis	Study Flow Chart (Optional)
2	ExPAND Adverse Event Reporting Guidelines	7 Methods	7.2.3 Adverse Events Definition and Reporting
3	Informed Consent Form for Patient DCS Survey	7 Methods	7.3.2 Informed Consent
4	Recruitment Letter/Email to Patients for DCS Survey	7 Methods	7.3.2 Informed Consent
5	eConsent REDCap Script	7 Methods	7.3.2 Informed Consent
6	Patient and Care Partner Information Sheet for Aim 2 Interviews	7 Methods	7.3.2 Informed Consent
7	Addendum to Patient ICF – Contact Info	7 Methods	7.3.2 Informed Consent
8	Data Safety Monitoring Plan	8 Trial Administration	8.12 Data Safety Monitoring Plan
9	DSMB Charter	8 Trial Administration	8.12 Data Safety Monitoring Plan

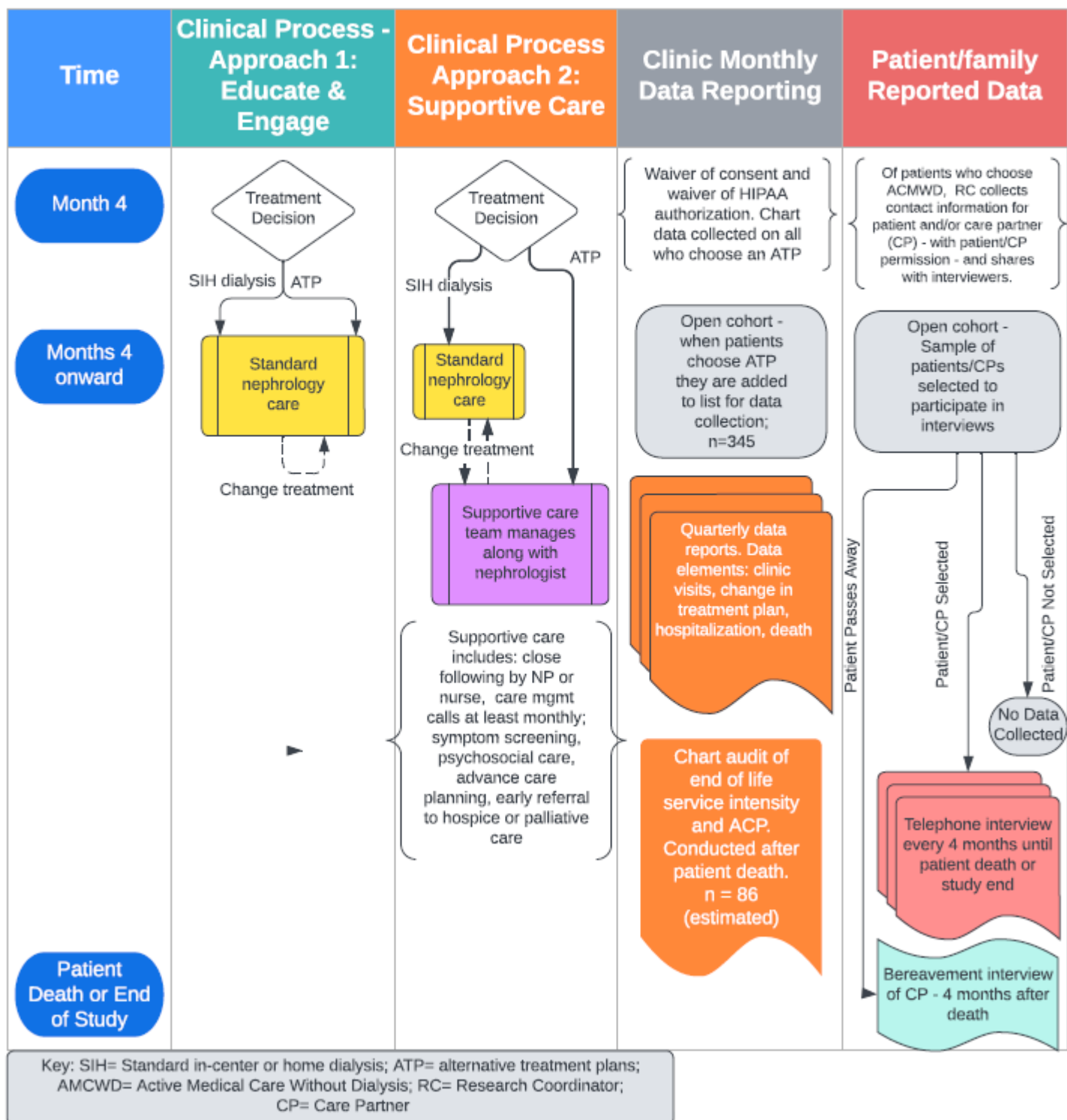
# **Appendix 1**

## **Flowchart of Study Activities and Outcomes**

## Aim 1 - Intervention and data collection in stepped wedge randomized trial



**Aim 2 - Intervention and data collection in descriptive and qualitative observation of patients who choose ATP or Deciding not to Decide**



## **Appendix 2**

### **ExPAND Adverse Event Reporting**

# ExPAND Working Instructions:

## Adverse Event and Serious Adverse Event Reporting

### Version 3.0 – 11/1/2024

- This document must be kept within the Site Investigator File
- Updates will be sent to centers periodically

### Amendment History

Version no.	Date issued	Details of changes made
1.0	9/20/2023	
2.0	3/22/2024	Prompt reporting requirement changed from unexpected or related SAE to unexpected and related SAE.
3.0	11/2/2024	Reporting requirement changed from reporting <u>all</u> AEs in REDCap to reporting <u>only</u> AEs <b>related</b> to the intervention or research procedures.

## 1. Safety reporting overview

No serious adverse events related to this minimal risk study are anticipated. However, to be comprehensive in our monitoring of adverse events, we have developed detailed policies and processes for monitoring and reporting adverse events. The key feature is distinguishing between adverse events that may be related to the study interventions from adverse events that are likely to happen in the study population but are unrelated to the study interventions. Local site PI's will assess all serious events and all unexpected events to determine whether or not they are related to study participation.

Due to the nature of advanced CKD and its treatment, especially in multi-morbid frail older people, SAEs would be expected to occur frequently throughout the course of the disease. These expected SAEs include:

- Abnormal electrolyte and hematological laboratory results that can be explained directly or indirectly by their advanced CKD
- Hospital admissions – elective and emergency – that can be explained directly or indirectly by their advanced CKD or comorbidities
- Hospice admissions – planned and emergency – that can be explained directly or indirectly by their advanced CKD or comorbidities
- Infections and cardiovascular events, including fluid overload and swelling, that can be explained directly or indirectly by their advanced CKD or comorbidities
- Commencement of dialysis
- Death that can be explained directly or indirectly by their advanced CKD or comorbidities

Given the high frequency of SAEs expected, the ExPAND trial utilizes the following risk-adapted safety reporting approach.

**Prompt Reporting:** These AEs must be reported on the AE form to the Principal Investigator within 24 hours of when the site becomes aware of the event:

- SAEs categorized as **causally related** to the intervention or research procedures.
- AEs (whether serious or not) categorized as **unexpected and causally related** to the intervention or research procedures.

**Other Reporting:** These will be regularly reviewed by the study team, the IRB, the Data Safety Monitoring Board, and the sponsor.

- All AEs (whether serious or not) categorized as **causally related** to the intervention or research procedures should be reported in REDCap.

## 2. Definitions

### Adverse Event (AE)

Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the intervention or to participation in research. AEs include both physical and psychological harms.

## Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening (actually, not hypothetically)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

Other ‘important medical events’ may also be considered serious if they jeopardize the participant or require an intervention to prevent one of the above consequences.

## 3. Collection and classification of AE data

Sites are requested to conduct an assessment of whether hospitalizations, deaths, and other AEs are expected and of whether they are causally related to the study procedures or treatment. These assessments need to be conducted by site PI. Guidance on conducting these assessments is provided in the remainder of this document.

Information on AEs and SAEs categorized as **causally related** to the intervention or research procedures should be reported in REDCap. This includes:

- Hospitalizations
- Deaths
- Other AEs

Within REDCap, sites should document their assessment of the event’s expectedness and of its relatedness (to the study procedures or treatment).

### Related events

Events are related if they resulted from administration of any of the procedures required by the ExPAND protocol. Relationship is described using the following categories:

- Definitely related
- Probably related
- Possibly related
- Unlikely to be related
- Not related

Events that are expected to occur in people with advanced CKD (see below) may be categorized as “Not related” to the research procedures unless there is reason to believe otherwise.

### Expected events

Events are expected if they are listed in the protocol (7.2.3) as an expected AE.

**Appendix 1** sets out a more detailed breakdown of events that are expected to occur in people with advanced CKD to assist in the classification of whether an event is expected.

This list is not meant to be exhaustive, but rather illustrative of the types of events that are expected. If an event is not listed in Appendix 1, please seek advice from the trial team and principal investigator before a decision is made.

#### 4. What events need prompt reporting as an AE or SAE?

- Any inpatient stay in hospital or death classified as definitely, probably, or possibly **related** to the intervention or the research procedures.
- Any AE classified as definitely, probably, or possibly **related and unexpected**.

All other **research-related** AEs are collected in the REDCap database.

Due to the benign nature of the study, study-related and unexpected SAEs are likely to be rare. An example would be psychological harm or distress related to participation in the trial, for example as a result of decision conflict, resulting in hospitalization or death.

#### 5. Reporting procedures for promptly reportable AEs

- AEs occurring from the time of consent until 30 days after the end of the trial must be reported
- Central trial team must be notified within **24 hours** of site being made aware
- Document the AE in REDCap
- Send an email to the study Principal Investigator and Study Manager notifying them of the event and providing the study ID of the patient.
- **Email (marked URGENT) to: Dale Lupu ([dlupu@gwu.edu](mailto:dlupu@gwu.edu)) and Matthew Ryan ([m.ryan@gwu.edu](mailto:m.ryan@gwu.edu))**
- **Receipt will be confirmed. Please follow up for confirmation if not received.**
- Any change of condition or other follow-up information relating to a previously reported AE should be documented in REDCap as soon as available. Study Principal Investigator and Study Manager should be notified.
- Events must be followed up until the event has resolved or a final outcome has been reached.

**Appendix 1. An illustrative list of events that would be considered as expected SAEs due to advanced CKD and common comorbidities**

Death or admission to hospital related to:

<b>Cardiac/Cardiovascular</b>  <i>Diagnoses</i> Hypertension Angina Chest pain, MI ruled out Acute myocardial infarction (MI) Cardiac arrest/sudden death Congestive heart failure Cardiomyopathy Valvular heart disease Atrial fibrillation Other arrhythmia Pericarditis &/or tamponade Hypotension  <i>Procedures</i> Cardiac catheterization Coronary angioplasty Coronary bypass graft (CABG) Valve repair or replacement Cardioversion Cardiac defibrillator placement Pacemaker placed Pericardial procedure	<b>CKD and Dialysis-Related<sup>†</sup></b>  <i>Diagnoses</i> Hyperkalemia Fluid overload PD peritonitis <sup>†</sup> Peritoneal catheter complication <sup>†</sup>  <i>Procedures</i> Extra dialysis treatment <sup>†</sup> Peritoneal catheter insertion/removal <sup>†</sup>	<b>Endocrine/Metabolic</b>  <i>Diagnoses</i> Hyperparathyroidism Diabetes complication (e.g., DKA) Thyroid disease Hypercalcemia Hypothyroidism  <i>Procedures</i> Parathyroidectomy
<b>Eye, Ear, Nose, Throat</b>  <i>Diagnoses</i> Diabetic retinopathy Cataract Glaucoma Blindness Epistaxis  <i>Procedures</i> Retinal laser surgery Cataract extraction	<b>Gastrointestinal</b>  <i>Diagnoses</i> GI bleed Gastritis/Peptic ulcer disease Gastroenteritis Abdominal pain Diarrhea Bowel obstruction Diverticulitis Malnutrition/cachexia Nausea/vomiting Other  <i>Procedures</i> OGD (upper GI endoscopy) ERCP Colonoscopy Gastric surgery Hernia repair Colectomy/colon surgery Appendectomy Parenteral nutrition	<b>Health investigation</b>  <i>Procedures</i> Diagnostic Tests unrelated to the HD/ HDF process
<b>Hematologic</b>  <i>Diagnoses</i> Anemia	<b>Infectious Diseases</b>  <i>Diagnoses</i> Pneumonia	<b>Liver, Biliary, Pancreas</b>  <i>Diagnoses</i> Viral hepatitis

<p><i>Procedures</i> Blood transfusion Bone marrow biopsy</p>	<p>Septicemia Endocarditis AIDS/HIV Urinary Tract Infection Wound Infection Abscess Meningitis Cellulitis/soft tissue infection Osteomyelitis Viral infection Fungal infection Fever or chills, source unknown</p> <p><i>Procedures</i> Abscess Drainage</p>	<p>Liver Failure Ascites Pancreatitis Gall bladder disease</p> <p><i>Procedures</i> Liver biopsy Liver surgery Gall bladder surgery Pancreas surgery</p>
<p><b>Musculoskeletal</b></p> <p><i>Diagnoses</i> Carpal tunnel syndrome Dialysis amyloidosis (B2-microglobulin deposition) Infectious arthritis</p> <p><i>Procedures</i> Carpal tunnel release (surgical)</p>	<p><b>Neoplastic/Cancer</b></p> <p><i>Diagnoses</i> Benign tumor Cancer, non-metastatic Cancer, metastatic Multiple myeloma Lymphoma/leukemia</p> <p><i>Procedures</i> Surgical resection Chemotherapy Radiation therapy</p>	<p><b>Neurologic/Cerebrovascular</b></p> <p><i>Diagnoses</i> Seizure Dementia Mental status change/confusion TIA Stroke (CVA) – hemorrhagic Stroke (CVA) – ischemic Stroke (CVA) – type unknown Subdural hematoma</p> <p><i>Procedures</i> Carotid revascularization Carotid endarterectomy Evacuation of hematoma</p>
<p><b>Obstetric/Gynecologic/Breast</b></p> <p><i>Diagnoses</i> Abnormal bleeding Breast disease Other</p> <p><i>Procedures</i> Breast Biopsy Hysterectomy</p>	<p><b>Orthopedic</b></p> <p><i>Diagnoses</i> Hip Fracture Other fracture Herniated intervertebral disk Other</p> <p><i>Procedures</i> Fracture repair Hip replacement Other joint replacement</p>	<p><b>Psychiatric/Mental Health</b></p> <p><i>Diagnoses</i> Depression * Suicide attempt * anxiety disorder * Alcohol abuse Substance abuse Psychosis</p>
<p><b>Pulmonary</b></p> <p><i>Diagnoses</i> Chronic Obstructive Pulmonary Disease Asthma Bronchitis Pneumonia Hemoptysis Pleural effusion Pulmonary oedema Respiratory Failure/ Arrest Shortness of breath</p>	<p><b>Skin</b></p> <p><i>Diagnoses</i> Psoriasis Cellulitis/Skin infection Calciphylaxis Rash</p>	<p><b>Social/Rehabilitation</b></p> <p><i>Diagnoses</i> Placement issues Failure to thrive Fall Rehabilitation Hospice/palliative care</p>

Pulmonary embolism  <i>Procedures</i> Ventilator-assisted breathing Bronchoscopy Thoracentesis		
<b>Transplant-Related</b>  <i>Diagnoses</i> Transplant evaluation Other  <i>Procedures</i> Kidney transplant Transplant nephrectomy	<b>Trauma/Injury</b>  <i>Diagnoses</i> Death Other  <i>Procedures</i> Laparotomy Skin graft	<b>Urologic</b>  <i>Diagnoses</i> Hematuria Renal cysts Kidney stone Other  <i>Procedures</i> Cystoscopy Prostate surgery Nephrectomy
<b>Vascular</b>  <i>Diagnoses</i> Claudication/Rest pain Ulcer of extremity Gangrene Aortic aneurysm Deep vein thrombosis Other  <i>Procedures</i> Angiogram Arterial bypass surgery Amputation Aortic aneurysm repair Wound debridement	<b>Vascular Access</b>  <i>Diagnoses</i> Clotted access <sup>†</sup> Infected access <sup>†</sup> Aneurysm <sup>†</sup> Failing access <sup>†</sup> Access bleeding <sup>†</sup> Other  <i>Procedures</i> Salvage procedure <sup>†</sup> Revision procedure <sup>†</sup> New access creation <sup>†</sup> Access removal <sup>†</sup> Catheter placement <sup>†</sup>	
<b>Other/Miscellaneous</b>  <i>Diagnoses</i> Drug reaction/allergy		

\* Unless thought to be related to participation in the trial.

<sup>†</sup> Dialysis related

## **Appendix 3**

### eConsent REDCap Script

# Informed Consent for Participation in a Research Study

This form gives you important information you need to know about the ExPAND study before you decide if you want to take part. The research coordinator will talk to you about the study and answer all of your questions.

We encourage you to discuss this study with your family and anyone else you trust before making your decision. It's important that you have as much information as you need and that all your questions are answered.

---

This is a placeholder for the content of the informed consent for participation in a research study for patients.

The electronic ICF(s) will be a complete and exact copy of the current, site-specific, IRB approved study consent document(s) and will be updated to match IRB-approved revisions.

## Signature

**By signing below, you agree that the above information has been explained to you and you have had the chance to ask questions. Your signature documents your permission to take part in this research.**

First name of adult participant

---

Last name of the adult participant

---

Check one payment method:

- ☐ Reloadable debit/credit card  
☐ Electronic deposit into my bank account  
☐ Paper check delivered by US mail

Enter email address:

---

Advarra will send you an email at this address to set up payment.

Do you want to receive newsletters about the study?  
other Check one:

- ☐ I do not want to receive newsletters and information about the study.  
☐ I give my permission for you to send me emails with newsletters and other information about the study.

Please enter the identification code provided to you by the research coordinator:

---

Electronic signature of participant

Please type your full name:

---

(For example, Mary Smith)

Date and time of  
signature

---

(Click the 'NOW' button to enter the time and date automatically)

## AFFIDAVIT OF PERSON OBTAINING CONSENT:

I certify that I have explained to the above individual the nature and purpose of the study, possible risks, and potential benefits associated with participation in this study.

I have answered any questions that have been raised.

Name of the person obtaining consent:

☐  
☐

---

CKD clinic (office) where patient seen:

Clinic A  
Clinic B

---

Electronic signature of the person obtaining  
consent. Please type your full name in the box to

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the right.

Date and time of  
signature:

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(Click the 'NOW' button to enter the time and  
date automatically)

## **Appendix 4**

### Data Safety Monitoring Plan



## **Data Safety and Monitoring Plan**

**Study Title:** Improving Shared Decision-Making and Access to Non-Dialytic Treatment for People with Kidney Disease (the ExPAND study)

**Sponsor:** Patient-Centered Outcomes Research Institute (PCORI)

**Contract Number:** IHS-2022C2-2678

**Principal Investigator:** Dale E. Lupu, PhD, MPH, Alvin H. Moss, MD, FACP, FAAHPM

**Site Investigator:** Dale E. Lupu, PhD, MPH

**Institutions:** George Washington University, West Virginia University

Version 2 – 11-01-24  
Submitted to PCORI for Approval  
Approved by the DSMB

## **Brief Description of Interventions**

The interventions being studied are Approach 1: Educate and Engage and Approach 2: Educate and Engage + Kidney Supportive Care in older patients with advanced chronic kidney disease. Approach 1 provides kidney disease education covering both dialysis and non-dialysis options in an unbiased way using a shared decision-making (SDM) approach and patient decision aids while Approach 2 includes these as well as the creation of a kidney supportive care program for patients who choose alternative (non-dialysis) treatment plans (ATPs).

## **Specific Aims**

**Aim 1.** Compare the effectiveness of two approaches: 1) improved kidney disease education (KDE) and SDM or 2) improved KDE and SDM plus the creation of a kidney supportive care program in a) increasing proportion of patients choosing ATP and b) reducing patient decisional conflict.

**Aim 2.** Compare the patient and family/care partner experience of an ATP between Approach 1 and Approach 2, with particular emphasis on TLT and AMCWD in terms of quality of life, services used, and end-of-life experience through medical record review and interviews with a sample of bereaved family members/care partners. Aim 2a will focus on experience while patients are receiving an ATP (several months to several years). Aim 2b will describe the end-of-life experience.

**Aim 3.** In order to evaluate implementation of each intervention (Approaches 1 and 2), the ExPAND research team will cooperate with a separate tandem evaluation conducted by an independent evaluation team based at NORC. The implementation evaluation is a mixed-methods design based on the expanded Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework. The implementation evaluation will consist of staff surveys, interviews, and site visits conducted by the NORC evaluation team. Regulatory oversight of AIM 3 will be handled by the NORC IRB.

## **Brief Description of Project Design**

This will be a repeated cross-sectional stepped wedge cluster-randomized trial (SW-CRT) with randomization at the nephrology clinic level. Twenty-five clinics will be randomly assigned to one of three sequences. Each sequence consists of four 10-month time periods during which patients are accrued and followed for study outcomes. To minimize contamination in the primary analysis, we will exclude patients recruited during the 4 months before each sequence moves to



Approach 2. These patients will be included in a sensitivity analysis. In the 4th study period, accrual of new patients will stop at 10 months, allowing a closing 4-month follow-up period to collect primary outcomes at the end of the study. All practices begin by implementing Approach 1 (Educate and Engage). Practices then "step" into Approach 2 (Kidney Supportive Care Program) at the assigned time based on their sequence. We have prepared for 15% drop-out of sites, leaving 21 sites in the final analysis sample. We expect to recruit approximately 2800 patients (1400 under Approach 1 and 1400 under Approach 2). Patients at least 65 years and with eGFR recently having dropped below 30 will be included in the study.

We will also recruit 35 family members/care partners of patients who chose ATP to be interviewed about their experiences.

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## 1.0 PARTICIPANTS SAFETY

This study includes three types of participants: *patient* participants, *care partner* participants, and nephrology *clinic employee participants*. Any mention of medical information below only applies to the *patient* participants. Caregiver participants and clinic employee participants are not the target of the intervention, and the study team will not be collecting any sensitive information about them.

### 1.1. Potential Risks and Benefits for Participants

#### 1.1.1. Potential risk and protections against risks

*Patients:* Because this study is implementing recommended best practices in the care of older patients with advanced chronic kidney disease, there are no anticipated major risks associated with it. Clinicians will employ recommended communication approaches and ask for permission to provide information about the patient's kidney disease and possible treatment options before doing so. Nonetheless, some patients might experience distress once informed that they have advanced chronic kidney disease if they were not previously aware of it. This distress is comparable to that experienced by patients in routine clinical practice who receive bad news. This study may differ from standard care in that patients might become better informed and more aware of the range of treatment options they have. Also, in taking the Decisional Conflict Scale and other surveys, they might realize more clearly that they don't know 1) what are the benefits of treatment that matter most to them, 2) what risks and side effects are most troublesome to them, and 3) overall, what treatment option is best for them. Interviewers will be trained to watch for indications of emotional distress and will be trained in how to respond calmly and empathetically. If the situation persists or worsens, the interview will be terminated, and the incident will be reported within 24 hours to the patient's treating clinician, who will develop a plan for supporting the patient including referral for further mental health services, as indicated.

*Care partners and clinic employees:* The main risk to these participants is loss of confidentiality of research data. Specific steps to minimize these risks are described below.

Before data collection starts, all study personnel will be required to undertake appropriate Collaborative Institutional Training Initiative (CITI) coursework, including Human Subjects Research and Health Information Privacy and Security training. All staff will complete an IRB approved training program developed by the study PIs. This training will include modules covering: (1) study overview, (2) recruitment procedures, (3) study arm procedures, (4) collection and management of study data, and (5) adverse event reporting and managing emergencies. The trial will be registered on ClinicalTrials.gov and the George Washington University (GWU) IRB will be the IRB of record. Participant recruitment will begin at each site only after that site's clinical trials office (or equivalent) has approved the study materials containing IRB-approved protocol, surveys, and data collection instruments. The following sections provide a detailed overview of our specific efforts to minimize risks including risks to privacy and confidentiality:

- 1) The majority of patient and care partner participant information collected for this project will be stored in a GW REDCap database, GW Box, or other GWU platform approved for regulated data. An additional copy of the site-specific study data may be housed securely at each participating site.
- 2) Patient chart data collected from the EMR under a HIPAA waiver of consent will only be shared with CITI-trained researchers from GWU, and will be stored securely at GWU as described above.
- 3) All enrolled patients will be assigned a unique study identification number. All data collected will be identified only by these study identification numbers. This will minimize risks regarding breach of confidentiality with respect to the study data. A site-specific link between each study identification number and participant name will be kept in a password-protected file on a password-protected computer at each participating site.
- 4) Before any patient is invited to participate in surveys or interviews, the patient's treating nephrologist or advance practitioner will have the opportunity to opt-out the patient. Reasons for exclusion include insufficient decision-making capacity, lack of proficiency with English or Spanish language, anticipated loss to follow-up, or if otherwise contra-indicated for the patient's health. The research assistant may also opt-out a patient if similar information is available in the EMR.
- 5) Printed forms with identifiable participant data, e.g., signed consent forms, will be stored in separate file folders in locked filing cabinets at each clinic site.
- 6) No medical records or protected health information (collected for the patient participants only) shall be re-disclosed, unless required by law.
- 7) After completion of the study, the completely deidentified research data from this project will be deposited with the digital repository, the Patient-Centered Outcomes Data Repository (PCODR), of the Inter-university Consortium for Political and Social Research (ICPSR), University of Michigan to ensure that the research community has long-term access to the data. This is required by PCORI and included in consent forms.

Avoiding undue influence or coercion in recruitment:

*Patients and care partners:* Information from the electronic medical record (EMR) will be collected on all eligible patients with a HIPAA waiver of consent. Participation in surveys and interviews is voluntary. Patients, family members, and care partners will be informed that participation is voluntary and that all patients, regardless of their participation status, will continue to receive standard care. They will be informed that they may stop participating at any time without penalty. Research staff will not provide final lists of participants to the nephrology center providers or staff. Therefore, in general, the people delivering patient care will not be aware of whether an individual patient or care partner participated.

*Clinic employees:* The intervention is at the clinic level, and supervisors at each clinic will decide which employees will be asked to attend training and participate in implementation. Participation in the evaluation of the training is voluntary. Participants will be informed that their employment will not be affected in any way by their participation status and that they may stop participating at any time without penalty. In summary reports to sites, participants will not be identified; however, due to the small sample sizes, it is possible that participant identities may be inferred in some cases.

### **1.1.2.Potential benefits**

Because this study mirrors recommended best clinical practices such as the use of shared decision-making, patient decision aids, and kidney supportive care to address unmet palliative care needs in the population of older patients with advanced chronic kidney disease, the investigators believe that there will be significant benefits for the participants. These include being aware that they have a choice about treatment to make, being fully informed of all treatment options, participating as a co-equal in treatment decisions and the development of a treatment plan, being offered the opportunity to participate in advance care planning, being routinely assessed for symptoms and being treated for them, and being referred to palliative care and/or hospice in a timely manner as appropriate.

## **2.0 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING**

No serious adverse events related to this minimal risk study are anticipated. However, to be comprehensive in our monitoring of adverse events, we have developed detailed policies and processes for monitoring and reporting adverse events. The key feature is distinguishing

between adverse events that may be related to the study interventions from adverse events that are likely to happen in the study population but are unrelated to the study interventions. Local site PI's will assess all serious events and all unexpected events to determine whether or not they are related to study participation. Specific reporting timetables for reporting events are detailed in the appendix.

## **2.1. AE/SAE definitions and expected events**

*Adverse Event (AE):* Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, 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 (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice). AEs encompass both physical and psychological harms. AEs are assessed in terms of seriousness, expectedness, and relatedness.

*Serious Adverse Event (SAE):* An AE that meets any of the following conditions:

- results in death
- is life-threatening (actually, not hypothetically)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- Other 'important medical events' may also be considered serious if they jeopardize the participant or require an intervention to prevent one of the above consequences.

*Related Adverse Event:* An AE is "possibly related" to the research procedures if, in the opinion of the investigator, the research procedures may have caused the harm.

*Unexpected Adverse Event:* An AE is "unexpected" when its nature, severity or frequency is inconsistent with risk information previously reviewed and approved by the IRB in the context of the study population.

*Expected SAEs:* Due to the nature of advanced CKD and its treatment, especially in multi-morbid frail older people, SAEs would be expected to occur frequently throughout the course of the disease. These expected SAEs include:

- Abnormal electrolyte and hematological laboratory results that can be explained directly or indirectly by their advanced CKD or comorbidities
- Hospital admissions — elective and emergency — that can be explained directly or indirectly by their advanced CKD or comorbidities
- Hospice admissions — planned and emergency — that can be explained directly or indirectly by their advanced CKD or comorbidities
- Infections and cardiovascular events including fluid overload and swelling that can be explained directly or indirectly by their advanced CKD or comorbidities
- Commencement of dialysis
- Death that can be explained directly or indirectly by their advanced CKD or comorbidities

*Expected study-related AEs:* Because of the nature of this minimal risk study, no physical harms are expected. It is possible that patients might suffer psychological distress. Some patients may become emotionally upset when thinking about their disease progression or the decisions they are making about their treatment. In standard CKD patient care, patients also need to make decisions about what treatment they want. This study may differ from standard care in that patients might become better informed and more aware of the range of treatment options they have. Also, in taking the Decisional Conflict Scale and other surveys, they might realize more clearly that they don't know 1) what are the benefits of treatment that matter most to them, 2) what risks and side effects are most troublesome to them, and 3) overall, what treatment option is best for them. Interviewers will be trained to watch for indications of emotional distress and will be trained in how to respond (see 7.1.5 of the study protocol).

## 2.2. AE/SAE Documentation and Reporting

Detailed guidance will be provided to the Site Principal Investigator and research coordinator about AE/SAE reporting (see Appendix 2). **The Site Principal Investigator will assess the severity, expectedness, and relatedness of the AE, which will be reported accordingly.**

*Prompt reporting:* The Site Principal Investigator will report the following events to the study Principal Investigator within 24 hours of becoming aware of the event. The study Principal Investigator will report the AE to the Institutional Review Board (IRB) within 48 hours of becoming aware of the event.

- SAEs that are **causally related** to the research procedures
- AEs, including SAEs, that are both **unexpected and causally related** to the research

*Other reporting:* All adverse events categorized as **related** to the research procedures will be recorded in Research Electronic Data Capture (REDCap) by the research coordinator (date, description, severity, expectedness, relatedness, and management/remediation of AE). The central data management team will assemble a list and summary of AEs, which will be reported to the IRB, DSMB, study sponsor, and site principal investigators as part of periodic reporting.

### 3.0 DATA AND SAFETY MONITORING

*Data quality:* The site research coordinator, under the supervision of the site PI, is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Participant tracking and survey data will be entered directly into electronic case report forms in REDCap, and clinical data will be entered directly from the source documents (EMR) into REDCap. REDCap includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Data will be regularly monitored by the data management team using human assessment as well as customized software to check for missing, improperly formed, or implausible data in the context of the study. Data quality reports will be sent regularly to the data collection personnel at the clinical sites, who will work with the data management team to correct missing and erroneous data.

The study will empanel a Data and Safety Monitoring Board (DSMB) to act in an advisory capacity to the PIs and to evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcomes. The DSMB will make recommendations to the PIs concerning the continuation, modification, or conclusion of the trial.

#### 3.1. Frequency of Data and Safety Monitoring

A Data and Safety Monitoring Board (DSMB) will be appointed to provide additional oversight of the trial and will meet prior to recruitment to review the study protocol and at the end of data collection. The PIs will attend these meetings, with minutes and any recommendations documented. The DSMB will consist of nine members, including geriatric nephrologists, a health equity specialist, biostatisticians, a CKD patient, a CKD patient's family member, a nurse practitioner, and an ethicist. A DSMB Charter for the study will be developed by the study team and approved by the DSMB members. The DSMB will then meet by Zoom to review study progress at minimum, every 12 months throughout the project. The DSMB will review enrollment and attrition rates and advise the PIs on any potential risks as well as on any risk mitigation plans. The DSMB recommendations will be discussed with the PIs. All data will be reviewed for



protocol adherence, including a data verification check that the appropriate outcome measures are given at the appropriate time points.

## APPENDICES

## Appendix 1. Adverse Event Log

Adverse Event Type	Relatedness to Study Intervention Relationship	Expected	SAE	Outcome of Event
1. Emergency room visit 2. Hospital admission 3. Other medical emergency 4. Other medical event (non-emergency) 5. Psychological 6. Death 7. Hospice admission 8. Other	1 = Definitely related 2 = Possibly related 3 = Not related	1 = Yes 2 = No	1 = Yes 2 = No	1 = Resolved, 2 = AE still present- no treatment 3 = AE still present- being treated 4 = Unknown 5 = Death 6 = Other

Participant Study ID	Age	Sex	Adverse Event (Description)	Adverse Event Type	Start Date	Relatedness to Study Intervention	Expected	SAE	Response/ Remediation (Description)	Outcome of Event	PI Initials & Date
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## Appendix 2. ExPAND Working Instructions: Adverse Event and Serious Adverse Event Reporting

# ExPAND Working Instructions: Adverse Event and Serious Adverse Event Reporting Version 3.0 – 11/1/2024

- This document must be kept within the Site Investigator File
- Updates will be sent to centers periodically

## Amendment History

Version no.	Date issued	Details of changes made
1.0	9/20/2023	
2.0	3/22/2024	Prompt reporting requirement changed from unexpected or related SAE to unexpected and related SAE.
3.0	11/2/2024	Reporting requirement changed from reporting <u>all</u> AEs in REDCap to reporting <u>only</u> AEs <b>related</b> to the intervention or research procedures.

## 6. Safety reporting overview

No serious adverse events related to this minimal risk study are anticipated. However, to be comprehensive in our monitoring of adverse events, we have developed detailed policies and processes for monitoring and reporting adverse events. The key feature is distinguishing between adverse events that may be related to the study interventions from adverse events that are likely to happen in the study population but are unrelated to the study interventions. Local site PI's will assess all serious events and all unexpected events to determine whether or not they are related to study participation.

Due to the nature of advanced CKD and its treatment, especially in multi-morbid frail older people, SAEs would be expected to occur frequently throughout the course of the disease. These expected SAEs include:

- Abnormal electrolyte and hematological laboratory results that can be explained directly or indirectly by their advanced CKD
- Hospital admissions – elective and emergency – that can be explained directly or indirectly by their advanced CKD or comorbidities
- Hospice admissions – planned and emergency – that can be explained directly or indirectly by their advanced CKD or comorbidities
- Infections and cardiovascular events, including fluid overload and swelling, that can be explained directly or indirectly by their advanced CKD or comorbidities
- Commencement of dialysis
- Death that can be explained directly or indirectly by their advanced CKD or comorbidities

Given the high frequency of SAEs expected, the ExPAND trial utilizes the following risk-adapted safety reporting approach.

**Prompt Reporting:** These AEs must be reported on the AE form to the Principal Investigator within 24 hours of when the site becomes aware of the event:

- SAEs categorized as **causally related** to the intervention or research procedures.
- AEs (whether serious or not) categorized as **unexpected and causally related** to the intervention or research procedures.

**Other Reporting:** These will be regularly reviewed by the study team, the IRB, the Data Safety Monitoring Board, and the sponsor.

- All AEs (whether serious or not) categorized as **causally related** to the intervention or research procedures should be reported in REDCap.

## 7. Definitions

### Adverse Event (AE)

Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the intervention or to participation in research. AEs include both physical and psychological harms.

### Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening (actually, not hypothetically)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

Other 'important medical events' may also be considered serious if they jeopardize the participant

or require an intervention to prevent one of the above consequences.

## 8. Collection and classification of AE data

Sites are requested to conduct an assessment of whether hospitalizations, deaths, and other AEs are expected and of whether they are causally related to the study procedures or treatment. These assessments need to be conducted by site PI. Guidance on conducting these assessments is provided in the remainder of this document.

Information on AEs and SAEs categorized as **causally related** to the intervention or research procedures should be reported in REDCap. This includes:

- Hospitalizations
- Deaths
- Other AEs

Within REDCap, sites should document their assessment of the event's expectedness and of its relatedness (to the study procedures or treatment).

### Related events

Events are related if they resulted from administration of any of the procedures required by the EXPAND protocol. Relationship is described using the following categories:

- Definitely related
- Probably related
- Possibly related
- Unlikely to be related
- Not related

Events that are expected to occur in people with advanced CKD (see below) may be categorized as "Not related" to the research procedures unless there is reason to believe otherwise.

### Expected events

Events are expected if they are listed in the protocol (7.2.3) as an expected AE.

**Appendix 1** sets out a more detailed breakdown of events that are expected to occur in people with advanced CKD to assist in the classification of whether an event is expected.

This list is not meant to be exhaustive, but rather illustrative of the types of events that are expected. If an event is not listed in Appendix 1, please seek advice from the trial team and principal investigator before a decision is made.

## 9. What events need prompt reporting as an AE or SAE?

- Any inpatient stay in hospital or death classified as definitely, probably, or possibly **related** to the intervention or the research procedures.
- Any AE classified as definitely, probably, or possibly **related and unexpected**.

All other **research-related** AEs are collected in the REDCap database.

Due to the benign nature of the study, study-related and unexpected SAEs are likely to be rare. An example would be psychological harm or distress related to participation in the trial, for example as a result of decision conflict, resulting in hospitalization or death.

## 10. Reporting procedures for promptly reportable AEs

- AEs occurring from the time of consent until 30 days after the end of the trial must be

reported

- Central trial team must be notified within **24 hours** of site being made aware
- Document the AE in REDCap
- Send an email to the study Principal Investigator and Study Manager notifying them of the event and providing the study ID of the patient.
- **Email (marked URGENT) to: Dale Lupu ([dlupu@gwu.edu](mailto:dlupu@gwu.edu)) and Matthew Ryan ([m.ryan@gwu.edu](mailto:m.ryan@gwu.edu))**
- **Receipt will be confirmed. Please follow up for confirmation if not received.**
- Any change of condition or other follow-up information relating to a previously reported AE should be documented in REDCap as soon as available. Study Principal Investigator and Study Manager should be notified.
- Events must be followed up until the event has resolved or a final outcome has been reached.

## Appendix 1. An illustrative list of events that would be considered as expected SAEs due to advanced CKD and common comorbidities

Death or admission to hospital related to:

<p><b>Cardiac/Cardiovascular</b></p> <p><i>Diagnoses</i> Hypertension Angina Chest pain, MI ruled out Acute myocardial infarction (MI) Cardiac arrest/sudden death Congestive heart failure Cardiomyopathy Valvular heart disease Atrial fibrillation Other arrhythmia Pericarditis &amp;/or tamponade Hypotension</p> <p><i>Procedures</i> Cardiac catheterization Coronary angioplasty Coronary bypass graft (CABG) Valve repair or replacement Cardioversion Cardiac defibrillator placement Pacemaker placed Pericardial procedure</p>	<p><b>CKD and Dialysis-Related<sup>†</sup></b></p> <p><i>Diagnoses</i> Hyperkalemia Fluid overload PD peritonitis<sup>†</sup> Peritoneal catheter complication<sup>†</sup></p> <p><i>Procedures</i> Extra dialysis treatment<sup>†</sup> Peritoneal catheter insertion/removal<sup>†</sup></p>	<p><b>Endocrine/Metabolic</b></p> <p><i>Diagnoses</i> Hyperparathyroidism Diabetes complication (e.g., DKA) Thyroid disease Hypercalcemia Hypothyroidism</p> <p><i>Procedures</i> Parathyroidectomy</p>
<p><b>Eye, Ear, Nose, Throat</b></p> <p><i>Diagnoses</i> Diabetic retinopathy Cataract Glaucoma Blindness Epistaxis</p> <p><i>Procedures</i> Retinal laser surgery Cataract extraction</p>	<p><b>Gastrointestinal</b></p> <p><i>Diagnoses</i> GI bleed Gastritis/Peptic ulcer disease Gastroenteritis Abdominal pain Diarrhea Bowel obstruction Diverticulitis Malnutrition/cachexia Nausea/vomiting Other</p> <p><i>Procedures</i> OGD (upper GI endoscopy) ERCP Colonoscopy Gastric surgery Hernia repair Colectomy/colon surgery Appendectomy Parenteral nutrition</p>	<p><b>Health investigation</b></p> <p><i>Procedures</i> Diagnostic Tests unrelated to the HD/ HDF process</p>

<b>Hematologic</b>  <i>Diagnoses</i> Anemia	<b>Infectious Diseases</b>  <i>Diagnoses</i> Pneumonia	<b>Liver, Biliary, Pancreas</b>  <i>Diagnoses</i> Viral hepatitis
<i>Procedures</i> Blood transfusion Bone marrow biopsy	Septicemia Endocarditis AIDS/HIV Urinary Tract Infection Wound Infection Abscess Meningitis Cellulitis/soft tissue infection Osteomyelitis Viral infection Fungal infection Fever or chills, source unknown  <i>Procedures</i> Abscess Drainage	Liver Failure Ascites Pancreatitis Gall bladder disease  <i>Procedures</i> Liver biopsy Liver surgery Gall bladder surgery Pancreas surgery
<b>Musculoskeletal</b>  <i>Diagnoses</i> Carpal tunnel syndrome Dialysis amyloidosis (B2-microglobulin deposition) Infectious arthritis  <i>Procedures</i> Carpal tunnel release (surgical)	<b>Neoplastic/Cancer</b>  <i>Diagnoses</i> Benign tumor Cancer, non-metastatic Cancer, metastatic Multiple myeloma Lymphoma/leukemia  <i>Procedures</i> Surgical resection Chemotherapy Radiation therapy	<b>Neurologic/Cerebrovascular</b>  <i>Diagnoses</i> Seizure Dementia Mental status change/confusion TIA Stroke (CVA) – hemorrhagic Stroke (CVA) – ischemic Stroke (CVA) – type unknown Subdural hematoma  <i>Procedures</i> Carotid revascularization Carotid endarterectomy Evacuation of hematoma
<b>Obstetric/Gynecologic/Breast</b>  <i>Diagnoses</i> Abnormal bleeding Breast disease Other  <i>Procedures</i> Breast Biopsy Hysterectomy	<b>Orthopedic</b>  <i>Diagnoses</i> Hip Fracture Other fracture Herniated intervertebral disk Other  <i>Procedures</i> Fracture repair Hip replacement Other joint replacement	<b>Psychiatric/Mental Health</b>  <i>Diagnoses</i> Depression * Suicide attempt * anxiety disorder * Alcohol abuse Substance abuse Psychosis

<b>Pulmonary</b>	<b>Skin</b>	<b>Social/Rehabilitation</b>
<i>Diagnoses</i> Chronic Obstructive Pulmonary Disease Asthma Bronchitis Pneumonia Hemoptysis Pleural effusion Pulmonary oedema Respiratory Failure/ Arrest Shortness of breath	<i>Diagnoses</i> Psoriasis Cellulitis/Skin infection Calciphylaxis Rash	<i>Diagnoses</i> Placement issues Failure to thrive Fall Rehabilitation Hospice/palliative care

Pulmonary embolism  <i>Procedures</i> Ventilator-assisted breathing Bronchoscopy Thoracentesis		
<b>Transplant-Related</b>  <i>Diagnoses</i> Transplant evaluation Other  <i>Procedures</i> Kidney transplant Transplant nephrectomy	<b>Trauma/Injury</b>  <i>Diagnoses</i> Death Other  <i>Procedures</i> Laparotomy Skin graft	<b>Urologic</b>  <i>Diagnoses</i> Hematuria Renal cysts Kidney stone Other  <i>Procedures</i> Cystoscopy Prostate surgery Nephrectomy
<b>Vascular</b>  <i>Diagnoses</i> Claudication/Rest pain Ulcer of extremity Gangrene Aortic aneurysm Deep vein thrombosis Other  <i>Procedures</i> Angiogram Arterial bypass surgery Amputation Aortic aneurysm repair Wound debridement	<b>Vascular Access</b>  <i>Diagnoses</i> Clotted access† Infected access† Aneurysm† Failing access† Access bleeding† Other  <i>Procedures</i> Salvage procedure† Revision procedure† New access creation† Access removal† Catheter placement†	
<b>Other/Miscellaneous</b>  <i>Diagnoses</i> Drug reaction/allergy		

\* Unless thought to be related to participation in the trial.

† Dialysis related

## **Appendix 5**

### **DSMB Charter**



## **Data Safety and Monitoring Board (DSMB) Charter**

**Study Title:** Improving Shared Decision-Making and Access to Non-Dialytic Treatment for People with Kidney Disease (the ExPAND\* study)

**Sponsor:** Patient-Centered Outcomes Research Institute (PCORI)

**Contract Number:** IHS-2022C2-2678

**Principal Investigators:** Dale E. Lupu, PhD, MPH, Alvin H. Moss, MD, FACP, FAAHPM

**Site Principal Investigators:** Dale E. Lupu, PhD, MPH

**Institutions:** George Washington University, West Virginia University

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\*Expanding and Promoting Alternative Care and Knowledge in Dialysis Care (EXPAND) Trial

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## Abbreviations

COI	Conflicts of Interest
DSMB	Data Safety and Monitoring Board
DSMP	Data Safety and Monitoring Plan
ExPAND	Improving Shared Decision-Making and Access to Non-Dialytic Treatment for People with Kidney Disease Study
IRB	Institutional Review Board
PCORI	Patient-Centered Outcomes Research Institute
PO	Program Officer



The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the Patient-Centered Outcomes Research Institute (PCORI) to monitor participant safety, data quality and study progress of “Improving Shared Decision-Making and Access to Non-Dialytic Treatment for People with Kidney Disease (the ExPAND study)”, contract number IHS-2022C2-2678 by PI Dale Lupu (George Washington University).

## **DSMB Responsibilities**

The DSMB responsibilities are to:

At the initial meeting,

- Review the entire IRB-approved study protocol, regarding data/participant safety including recruitment, randomization, intervention, data management, quality control and analysis and the informed consent documents.
- Recommend changes to the protocol related to data/participant safety and the informed consent forms, when applicable.
- Identify the relevant data parameters (including those related to adverse events (AEs), serious AEs (SAEs) and unanticipated problems (UPs)) and the format of the information to be regularly reported.
- Recommend participant recruitment be initiated after receipt of a satisfactory protocol. If the need for modifications to the protocol, consent forms, Data Safety and Monitoring Plan (DSMP) or any other study document is indicated by the DSMB, the DSMB will postpone its recommendation for the initiation of participant recruitment until after the receipt of a satisfactory revised protocol(s) or other study documents.

During the study meetings,

- Review masked (if masking is feasible) and unmasked data. These data can be related to safety, recruitment, randomization, retention, protocol adherence, trial operations, data completeness, form completion, intervention effects on primary endpoints, gender and minority inclusion.
- Identify needs for additional data relevant to safety issues and request these data from the study investigators.
- Propose additional analyses.
- At each meeting, consider the rationale for continuation of the study, with respect to progress of recruitment, randomization, retention, protocol adherence, data management, safety issues, and outcome data (if relevant) and make a recommendation for or against the trial's continuation.

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- Review and make recommendations on proposed protocol changes, and/or new protocols proposed during the trial. The DSMB may recommend to PCORI to appoint a blinded working group of the DSMB to review the proposed protocol changes and make recommendations to PCORI on whether to approve the requests.
- Provide advice on issues regarding data discrepancies found by the data auditing system or other sources.
- DSMB members with expertise in a particular area may be asked to contribute their thoughts regarding the conduct of the ExPAND trial (e.g. asked Review manuscripts of trial results if requested).

The DSMB will discharge itself from its duties when the study is complete.

## Membership

The DSMB consists of nine members that have been appointed by the study investigators. Members are completely independent of the study investigators and have no financial, scientific or other conflict of interest with the trial. The DSMB members and their expertise are as follows:

- Geriatric Nephrologist: **Ann O'Hare, MD**
- Geriatric Nephrologist: **Vanita Jassal, MD**
- Health Equity Nephrologist: **Vanessa Grubbs, MD**
- Biostatistician: **Denise Esserman, PhD**
- Biostatistician: **Jonathan Yabes, PhD**
- Patient: **Patrick Gee**
- Nurse Practitioner: **Suzanne Ward, NP**
- Ethicist: **Donna Chen, MD, MPH**
- Patient Family Member: **Melissa Tolzien**

Dr. Ann O'Hare will serve as the Chairperson and is responsible for facilitating the meetings, reviewing the first draft of the meeting notes and any decision making in the case of a tie vote. The Chair will act as the official contact for the DSMB. At each DSMB meeting, the Chairperson will prepare a formal summary of the DSMB's recommendations regarding continuation or termination of the study as well as any other changes requested by the DSMB. The GWU School of Nursing will provide the logistical management and support for the DSMB.

## Meetings

### Meeting Format

Meetings of the DSMB will be held at a minimum every 12 months after the protocol is approved by the DSMB, including: 1) prior to data collection to approve the study protocol and 2) within three months of the completion of data collection. An emergency meeting of the DSMB may be called at any time by the DSMB Chair, should participant safety questions or other unanticipated problems arise.

A quorum will require 5 DSMB members including the chair and a statistician. Meetings will be held in-person, by telephone conference, or a combination of the two.

DSMB meetings will consist of open, closed, and optional executive sessions, all closed to the public because discussions may address confidential participant data.

The **open session** is attended by study PIs, key staff members, including the study biostatistician, and DSMB members. Discussions at these sessions focus on the review of the aggregate study data, conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered. Data by treatment group are not presented in the open session.

The **closed session** will be attended by the DSMB members and the unblinded study biostatistician. The primary objective of the closed sessions is to review safety-related outcomes, adverse events and serious adverse events data by study group, and recommend any safety-related protocol changes required to the study team.

If necessary, an **executive session** may be requested by the DSMB and will be attended only by voting DSMB members.

### Meeting Agenda

The DSMB Chair or the Principal Investigators will prepare the meeting agenda that usually includes the following:

1. **Welcome and introduction** – study team and DSMB members
2. **Open session** (review study protocol and its amendments, consent form, open study report, etc.) - study team and DSMB members
3. **Closed session** (review closed session report, including unmasked safety data, etc.) – DSMB members, study team if invited
4. **Executive session** (optional, upon DSMB request) – DSMB members, PCORI staff if invited

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5. **Debriefing** (optional, upon DSMB request, time permitting) - study team and DSMB members

The DSMB may modify its processes and procedures at any time as needed.

### **Meeting Materials**

DSMB interim report templates developed by the study staff for both the open and closed sessions and plans for interim analyses will be reviewed and either approved at the initial DSMB meeting or changes requested. Upon DSMB request, reports could be modified at any time during the study.

**Part 1 - Open Session Reports.** Open session reports will include administrative reports that describe participants (screened, enrolled, completed), fidelity to study procedures, as well as baseline characteristics of the study population that is not grouped by treatment. Other general information on study status may also be presented. Listings of adverse events and serious adverse events, and unanticipated problems will also be presented (also not grouped by treatment). See DSMB Report Template.

**Part 2 – Closed Session Reports.** Closed session reports will present the same information but additionally summarized by treatment group. The Closed Session Report is considered confidential and should be destroyed at the conclusion of the meeting.

### **Meeting Minutes**

The minutes will be taken by the DSMB support staff. Minutes will be circulated to all DSMB members for approval.

## **Reports from the DSMB**

The DSMB Chair will prepare the report based on the meeting minutes from the open session and any recommendations from the closed and executive session and circulate the report to the DSMB members for feedback and revision. After DSMB review and approval of the minutes, the DSMB chair will forward the report to the study PIs.

The report will contain the recommendations for continuation or modification of the study. As stated above, each meeting must include a recommendation to continue the study made by a formal DSMB majority or unanimous vote. Should the DSMB decide to issue a termination recommendation, the full vote of the DSMB is required. In the event of a split vote, majority vote will rule, and a minority report should be appended. The DSMB Chair provides the tie-breaking vote in the event of a 50-50 split vote.

A recommendation to terminate the study may be made by the DSMB at any time by majority vote. If this recommendation was made during the DSMB's Executive session, the Chair should notify PCORI immediately by telephone and email.

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The study PIs will ensure that a summary of recommendations based on the report is sent to all participating Institutional Review Boards (IRBs) after each DSMB meeting.

## **Confidentiality**

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

## **Conflicts of Interest**

Each member of the DSMB will complete a COI form before attending the first DSMB meeting. The DSMB Chair will be responsible for deciding whether any disclosed COIs materially affect their objectivity on the DSMB. Members of the DSMB will be responsible for notifying the DSMB Chair of any changes in conflicts of interest. Members will be polled at the beginning of each DSMB meeting to disclose whether status has changed. Members of the DSMB who develop potential or significant perceived conflicts of interest will be asked to resign from the DSMB.