Controlling Hypertension through Education and Coaching in Kidney Disease (CHECK-D)

Protocol Number: HUM00136011

A related sub-project to: "Quality Improvement and Evaluation of the Integration of a CKD Education Tool in a Primary Care Clinic" (HUM00152989, unregulated)

National Clinical Trial (NCT) Identified Number: NCT04087798

Principal Investigator: Julie Wright, MD, MPH

Funded by: NIH, National Institute of Diabetes and Digestive and Kidney Diseases

Version Number: v.2.0

February 3, 2026

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
10.5 Appendices	Update Appendix 1: Outcome Measures	Clarify that the zipcode data includes patients' home and clinic 5-digit zipcodes. The intent is to use both for analysis.
1.1 Synopsis 1.3 Schedule of Activities (SoA)	Expand Acronym and Abbreviation	Expand acronyms and abbreviations (and include the acronyms in parentheses) the first time they are used in the protocol.

Table of Contents

STATEMENT OF COMPLIANCE

This study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, and 21 CFR Part 56)
- NIH Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training. The protocol and informed consent form(s) will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will first go through IRB review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form, if this becomes applicable. (i.e. if there is a requested change to the consent form during the course of this study)

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Controlling Hypertension through Education and Coaching in Kidney Disease (CHECK-D)
Study Description:	This project aims to deliver an evidence-based, patient-focused intervention that will improve blood pressure (BP) control and outcomes early in chronic kidney disease (CKD) care. It uses continuous quality improvement (CQI) methods to make education and coaching streamlined and efficient. We hypothesize that compared to patients in a control group, patients in the intervention group will have lower systolic blood pressure, and improved patient-reported measures.
Objectives:	Primary Objective: Identify the impact of a provider-led, coach-supported patient education intervention on patient blood pressure over one year using a cluster-randomized controlled trial. Secondary Objectives: 1) Optimize the process of delivering a provider-led, coach-supported patient education intervention prior to using it in a cluster-randomized controlled trial (under "Quality Improvement and Evaluation of the Integration of a CKD Encounter Decision Intervention (EDI) in a Primary Care Clinic", HUM00152989); 2) Identify the impact of a provider-led, coach-supported patient education intervention on patient clinical and self-reported outcomes over one year using a cluster-randomized controlled trial; and 3) Identify whether and to what extent implementation outcomes (provider adoption, fidelity, perceived usefulness) are associated with clinical and patient-reported outcomes.
Endpoints:	Primary Endpoint: Change in systolic BP between baseline and 12 months Secondary Endpoints: Change in diastolic BP between baseline and 12 months; Slope of systolic and diastolic BP across all time points; serum creatinine; urine protein-creatinine ratio; estimated glomerular filtration rate (eGFR); patient medication adherence; chronic kidney disease (CKD)

	knowledge; self-efficacy; motivation; satisfaction with care; self-reported blood pressure-related behaviors; perceptions of health coaching; provider adoption, fidelity, and perceived usefulness; visit time, total time patient spends in clinic visit at enrollment; change in Electronic Medical Records (EMR) BP between baseline and 12 months; change in study visit BP supplemented with EMR BP if missing; change in BP using all study visit and EMR BP values Not an 'endpoint' or outcome, but important to capture, will be patient characteristics.
Study Population:	Adults (21-85 years old) seen in participating clinics at the University of Michigan and Detroit Medical Center/ Wayne State University (DMC/WSU), who meet eligibility criteria (uncontrolled hypertension, CKD stages 3–5, full eligibility criteria in sections 5.1 and 5.2). Our target sample size is 450 patients. We expect an approximately equal distribution of men and women. Demographics are expected to reflect local community populations from which we recruit. These communities include clinics in Ann Arbor and outlying areas, and in and around Detroit, Michigan. Patients in the study have high blood pressure and kidney disease and thus are inherently more sick than the general population.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	All 10 sites are located in the southeast Michigan area. The UM Family Medicine sites include Chelsea, Livonia, Dexter, Briarwood, Ypsilanti, and Domino's Farms. The UM Internal Medicine sites include Northville and Brighton. DMC/WSU sites include the Canfield Med-Peds clinic and Internal Medicine clinic on Canfield.
Description of Study Intervention:	The entirety of the study intervention consists of a provider-led CKD worksheet called the Encounter Decision Intervention (EDI) and 4-6 health coaching calls.
Study Duration:	In total, 60 months, although additional analyses and manuscript writing may continue after the study has ended.
Participant Duration:	Twelve months.
Related separate QI initiatives for this study	A separate, unregulated QI sub-study (HUM00152989) covers the integration of the EDI into participating clinics. However, collection of study data from individual participants does not fall under the unregulated research category and will take place independently of the QI sub-study. Therefore, this study (HUM00136011) will cover collection of data for enrolled participants. This study will also cover health coaching for participants in intervention clinics. Patients who do not enroll in this study are not excluded from the related QI sub-studies.

1.2 SCHEMA

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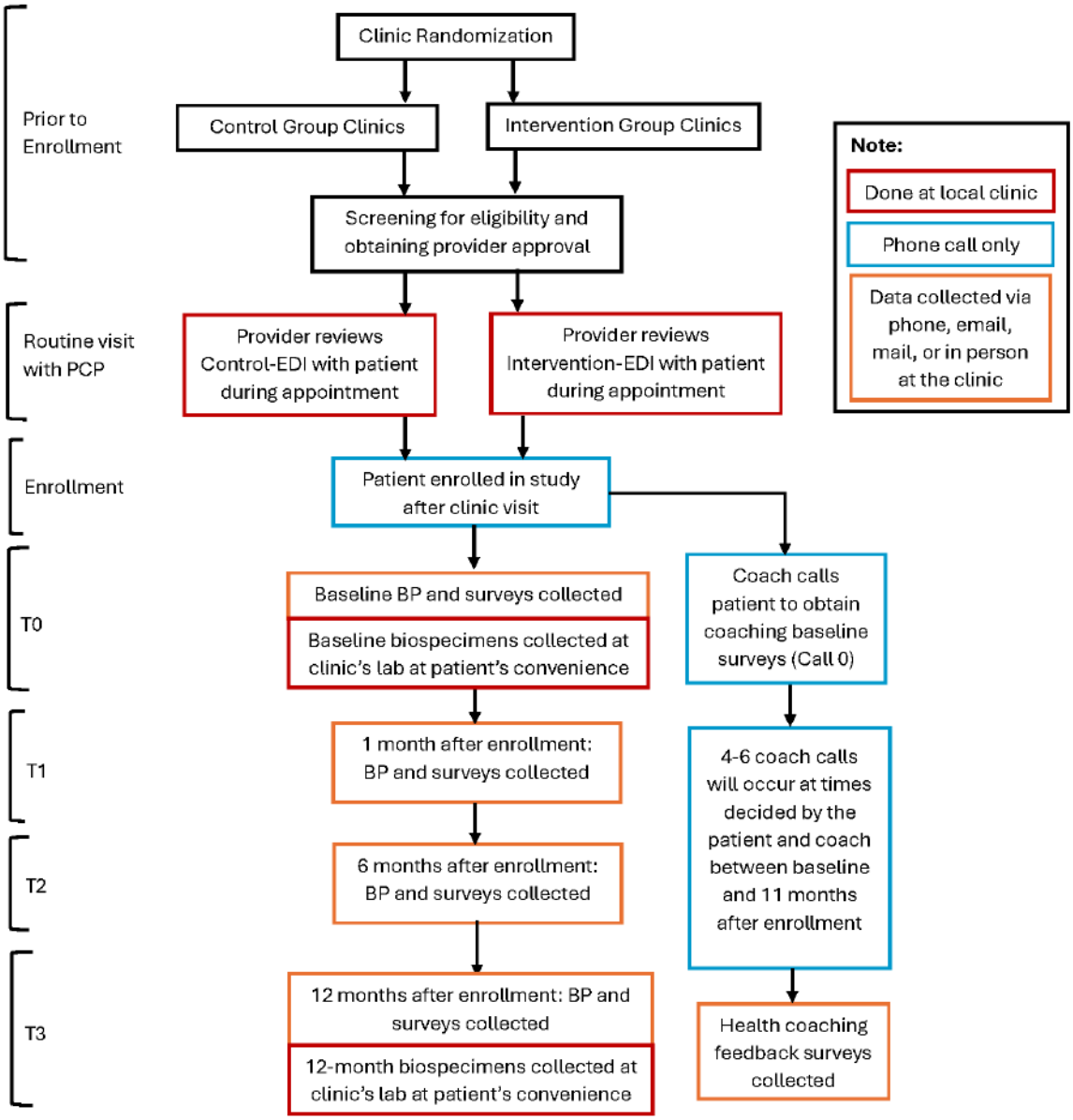
Prior to Enrollment
Routine visit with PCP
Enrollment
T0
T1
T2
T3
Clinic Randomization
Control Group Clinics
Intervention Group Clinics
Screening for eligibility and obtaining provider approval
Provider reviews Control-EDI with patient during appointment
Provider reviews Intervention-EDI with patient during appointment
Patient enrolled in study after clinic visit
Baseline BP and surveys collected
Baseline biospecimens collected at clinic's lab at patient's convenience
1 month after enrollment: BP and surveys collected
6 months after enrollment: BP and surveys collected
12 months after enrollment: BP and surveys collected
12-month biospecimens collected at clinic's lab at patient's convenience
Coach calls patient to obtain coaching baseline surveys (Call 0)
4-6 coach calls will occur at times decided by the patient and coach between baseline and 11 months after enrollment
Health coaching feedback surveys collected
Note:
Done at local clinic
Phone call only
Data collected via phone, email, mail, or in person at the clinic

1.3 SCHEDULE OF ACTIVITIES (SOA)

Note: Times indicated in this table guide our study measures and time points. Our pilot work has shown that patient scheduling for activities requires flexibility to accommodate not only the study but the needs and schedules of patients. As such, times for data collection may show 'windows +/- x days). Exact time points of data collection will be documented in study logs, and also accounted for during analyses.

Procedures	Before routine Primary Care Provider (PCP) appointment	At routine PCP appointment	Immediately after PCP appointment, but will allow up to + 7days	Immediately after enrollment, but will allow up to 3 weeks**	1 month after participant enrollment, +/- 7days**	6 months after enrollment, +/- 7 days**	12 months after enrollment, +/- 14 days**
Screening and provider approval	X						
Control-EDI or Intervention-EDI		X					
Consent and Enrollment			X				
Survey t0				X*			
Survey t1					X*		
Survey t2						X*	
Survey t3							X*
Coaching baseline survey				X			
Coach calls				4-6 coach calls will take place between coaching baseline survey until 11 months after enrollment			
Blood pressure				X	X	X	X
Biological Specimens (urine, blood)				X			X

*Surveys may be completed online or on paper at home for subjects who cannot complete in clinic.
** Please note that timeframes have been extended to allow for a larger tolerance window, now ranging from 3-6 months.

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic kidney disease (CKD) is a serious and growing public health problem. A total of 20 million people, or 20% of U.S. adults ages 60 years and older, have CKD.[1] The number of patients with end-stage renal failure is expected to reach over 750,000 by the year 2020.[2,3] Patients with CKD are often not controlled to optimal blood pressure targets, and experience 3.5 times higher rates of cardiovascular events, and 6 times higher rates of mortality compared to patients without CKD.[4] Cardiovascular risk grows exponentially as disease advances[4].

The scientific premise and rationale for this research is based on evidence that education and coaching improve outcomes in patients near dialysis and in patients with other chronic conditions, and will be successful in improving outcomes in pre-dialysis CKD as well. Education and coach support for patients near or at end-stage renal disease[5-7] delays initiation of dialysis and increases survival.[7] Patient education and health coaching improves outcomes in diabetes mellitus.[8-10] Applying CKD-specific patient education and health coaching in primary care, with patients at earlier stages of kidney disease would likely improve BP control, reduce risk of cardiovascular events, and delay or abate renal failure. This project builds on pilot studies of a provider-delivered patient education intervention that improved patient-centered outcomes in pre-dialysis CKD,[11] and is informed by studies identifying what patients and providers want and need from education interventions.[12,13] It also takes advantage of CQI methods to make education and coaching streamlined and efficient, which is critical to intervention success and future dissemination. The six specific hypotheses to the aims are summarized in three overarching bullets below are further described in more detail in later sections:

1. Compared to patients in a control group, patients receiving tailored education and health coaching will have lower blood pressure, more knowledge about CKD, higher self-efficacy, motivation and satisfaction with CKD care.
2. Continuous quality improvement and systems engineering approaches will facilitate resources and process efficiency of this research and future dissemination.
3. Providers will adopt with high fidelity the EDI and perceive it as beneficial and useful to care.

2.2 BACKGROUND

The name and description of the study intervention: The name of this study is CHECK-D (Controlling Hypertension through Education and Coaching in Kidney Disease). The objective of this research study is to test the impact of a provider-delivered patient EDI, followed with 12 months of health coaching focused on blood pressure control in patients who have moderate to severe CKD. A cluster-randomized controlled trial will compare outcomes in patients with CKD stages 3-5 between intervention and control groups in 10 primary care clinics (8 at the University of Michigan (UM), and 2 at Detroit Medical Center / Wayne State University Health System (DMC/WSU)). This study uses continuous quality improvement and systems methodologies to understand current clinic processes of care in order to optimize resource neutrality. This methodology will support implementation and success of the study (HUM00152989) as well as allowing assessment of how an intervention like this can work in the 'real world' and not just for research.

A summary of findings from nonclinical in vitro or in vivo studies that have clinical significance:
Conclusive evidence shows that good blood pressure (BP) control reduces cardiovascular events and death in patients with moderate to advanced kidney disease (stages 3–5).[14,15] A recent randomized controlled trial comparing the benefit of intensive versus standard BP control shows that intensive BP control lowers rates of fatal and nonfatal cardiovascular events and death (hazard ratio 0.75 in all patients; 0.82 in subgroup with CKD).[15] It also reduces risk of all-cause mortality.[15] When BP is well controlled, patients experience lower risk of CKD progression as well.[16-18 15 19 20,21]
Current mechanisms of care do not ensure patients who have CKD are educated and supported to achieve optimal blood pressure (BP) management. High BP is common, severe, and not well controlled in patients with CKD.[17,22,23] As few as 40% of CKD patients achieve recommend BP targets.[1,22] There are many barriers to achieving good BP control. At least two are patient-centric. First, many patients who have CKD do not understand their diagnosis, its implications or how important achieving good BP is for reducing their risk of cardiovascular events and CKD progression.[24,25] Currently, patients who have CKD fare no better adhering to medications or lifestyle changes, despite their high risk for complications,

compared to patients without CKD.[26] Second, promoting patient behaviors to improve outcomes, including BP control, requires coordinated programs of education and support over time. The best model of education and support for patients with CKD is yet to be determined.[27,28]

A summary from relevant clinical trials: Patient-focused education and health coaching may improve BP control and outcomes in patients with CKD. This is based on success from prior studies in other chronic conditions. Patient motivation and healthy behavior change require patients to have knowledge of their chronic condition and the self-efficacy to do what is needed to stay healthy.[29] National models of chronic care promote educating and supporting patients early in the care continuum.[30] Patient education and coaching reduces hemoglobin A1C% in patients with diabetes mellitus,[31,32] lowers re-hospitalization rates in patients with pulmonary disease,[33] reduces complications in spinal cord injury,[34] and improves care experiences in low-income patients with multiple chronic conditions.[35]
While not all interventions have been successful,[36-38] multiple projects targeting patient education and support have met goals of improving clinical outcomes,[8-10,39] reducing disease-related complications,[33,34] and improving the patient care experience.[32,35] Coaching varies, but is generally accepted to be "the practice of health education…and promotion…to enhance the well-being of individuals and to facilitate the achievement of health related goals."[40] A successful coaching program, and the model for this proposal, is Sepucha, Belkora et al.'s "Consultation Planning Program."[41-44] In addition, this study benefits from a robust study team that includes experts with years of research and practical experience in health behavior, shared medical decision making, and health coaching. Patients using education and coaching programs such as these, experience higher quality care, make better care decisions, and have greater satisfaction.[41-44] Providers report higher satisfaction with patient-provider visits as well.[41]

Discussion of important literature and pilot data that are relevant to the trial (reference citations are listed in Section 17): Relevant literature to this study is highlighted above. However, in addition to literature, the PI and investigative team have put a ***significant amount*** of work into developing pilot data that supports this research. Below describes this pilot work. Dr. Wright Nunes led the design, administration, and validation of a comprehensive survey that quantitatively measured disease knowledge in 556 patients with CKD.[25] Results showed most patients do not understand their CKD diagnosis, its implications, treatments, or what they must do to optimize kidney health—even when under care of nephrologists.[25] ***Thirty-percent of patients under care of a kidney doctor do not even realize that they have chronic kidney disease.*** The survey identified an important link between BP control and knowledge. Patients who know their BP goals achieve better BP control compared to those who do not.[13] But patients do not understand how dietary behaviors impact their BP or how to implement dietary sodium restrictions.[45] Additional unpublished analyses revealed that patients perceive physician-providers as their most valuable and trusted resource for CKD information. Work in other diseases supports this.[46,47]

This preliminary data informed an educational intervention (referred to from now on as an encounter decision intervention, or "EDI") that was pilot tested in 155 patients.[11] The EDI was adapted from the National Kidney Disease Education Program patient education worksheet. [48] It is a one-page paper document designed for providers to use during visits when talking to patients about CKD and management goals.[48] The EDI was tested in nine nephrology clinics. Patients who received the EDI had more knowledge about their CKD diagnosis compared to a usual care cohort, and 98% recommended it for future use. It took minutes to review, and providers liked it.[11]

To develop this for use in primary care, Dr. Wright Nunes led a series of structured interviews in 50 patients and 25 physician-providers at the University of Michigan. Patients said they wanted CKD information earlier in care. Patients feel CKD diagnosis information from providers is lacking and too general. Patients feel that current mechanisms of care do not provide them with the support they need

to effect behavior change to avoid CKD complications and disease progression.[12] Both primary care[49] and nephrology providers[50] say discussing a CKD diagnosis with patients is challenging and that education for patients early about CKD is important. But evidence-based patient education tools are lacking.[50] Additional surveys in 202 patients enabled the study team to quantitatively summarize patient priorities for education topics, select the best format for education materials, and identify resources patients felt were most important. Patients also prioritized their barriers to optimal CKD self-management. The number one barrier patients cited was not having motivation to do what is needed to improve health, in particular when it came to being active and eating healthy. [51,52]

Informed by the work above, Drs. Wright Nunes and Co-I's launched a pilot study to optimize CKD education and support in primary care. Using a collaborative multidisciplinary team (including 1 CKD patient, 2 primary care physicians, 1 medical assistant, 1 check-out staff, 2 clinic admin leads, 1 information technology representative) they adapted the paper EDI into an electronic format for the EMR, and created a process map for using it in clinic, by the PCP, during routine follow up visits for patients.

Lastly, investigators in this study have developed and tested a formalized coaching protocols based on years of leading research developing patient decision aids for patient shared decision making, communication tools, and coach support interventions.[53-58] Investigators on this team (Drs. Fagerlin, Resnicow) and tested coaching protocols in a precursor conditions of CKD—diabetes mellitus and obesity. From this work we've learned that most patients (82%) felt it helpful to talk with the coach about their questions, and 85% found it helpful to talk about their values in care (remaining were neutral). Physicians also like the coaching—80% thought coaching helped patients ask better questions and helped patients better understand their treatments.

Applicable clinical, epidemiological, or public health background or context of the study: As stated in section 2.1, chronic kidney disease (CKD) is a serious and growing public health problem..[1] The number of patients with end-stage renal failure is expected to reach over 750,000 by the year 2020.[2,3] The risks of progression to renal failure, cardiovascular events, and death are significantly higher in patients with CKD compared to those without CKD.[4] High blood pressure accounts for one of the top two leading causes of progression of CKD to renal failure, yet over 40% of patients with CKD are uncontrolled. This research will deliver a tested educational and coaching intervention with an efficient process of delivery, to reduce blood pressure in patients who are not controlled to ultimately improve outcomes.

Importance of this study and relevant issues / controversies: Reviews show that rigorous evidence-based patient education and support programs are lacking early in CKD care.[59-61] There are several additional limitations of existing research: 1. Prior research has often focused only on one-way delivery of patient education, 2. Health coaching is not well studied in CKD, and 3. Prior studies have often given education interventions to patients too late in the process of disease—often when they have already approached total renal failure (end-stage renal disease, ESRD) [5-7] In addition, most education-related studies in CKD are of short duration (6 months or less) and are not focused on clinical outcomes.[59] There is little examination of how implementation or system factors mediate intervention success or whether interventions can be sustained in the real world.[60,62]

This research will address many of these issues / controversies: 1. This proposal will deliver an intervention to address gaps in education and coaching early in the CKD care continuum. 2. This research includes an examination of impact on clinical outcomes over a long duration. 3. This research uses continuous quality improvement (CQI) and a systems-driven approach to make patient education and coaching unified and efficient (HUM00152989). Further, it will examine whether provider and system factors mediate intervention impact. 4. This research benefits from a pilot-tested patient EDI

that was informed by patients and primary care providers, and serves as launch for coaching support calls that will follow.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Participants face certain potential risks. This study is no more than minimal risk. The potential risks to participants include 1) breach of confidentiality of medical records, surveys, or conversations which could result in psychological distress, 2) Risk of psychological distress from coaching or surveys related to answering questions, 3) potential distress caused to patients who may have a better understanding about their diagnosis, disease management, and self-care after receiving our intervention, 4) the time it takes to fill out surveys, or for patients enrolled who will get the coach calls—the time to participate in coach calls, and 5) A small risk of bruising and a rare chance of local infection associated with standard venipuncture to collect blood samples at two time points in the study.

Risks related to surveys and coaching or provider conversations will be minimized in that these conversations will only be done in an environment that supports individual discussion and confidentiality of responses. Any patient experiencing any untoward reaction will have the option to discontinue their participation in the study. Removal of participants from further participation in the study will be mandatory for serious or potentially serious side effects. There is a potential risk of loss of confidentiality and patient privacy. We are mindful of the sensitive nature of patient's medical records and have the utmost concern for the human subjects who will be part of this study and will take steps to ensure protection of confidentiality (outlined in section 10.1.3).

2.3.2 KNOWN POTENTIAL BENEFITS

Overall, the risks are relatively small, and the potential information gained will add critical knowledge necessary to optimize care and improve cardiovascular and renal disease related outcomes in a population of patients at high risk for morbidity and mortality (with CKD and HTN). Information gained from this research will form more evidence-based medical literature in early CKD. It will provide critical evidence for future steps in planning and potential dissemination. Patients will obtain direct benefits by receiving education and coaching aimed to modify their risks and improve their health outcomes.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The potential benefits at both the national level (knowledge to be gained and potential future dissemination) and at the individual-level outweigh the potential risks. This study is no more than minimal risk; Therefore, the risks are reasonable in relation to the anticipated benefits.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Identify the impact of a provider-led, coach-supported patient EDI on patient blood pressure over one	Change in systolic blood pressure between baseline and 12 months	Blood pressure control is a primary educational focus of the EDI. Systolic BP

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
year using a cluster-randomized controlled trial.		was chosen because it most consistently relates to cardiovascular and other end outcomes in kidney disease.[63,64]
Secondary		
Optimize the process of delivering a provider-led, coach-supported patient EDI prior to using it in a cluster-randomized controlled trial. (These QI activities are covered in approved QI IRB HUM00152989 and will be support seamless implementation into current patient flow at the clinics)	Visit time (length of time provider spends with patient), total time in clinic (length of time between patient check-in and check-out)	We will create the most efficient process for integrating and applying the patient EDI and coaching so as not to disrupt clinic flow and patient follow up.
Identify the impact of a provider-led, coach-supported patient EDI on patient clinical and self-reported outcomes over one year using a cluster-randomized controlled trial.	Slope of systolic BP between all timepoints, change and slope of diastolic BP between all timepoints, serum creatinine, urine protein:urine creatinine, Egfr, medication adherence, CKD knowledge, self-efficacy, motivation, patient satisfaction with CKD care, self-reported blood pressure-related behaviors, perceptions of health coaching, change in EMR BP between baseline and 12 months, change in study visit BP supplemented with EMR BP if missing, change in BP using all study visit and EMR BP	We are interested in knowing the impact of the EDI and health coaching on other clinical and patient-reported outcomes related to kidney disease – as well as in knowing whether patients like the intervention.
Identify whether and to what extent implementation outcomes (provider adoption, fidelity, perceived usefulness) are associated with clinical and patient-reported outcomes.	Provider adoption, fidelity, and perceived usefulness	An unresolved issue in the field of patient education and support is how to evaluate and conceptualize successful implementation of education and support programs.[65] This research proposal is not an implementation science study, however, will evaluate the intervention

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		implementation by asking provider perceptions of the intervention usefulness and whether providers adopt its use.
Tertiary/Exploratory		
Cost effectiveness of coaching	Hours worked x wages of coaches at study end—this is NOT a formal cost analysis.	For dissemination, replicability planning.

A list of all study measures is included in the appendices, section 10.5.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study examines the impact of an education and coaching intervention in primary care for patients who have CKD and high blood pressure. It is a multi-site cluster-randomized controlled trial, where the units of randomization are 10 clinics. Patients who meet eligibility criteria in intervention clinics and who enroll in the study will receive: An Encounter Decision Intervention (EDI) reviewed by their primary care doctor that gives the patient information about their CKD diagnosis and BP goals. Then, the patient will receive health coaching to improve blood pressure via 4-6 coach calls over the next 11 months. Patients who meet eligibility criteria in control clinics and who enroll will receive: A Control-EDI that provides only generalized information about CKD and where patients can go to get more information. Outcome measures are systolic and diastolic BP, clinical laboratory measurements (blood, urine), patient, provider, and clinic characteristics, and surveys administered to patients and providers.

This protocol outlines in detail the patient enrollment for implementing the EDI, collecting study measures, and health coaching. One related but separate study covers activities on optimizing implementation of study activities using continuous quality improvement (CQI) methods:

> Quality Improvement and Evaluation of the Integration of a CKD Education Tool in a Primary Care Clinic – HUM00152989: This IRB applies to optimizing implementation of intervention activities to ensure they will be most efficient and seamless so as not to disrupt current clinical practices nor patient flow at the participating clinics.

In this multi-site cluster-randomized controlled trial, clinics are the unit of randomization and will be randomized to either the intervention or control groups. Clinics will be stratified by primary care provider discipline, geographic location and socio-economic status to ensure treatment balance on those factors.

Aim 1: Optimize the process of delivering a provider-led, coach-supported patient education intervention prior to using it in a cluster-randomized controlled trial.
Hypothesis 1: CQI and systems approaches will facilitate resource and process efficiency comparing intervention and control groups.

Aim 2: Identify the impact of a provider-led, coach-supported patient education intervention on patient clinical and self-reported outcomes over one year using a cluster-randomized controlled trial.
Hypothesis 2: Compared to patients in the control group, patients in the intervention group will have lower blood pressure.
Hypothesis 3: Compared to patients in the control group, patients in the intervention group will experience higher Egfr, greater reductions in urine protein, and higher medication adherence.
Hypothesis 4: Compared to patients in the control group, patients in the intervention group will have greater knowledge about CKD, and higher self-efficacy, motivation, and satisfaction with CKD care.

Aim 3: Identify whether and to what extent implementation outcomes (provider adoption, fidelity, perceived usefulness) are associated with clinical and patient-reported outcomes.
Hypothesis 5: Within intervention clinics, provider adoption, perceived usefulness of, and fidelity to the provider-delivered EDI will be high and positively associated with clinical and patient-reported outcomes.
Hypothesis 6: Providers will perceive the intervention as beneficial and feasible for future translation into community settings.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This design minimizes the potential problem of contamination.[66] It would be difficult for trained providers who are accustomed to using the EDI and whose patients have access to regular health coaching over a year not to change practice patterns depending on the patient to whom they are providing care. It is also an appropriate design for optimizing pragmatic trials such as this.[66]

4.3 JUSTIFICATION FOR DOSE

Not applicable

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including from enrollment through the last study measures, 12 months after enrollment (see Schedule of Activities (SoA), Section 1.3).

For participants who request more information about the survey, we may refer them to resources where the survey have been validated and published at the end of their participation as appropriate.

Study enrollment will be complete after meeting the study's pre-specified number of target participants through 12 months of enrollment and completion of their final study measures. Thereafter, analyses, reporting and evaluative steps will occur through completion of the 60-month research project timeline.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

All patients coming in for appointments at participating clinics will be screened for eligibility, and healthcare providers will be prompted to review the EDI with eligible patients. A waiver of consent is

requested for the EDI to ensure the safety of patients and that the intervention is reaching an unbiased population of CKD patients. Patients will provide informed consent after the EDI, but prior to completing study measures and health coaching.

Inclusion criteria will include:

1. Aged ≥21 and ≤ 85 years
2. Has diagnosis of CKD stage 3, 4, or 5 documented in medical record (which is equivalent to an estimated glomerular filtration rate, Egfr < 60 ml/min/1.73 m2).
3. Aware of CKD diagnosis* (assessed by screening questions)
4. Has diagnosis of hypertension documented in medical record AND most recent BP within the last year meets criteria of uncontrolled hypertension (>130 mmHg, and/or a diastolic blood pressure >80 mmHg noted in an ambulatory care setting within the past one year[15,67])
5. Estimated glomerular filtration rate (Egfr) of <60 within the last 18 months documented in the medical record.

*Note: This is only assessed after the patient completes the visit. The patient does not need to be aware of CKD diagnosis prior to receiving the EDI; they only need to be aware prior to consenting to complete the study measures and/or receive health coaching. Whether or not the patient actually received the EDI in clinic does not affect their eligibility for the health coaching and study measures.

In addition, patients must be able to provide informed consent (see below for exclusion criteria). Prior to collecting study measures and health coaching, we will obtain either a signed and dated informed consent form or a verbal consent when using phone consent. Inherent in informed consent is a stated willingness to comply with all study procedures and availability for the duration of the study.

5.2 EXCLUSION CRITERIA

Exclusion criteria are:

1. Currently on dialysis permanently (i.e. are considered “end-stage renal disease” and receiving dialysis)
2. Previous kidney transplant
3. Pregnant (indicated by medical record or if patient self-identifies as pregnant)
4. Has cognitive, language, or vision impairment(s) or language barrier that would prohibit participating in education, taking surveys, or participating in coaching activities
5. Has terminal illness.

It is not our intent to recruit terminally ill patients. If there are flags in the chart or a patient’s provider raises the issue, we will not approach for recruitment.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

For the purposes of this study, we will define screen failures as patients who complete the screening questions to determine if they are aware of their CKD diagnosis (“Has your doctor ever told you that you

have, or do you have, any of the following: kidney disease, renal insufficiency, chronic kidney disease, low kidney function, or a kidney problem?") but deny having any of these conditions, and are not subsequently entered in the study. If a patient is found to be unaware of their CKD diagnosis, a member of the study team will inform the patient's primary care provider, who will determine the appropriate next steps for discussing CKD with the patient (as in usual care). The role of research personnel is not to inform the patient of their diagnosis; this will remain the responsibility of the healthcare provider caring for the patient.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because they are not aware of their diagnosis of CKD may be rescreened at a future date for study enrollment.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

There are ten outpatient clinics participating in this research study. Of these, eight are affiliated with the University of Michigan, located in Ann Arbor and surrounding areas. Two clinics are affiliated with Wayne State University/Detroit Medical Center, located in Detroit. All clinic directors have agreed to have their clinics participate in this study. Using site representatives to provide input on how we implement study activities seamlessly into clinics will also foster local champions for project participation. It is possible that a clinic will drop out of the study. We feel this is very unlikely given strong support from clinics and leadership. However, if this occurs prior to enrollment, we will try to identify other clinics to participate, a strength being that clinics in this study are affiliated with large health systems that have many other potential clinics.

Based on administrative data and queries, the annual number of unique adult patients meeting eligibility criteria at each clinic is on average 40-60 yearly. These are conservative numbers because estimates are drawn from queries of patients with an Egfr <45 ml/min/1.73 m^2. Our eligibility criteria (CKD stages 3-5, Egfr <60 ml/min/1.73m^2) will likely yield a larger number eligible. The clinics were selected because they 1) all met eligibility criteria, 2) have reasonably large case volume for patient enrollment, 3) offer a mix of academic-community and academic-urban practices, 4) include diverse geographical and socio-demographic variability that will increase the generalizability of the data, and 5) share previous successful collaborations with investigators.

The target sample size for this study is 450 participants, but we may enroll more to ensure we have sufficient data for analysis. Eligible participants will be recruited without regard to gender, race, or ethnicity. Although for this study we will not aim to meet a specific quota for any particular age group, gender, race, or ethnicity, typical gender and race/ethnic distributions for ambulatory clinics at both institutions are combined for total enrollment and include approximately 24% African American patients, 50% female, 7% Hispanic or Latino, 12% other or combined races (American Indian/Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, more than one race) of the ages 21 to 90 years old. Demographics are expected to reflect local community populations around clinics participating, including Ann Arbor and outlying areas and Detroit and its outlying areas. By nature of kidney disease many eligible patients may be older; however, any adult meeting eligibility criteria may participate. Patients in the study will have high blood pressure and kidney disease and thus are inherently more sick

than the general population. They are at higher risk of cardiovascular events, death, and morbidity compared to other patients with other chronic conditions and compared to the general population.

Eligible participants will be identified by screening the clinics of participating primary care providers. Participants may be screened for eligibility and consented either by phone or in person at their appointment with the primary care provider in a participating clinic. As required, this study will be posted on ClinicalTrials.gov, where interested, eligible participants may contact the study team to enroll.

Lastly, we will also use patient incentives as they've shown beneficial to patient participation in ongoing studies. Remuneration will occur at enrollment and with additional incentives along the study duration.

5.6 ADDITIONAL SUBGROUP (AIM 3)

In Aim 3 of this study, we will evaluate the adoption, fidelity, and perceived usefulness of the intervention among primary care providers. This will include primary care providers who have permitted the study team to screen their patients for eligibility and have been asked to discuss the EDI with their patients. We will distribute a provider survey to these providers via email, mail, or in person at the clinics.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

We will use a cluster-randomized controlled trial design to assess the impact of patient education and coaching on outcomes. Ten clinics are the unit of randomization and will be randomized to either the intervention (5 clinics) or control groups (5 clinics). This design minimizes the potential problem of contamination between patients or providers within one clinic.[66]

Patients within clinics assigned to the control group will be given a Control-EDI about kidney disease in general (not tailored to the patient) during their enrollment visit. A waiver of consent is requested for the EDI, and an informed consent for the data and biospecimen collection will be obtained after their visit. This information sheet will be given to the patient by a primary care provider during their enrollment visit. After the enrollment visit, if they consent, patients in the control group will answer survey questions, have blood pressure taken and be asked to provide one blood test (to check Egfr and serum creatinine) and one urine test (to check urine protein:creatinine—which is one urine test that combines analysis of protein and creatinine into one test). The patient will receive follow up calls from study personnel at approximately 1, 6, and 12 months after their enrollment visit. The purpose of these calls is to remind patients to meet with the study team for their study visits at 1, 6, and 12 months after initial enrollment, where the patient will answer survey questions, have blood pressure taken, and at the last visit (12 months after enrollment) provide one blood (Egfr and serum creatinine) and urine test (urine protein:creatinine).

Patients within clinics assigned to the intervention group will be given a personalized Intervention-EDI during their enrollment visit. A waiver of consent is requested for the EDI, and an informed consent for the data and biospecimen collection and health coaching will be obtained after their visit. The Intervention-EDI will be tailored with personalized information specific to the patient (the patient's most

recent blood pressure, their urine protein level and most recent Egfr-estimated glomerular filtration rate). There is also a space for their provider to type in a sentence about any goals or take away points they want the patient to remember. After the enrollment visit, patients will answer survey questions, have blood pressure taken and be asked to provide one blood test (to check Egfr and serum creatinine) and one urine test (to check urine protein:creatinine). The patient will receive follow up calls from study personnel at approximately 1, 6, and 12 months after their enrollment visit. The purpose of the calls is to remind patients to meet with the study team for their study visits at 1, 6, and 12 months after initial enrollment, where the patient will answer survey questions, have blood pressure taken, and at the last visit (~12 months after enrollment) provide one blood (Egfr and serum creatinine) and urine test (urine protein:creatinine).

Patients in the intervention group will also receive health coaching through calls from a health coach after their enrollment. The goal for the number of coach calls will vary based on individual patient needs, however, we are targeting approximately 4-6 calls in number, over the 12-month period of the study. There are 4 topics areas related to blood pressure and CKD coaching that will be the focus of the calls, so the target number of coach calls is expected to take approximately four to align with one call per topic area. However, the actual number of coach calls will include first, getting a baseline assessment on where the patient feels they are at related to each health behavior which may take for some patients a full 30 minutes. Further, additional calls to the patient may be more or less depending on individual patient needs. It is important to the patient-centered autonomy and values/goals setting upon which coaching is grounded to be flexible to the patient. Coaches work with the patients to determine the areas patients feel they need for support in health behavior changes related to blood pressure control and CKD. Further, coaches provide motivational interviewing with the patient to support implementation of those changes. Lastly, coaches will have pre-determined and vetted educational resources that are pulled from and adapted from the UM patient education online resources (careguides.umich.edu/kidney). These are sent to patients who may need or request specific information on behavior topics related to blood pressure and kidney disease.

6.1.2 DOSING AND ADMINISTRATION

Not applicable

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Not applicable

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not applicable

6.2.3 PRODUCT STORAGE AND STABILITY

Not applicable

6.2.4 PREPARATION

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The nature of this education and coaching study does not allow for blinding of patients or their providers to education or coaching, or to getting study measures at time points along the study. Therefore, providers and patients might be prompted to engage more in care than they might otherwise. However, if this occurred, it would occur in both patients from control and intervention clinics, and thus likely work against our hypothesis uniformly–so it is unlikely we would have Type I error. It is also possible that patients who agree to participate in this study will be significantly different than those who decline. However, we believe patients should choose the level of involvement they have in their care. We do not endorse mandatory autonomy[70] and believe that patients who are uncomfortable taking a fuller role in their own care should not be forced to.

This cluster randomized trial design (each clinic is a cluster) was chosen because it minimizes the potential problem of contamination.[66] Clinics are randomized and assigned to either intervention or control. Thus, patients and providers within each cluster will only be exposed to either the intervention or control. It is also an appropriate design for trials that include pragmatic aspects such as this.[66]

6.4 STUDY INTERVENTION COMPLIANCE

All proposed research activities will be approved by the Institutional Review Boards at UM (the University of Michigan) and DMC/WSU (Detroit Medical Center / Wayne State University (WSU) Health Systems). A Data Safety and Monitoring Plan will be put into place as part of the study's manual of operations–to monitor patient safety and evaluate the ability of the investigators to conduct the proposed study with utmost regard for patient / provider protection and confidentiality, and is further described in section 10, and will be included in the MOP.

At study start, all research personnel, coaches and staff will undergo training and in-service meetings about the study, their role in the study, all applicable procedures relevant to their job duties, and the importance of data security and compliance. Further, all study personnel are required to complete and be certified by the Program for Education and Evaluation in Responsible Research and Scholarship (PEERRS) or equivalent, and maintain this certification.

Standard reporting forms to track study activities (research screening, recruitment, enrollment and obtaining study measures) will be created and included in the MOP. All research personnel will be trained in the forms, how to use them, with review of confidentiality, secure storage and documentation protocols. A review of these reporting forms will occur no less frequently than quarterly for all participating sites (UM and DMC/WSU). Any diversions from expected protocols will be reviewed by study team members and PI, with root cause analyses to identify contributors, and resolution.

Providers within clinics assigned to the control group will receive a standardized CKD education session, to review the project, reinforce meaning and management principles of CKD, BP targets, and BP management aligned with current guidelines. During this session providers will receive brief didactics to reinforce communication principles at the patient-provider interface,[71] and examples of how to review the control-EDI with patients during clinic visits.

Providers in intervention clinics will also receive standardized CKD education sessions,[71] with additional training for intervention providers on using the Intervention-EDI. Education sessions are based on prior training that the PI developed and led which on average took ~45 minutes to complete.[11] The slide set for the providers along with instructive materials will be included in the MOP.

Providers are often busy, and every provider may not be able attend in person sessions. Thus, a web-based, concise overview of the provider training for providers in both control and intervention clinics will be made available for providers to refer back to, that will include a short online video explaining the study purpose and a step by step tutorial on expectations for the study. The materials adapted for this online resource, along with its URL will be included in the MOP.

Coach recruitment: Health coaches will have a Master's Degree in health education and health behavior, counseling psychology, or social work, or training in health behavior with degrees in nutrition (i.e. registered dieticians). Coaches will be evaluated and hired that demonstrate empathetic and interpersonal skills as determined by their responses to appropriately crafted scenarios.

Coach training: Coaches will receive a 2-3 day training program led by the PI and study team members with expertise in health coaching, and advised by Dr's Resnicow and Fagerlin.

A core element is that this training is interactive and in-person to enhance coach confidence, skills, and effectiveness for this study. This training session offers approximately 8-10 hours of face-to-face training in Motivational Interviewing (MI), 1 hour of face-to-face training in behavioral therapy, and additional training for CKD, high blood pressure and the study protocol. Training sessions will be led by Dr. Resnicow with input from Dr. Fagerlin and with assistance from study team members with expertise in health coaching.

For two decades, Dr. Fagerlin has developed through research pragmatic approaches to shared decision making and patient engagement in chronic disease. For over 25 years, Dr. Resnicow has developed and refined a curriculum that includes a mix of didactic and experiential activities, teaching MI skills with real time constructive feedback. Core MI techniques include the use of reflective listening, allowing the client to interpret information, agenda setting, rolling with resistance, building discrepancy and eliciting self-motivational statements or "change talk." Training will include standardized, role-played patient encounter that is videotaped during the training session, with scoring using the One Pass system.

One Pass is a MI fidelity assessment and supervision tool; it requires raters to listen to a clinical encounter only once before providing feedback. While preliminary feedback will be given immediately to the coach, they will also receive a consultative phone call from an MI trainer at the University of Michigan several weeks later, during which they will discuss their performance in greater detail. To enhance skill acquisition and reduce skill atrophy, we will provide each participant with training materials to enhance their core skills of reflective listening, building motivation, and eliciting change talk. The training materials will demonstrate a range of full clinical scenarios relevant to the project using simulated examples.
Remaining time in the training session will be used to review the study protocol.

Coach call logging, tracking, monitoring: A novel aspect of ensuring compliance and documentation of coach calls for enrolled patients in the intervention clinics, is in the fact that this study will be using and online study dashboard, referred to as the health coaching portal. The study team at UM has created this in concert with the Center for Health Communications Research, and it is based on prior work (copied from and adapted) using a similar online portal by co-investigator, Dr. Ken Resnicow for a study of 3000 patients to use coaching to reduce childhood obesity. The portal provides a graphical user interface, for coaches that include coach surveys and scripts to use during coach calls for each participant. Its primary function is to allow coaches to schedule, track, deliver and document their coach calls with enrolled patients during the intervention, within one centralized location –i.e. the portal. It

supports standardization, and excellent means for tracking and monitoring coaching for participants. It also provides study personnel, password protected access to study related coach activities as described below:

Content	Use	Access	Storage
Participant contact information	Research intervention delivery only.	Coach, study team members, patient participant	UM secure server
Baseline coach surveys/scripts	Research and intervention.	Coach, study team members, patient participant	UM secure server
Follow up coach surveys/scripts	Research and intervention.	Coach, study team members, patient participant	UM secure server
>Coach counseling notes >Summary notes that can be sent to primary care provider >Summary notes for participants	Research and intervention delivery and clinical.	Above, plus providers of patients enrolled in intervention	UM secure server
>Education resources for patients >Education and support resources for coaches	Research and intervention delivery and clinical. Study procedures reference.	Coach, study team members, patient participant	UM secure server

Once participant enrollment begins, all calls will be recorded to facilitate the provision of ongoing feedback by an MI (motivational interviewing) supervisor to coaches about their MI skills, and to review and resolve any concerns related to adherence and compliance with coaching surveys and scripts. MI supervisors are also clinicians and researchers who are on the study team—with expertise in MI.

6.5 CONCOMITANT THERAPY

Not applicable.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from coaching does not necessarily mean discontinuation from the study, and remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation
- Whether discontinuation was patient-driven (patient non adherence or chose to discontinue), study-related (investigator-driven per discontinuation protocols), or other
- The time from enrollment to discontinuation.

For any patients lost to follow up, we will use any data collected from participants lost to follow up from enrollment to the point at which they were lost to follow up

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Clinic 'participants' (i.e. the specific clinics that each are a cluster) may drop out of the study. We feel this is very unlikely given strong support from clinics and leadership at each clinic. However, if this occurs prior to enrollment, we will try to identify other clinics to participate, a strength being that clinics in this study are affiliated with large health systems that have many other potential clinics.

Patient-Participants are free to withdraw from participation in the study at any time upon request. They can withdraw by informing their coach (if receiving the intervention), a study team member, or directly to Dr. Julie Wright, the study Principal Investigator. If a patient withdraws from the intervention clinics, his/her study-related coach calls will end, he/she will no longer receive surveys / coach calls, he/she will no longer have access to the health coaching portal, and all contact information will be deleted. If a patient withdraws from the control or intervention clinics, they will no longer be contacted to be reminded to come in for study measures/visits or to take surveys or when applicable, provide biological samples (enrollment and last visit). We will continue to securely store and analyze all data that the parent has provided up to the date of withdrawal.

An Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Newly patient self-identified pregnancy during course of the study (this is exclusion criteria)
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention, such as:
    - Patient reaches ESRD and receives ongoing Hemodialysis/Peritoneal dialysis.
    - Patient receives kidney transplant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized)
- Newly patient terminal illness diagnosis during the course of the study
- If the participant changes their primary care provider to be outside of the health system

While we do not anticipate provider initiated withdrawal of patient-participants, these events will be addressed on a case-by-case basis.

The reason for participant discontinuation or withdrawal from the study will be recorded on the "Reason for Withdrawal" Case Report Form (CRF) in REDCap. (Procedures for this will be included in the MOP) Subjects who have consented and are randomized but do not receive the study intervention may be replaced. Subjects who have consented, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for four scheduled research visits plus 4-6 health coaching calls and is unable to be contacted by the study site staff.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit prior to the next scheduled study visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls + emails, and, if necessary, a lost to follow up letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 PATIENT OUTCOME ASSESSMENT (AIM 2)

Eligibility: All patients coming in for appointments at participating clinics will be screened for eligibility. Patients will be eligible if they are adults (21-85 years-old), have a diagnosis of hypertension and meet criteria of uncontrolled hypertension, have CKD stages 3–5, are not pregnant, and do not have cognitive, language, or vision impairments that would prohibit seeing the EDI or participating in coaching activities.

Uncontrolled BP is defined as a systolic blood pressure >130 mmHg, and/or a diastolic blood pressure >80 mmHg noted in an ambulatory care setting within the past one year. The University of Michigan has a registry of all patients within the system's ambulatory clinics with CKD and hypertension. Through this registry we have found that a single, most recent BP correlates very closely with an average of the three most recent BPs taken within ambulatory clinics. Pregnant women with CKD have care goals that are unique compared to the general population with CKD and hypertension. Thus, their educational needs are outside the scope of this study and they will be excluded.

Screening: We are working with UM and DMC/WSU IT to develop secure screening lists of eligible patients and for the ten sites. These lists will likely be generated on the order of weeks prior to the scheduled appointments. The study team will obtain approval from the provider before approaching the patient. We are also working with UM and DMC/WSU IT to explore the use of BPAs and how a BPA may

be used for patients with CKD. However, the study team will not implement a BPA without obtaining approval from the IRB first.

Quality initiative to improve CKD education: Prior to recruitment, patients at the control clinics will get a generic Control-EDI from their provider with CKD educational resources. Patients at the intervention clinics will review a pilot-tested Intervention-EDI with their provider in clinic, and receive a printed version at check out. This Intervention-EDI will cover basic CKD knowledge as well as review their recent lab results. Patients in the control clinic will just receive a generic Control-EDI about CKD. Copies of each handout are to be included in the MOP.

Recruitment and study procedures: After patients check out, a study team member will approach them for recruitment. A pre-screening script will be used to ensure that the RA does not ever inform the patient of their CKD diagnosis. As stated above, up to 80% of people seen by primary care doctors do not know they have CKD. If the patient consents to be in the study, the first research survey will be administered and their BP and blood and urine specimens collected.

For the intervention group, a health coach will call the patient approximately within one week of enrollment to obtain coaching baseline survey measures. Between the time of enrollment and 11 months after enrollment, the health coach will schedule 4-6 coaching calls with the patient depending on their needs and availability.

Both groups will have follow-up visits scheduled with the study team at approximately 1, 6, and 12 months after enrollment to obtain research survey measures and BP. These visits will either take place at their original clinic, at other on-site clinic visits within the health system, at core lab facilities at UM for UM clinics that are not set up to offer research activity space on premises, or over the phone. When follow-up visits take place in person, we will find a private space to work with the participant. At the last patient study visit, blood and urine samples will be collected along with final surveys. We will allow some flexibility with the time points to accommodate the schedules of patients. A project flow diagram and schedule of activities are included in sections, 1.2 and 1.3 respectively.

The specific outcomes of interest are in appendices, section 10.5. Efficacy of the study is primarily based on examination of whether patient CKD-specific education and subsequent health coaching improves systolic blood pressure compared to patients who only receive general kidney information and no health coaching. Additional clinical and patient reported measures will be assessed as time points along the study and at study conclusion to determine efficacy of the intervention on additional clinical and behavioral/knowledge outcomes important to patients.

8.1.2 IMPLEMENTATION OUTCOME ASSESSMENT (AIM 3)

Aim 3 of the study aims to examine whether and to what extent implementation outcomes (provider adoption, fidelity, and perceived usefulness) are associated with clinical and patient-reported outcomes. The participants will be primary care providers who has allowed the study team to screen their patients for eligibility and approach for recruitment in the study.

Provider adoption will be assessed through several methods: (1) a provider survey, (2) patient surveys incorporating a question regarding whether the EDI was used during their visit, which has been completed in Aim 2, and (3) an EMR query to check if the EDI was populated into the patient's EMR, or via research staff for instances where the EDI was used in its paper format in the clinic.

Provider fidelity to the EDI will be measured by checking if the provider entered 1-2 additional messages as recommended (queried through the EMR), or by observation during face-to-face encounters when using the paper version.

Provider perceived usefulness of the intervention will be evaluated using specific questions included in the provider survey.

The provider survey will be distributed via email, mail, or in person at the clinics. We will primarily contact these providers through their work emails. If they have left the health system, we will use the alternative email addresses or mailing addresses they provided.

Additionally, as an exploratory outcome, **health coach perceptions of the intervention** will be assessed as part of the implementation outcome evaluation. Health coaches involved in delivering the intervention will be asked to complete an open-ended survey to share their experiences, aiming to identify areas for refinement and inform future implementation strategies. The health coach survey will be distributed via email.

8.2 SAFETY AND OTHER ASSESSMENTS

A Data Safety and Monitoring Plan will be put into place as an integral part of the study's manual of procedures—to monitor patient safety and evaluate the ability of the investigators to conduct the proposed study with utmost regard for patient / provider protection and confidentiality. The study will not begin without approvals of the University of Michigan IRB, as well as any local IRBs (DMC/WSU). The PI and study team will conduct periodic reviews of regulatory requirements.

In addition, in accordance with federal regulations, the Data Safety and Monitoring Study Board will convene to act in an advisory capacity to the study and NIH NIDDK to monitor patient safety and evaluate the ability of the investigators to conduct the proposed research with utmost regard for patient protection and confidentiality. The DSMB will undertake the following tasks:

1. Approve initiation of the proposed study prior to study enrollment.
2. Review the research protocol, informed consent documents, and plans for data safety and monitoring.
3. 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 the clinical centers, and other factors that may affect study outcomes. This will occur at a minimum at the study initiation, when enrollment is ~25% complete, ~50% complete and 100% complete. Additionally, if the study is slow to recruit the DSMB will meet at least yearly.
4. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.
5. Protect the safety of the study participants.
6. Report on the safety and progress of the study.
7. Make recommendations to the study team and NIH NIDDK, and if required, to the IRBs concerning continuation, termination or other modifications of the study based on the observed beneficial or adverse effects of the study procedures.

8. Review interim analysis in accordance with stopping rules that will be developed for the study protocol and that will be defined in advance of data analysis and have approval of the DSMB.
9. Ensure the confidentiality of the study data and the results of monitoring.
10. Assist the funding agency by commenting on any problems of study conduct, enrollment, sample size, and / or data collection.

All aspects of the proposed research will be conducted with utmost regard for the welfare and privacy of the volunteer participants. The DSMB meetings shall be closed to the public because discussions may address confidential patient data. Urgent or emergent meeting of the DSMB may be called at any time by the Chair of the DSMB or by the NIH Project Officer in the event of issues regarding patient safety. The format for the DSMB meetings may be open or closed as dictated by the agenda of the meeting.

Termination of the Study: A majority vote of the DSMB will be required to issue a study termination recommendation. Potential reasons could be but are not limited to:

1. An exceedingly large number of serious and unexpected adverse events.
2. Severe and not rectifiable logistical or data quality problems.

The DSMB will consist of selected members who are external to the study and who have no conflicts of interest or scientific involvement with the study. The DSMB will be lead / chaired by a Dr. T. Alp Ikizler M.D. He has served on other DSMBs and is both a clinical leader and well-established researcher. As needed, the PI and study biostatistician will be available to provide input and/or attend the DSMB's meetings, at request of DSMB.

In addition, any data integrity and patient safety-related issues will be prioritized. At study start, all research personnel, coaches and staff will undergo training and in-service meetings about study procedures. The importance of data security and compliance with procedures will be emphasized. All study personnel are required to complete and be certified by the Program for Education and Evaluation in Responsible Research and Scholarship (PEERRS) at the University of Michigan every 3 years (or equivalent, i.e. CITI training as applicable depending on University/site affiliation). A standard reporting form for adverse events will be created and completed by study personnel on an as-needed basis. Adverse events will be discussed at biweekly team meetings or sooner if needed and reported to the IRB. Documentation of completion of tasks and DSMB activities will be filed in the Regulatory Binder. The binder will also contain all communications to the IRB, including the initial application, study protocol, any amendments, annual IRB renewal, IRB approvals, and a summary of adverse events. It will be the responsibility of the project team to maintain and update the Regulatory Binder. In addition, the Project Manager/Coordinator will review consent forms, and source data at regular intervals along the study, with reviews documented in a Monitoring Log, accompanied by a Monitoring Report, which will be filed in the Regulatory Binder.

Lastly, this project includes an applicable clinical trial that will be registered with ClinicalTrials.gov.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

According to the UM Medical School Office of Research definition, an adverse event (AE) is any experience or abnormal finding that has taken place during the course of a research project and was

harmful to the subject participating in the research, or increased the risks of harm from the research, or had an unfavorable impact on the risk/benefit ratio.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

According to the UM eResearch definition, adverse events are categorized according to the following grading system:

0 – No adverse event
1 – Mild AE – No treatment needed
2 – Moderate AE – Resolved with treatment
3 – Severe AE – Inability to carry on normal activities, required professional medical attention
4 – Life-threatening or disabling AE
5 – Fatal AE

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

We will use the following levels of relationship to study intervention, which is in accordance to eResearch:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other

concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.3.3.3 EXPECTEDNESS

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. *It is important to note in this population of patients with moderate to severe kidney disease AND uncontrolled high blood pressure, that they are already at high risk compared to the general population of the following:*

- Cardiovascular and cerebrovascular events (e.g. heart attack, congestive heart failure, stroke)
- Complications from CKD itself that are expected and a part of CKD (especially in more advanced CKD):
    - Hematologic problems e.g. anemia, low counts of cells if on immune suppression
    - Any infection because of immune suppressed state in chronic disease or medications
    - Bone and mineral problems e.g. with calcium, phosphorus in blood, stones, bone fractures, hyperparathyroidism
    - Cardiac arrythmias
    - Flank pain from stones, cysts, or that can occur in certain types of CKD e.g. due to IgA nephropathy
    - Fatigue and being tired
- Complications related to often-times related co-morbid conditions, e.g. diabetes with high or low blood sugar, retinopathy, neuropathy
- Progression of kidney disease to end stage renal failure
- Weight gain or weight loss due to kidney disease or co-morbid conditions
- Exposure to medications that can result in hypotension, muscle breakdown, syncope, leg swelling, drug-drug interactions, and electrolyte imbalances/which can sometimes be severe and even fatal
- Exposure to medications that can cause or be related to cancer or increase risk of cardiovascular events or infection (immune suppressive therapies)
- Electrolyte imbalances due to their kidney disease
- Infection due to immune suppression associated with kidney disease and/or medications used to manage kidney disease
- Difficulty coping with multiple co-morbid conditions and sometimes even depression
- Psychosocial difficulties
- Difficulty breathing, with shortness of breath
- Scheduled surgery or procedures or post-operative complications
- Common conditions in older adult population e.g. fall, altered mental status, syncope
- Acute kidney disease

As such, these events are expected in this population regardless of whether or not they receive CKD-education and health coaching, and it would not be considered unusual for any of these events to occur in this population during the course of the study. However, these potential expected and unexpected risks will be outlined for patients in the informed consent document(s).

The definitions from eResearch on expectedness is as follows:

- Unexpected adverse events (i.e., has NOT been addressed or described in one or more of the following: Informed consent document(s) for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators' brochure or equivalent (for FDA regulated drugs or devices), DSMB/DSC Reports, published literature, other documentation)
- Expected adverse events (i.e., has been addressed or described in one or more of the following: Informed consent document(s) for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators' brochure or equivalent (for FDA regulated drugs or devices), DSMB/DSC Reports, published literature, other documentation, or characteristics of the study population)

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All Aes including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All Aes occurring while on study must be documented appropriately regardless of relationship. All Aes will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Aes characterized as intermittent require documentation of onset and duration of each episode.

The study team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious Aes) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

We will report all adverse event according to the UM Medical School Office of Research reporting timetable:

Standard Adverse Event Reporting Guidelines for INTERNAL AEs Occurring at UM

This chart is for studies following IRBMED standard AE reporting and requiring CR. It may be appropriate for some studies to consider a Study Specific AE Reporting Plan. See the gray boxes for information about External AE and UaP reporting.

		RELATED	UNRELATED
UNEXPECTED	Potential Unanticipated Problems (UaPs)[3] Note: Some UaPs are not AEs. Report these events via an ORIO.	**Serious Adverse Event[1] –** resulting in • **Death** • **Life-threatening outcome** Submit AE/ORIO report as *soon as possible*, **but** *within 7 calendar days* of becoming aware of event. Assess SAE to determine if UaP (see below for UaP criteria).	**Serious Adverse Event[1]-** resulting in • **Death** • **Life-threatening outcome** Report in aggregate form via separate AE/ORIO submission *in conjunction with SCR*
		Serious Adverse Event[2] Submit AE/ORIO report *within 14 calendar days* of becoming aware of event. Assess SAE to determine if UaP (see below for UaP criteria).	**Serious Adverse Event[2]** Report in aggregate form via separate AE/ORIO submission *in conjunction with SCR*
		Non-Serious Adverse Event Report in aggregate form via AE/ORIO report *in conjunction with completion of the SCR*. Assess AE to determine if UaP (see below for UaP criteria).	**Non-Serious Adverse Event** **-Do not report to IRB-** Study teams should continue to monitor and log events as they occur for sponsor reporting purposes.
EXPECTED		**Serious Adverse Event[1],[2]** Submit AE/ORIO report *within 14 calendar days* of becoming aware of event.	**For ALL Unrelated & Expected Adverse Events** **-Do not report to IRB-** Study teams should continue to monitor and log events as they occur. If any events appear to be occurring at a severity or frequency greater than previously known or expected, report as 'unexpected' per these guidelines *within 14 calendar days* of identifying this trend.
		Non-Serious Adverse Event (Moderate/Grade 2*) **-Do not report to IRB-** Study teams should continue to monitor and log events as they occur. If any events appear to be occurring at a frequency greater than previously known or expected, report as unexpected *within 14 calendar days* of identifying trend.	
		Non-Serious Adverse Event (Mild/Grade 1*) **-Do not report to IRB-** Study teams should continue to monitor and log events as they occur. If any events appear to be occurring at a frequency greater than previously known or expected, report as unexpected *within 14 calendar days* of identifying trend.	

8.3.6 SERIOUS ADVERSE EVENT REPORTING

We will report serious adverse events according to the Office of Research timetable above. DSMP/DSMB described in section 8.2. We do not anticipate any study-related serious adverse events to occur as this is a study with no more than minimal risk.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable – Any adverse events that may happen will likely be due to individual differences, e.g. baseline health status, instead of systemic issues.

8.3.8 REPORTING OF PREGNANCY

Pregnancy is an exclusion criteria for our study. Within the informed consent form we will include a statement that should a patient become pregnant they must withdraw, in line with procedures stated above in section 7.2. An additional statement will be included to explain why pregnancy is an exclusion criteria, specifically, because the CKD education and health coaching needs of women with high blood pressure and CKD are beyond the scope of this study's intent. Further, blood pressure management and

self-care needs to be carefully led and guided by specialist providers (e.g. maternal fetal medicine doctors).

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, 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 protocol-related documents, such as the Institutional Review Board (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); and
- 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.

8.4.2 UNANTICIPATED PROBLEM REPORTING

According to UM Medical School Office of Research guidelines:
Serious unanticipated problems and Unanticipated Adverse Device Effects (UADEs) must be reported within 7 calendar days of the problem (or within 7 calendar days of the study team becoming aware of the problem). Non-serious unanticipated problems must be reported within 14 calendar days of the problem (or within 14 calendar days of the study team becoming aware of the problem).

If the unanticipated problem involved one or more persons experiencing actual harm, report the unanticipated problem as an adverse event. Refer to the AE Reporting page (*https://az.research.umich.edu/medschool/guidance/adverse-event-reporting*) and follow the instructions provided, using the external or internal form as appropriate.

If a person did not experience actual harm but an unanticipated problem entailed potential harm, and/or risk of harm to subjects or others, refer to the ORIO Reporting page (*https://az.research.umich.edu/medschool/guidance/other-reportable-information-or-occurrence-orio*) and follow the instructions provided.

If the IRB concurs that an event is an unanticipated problem the study team will follow the policies and procedures outlined in the University of Michigan Human Research Protection Plan Operations Manual, part 12.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STUDY HYPOTHESES

Study hypotheses are aligned with our study aims. All aims related to this study are outlined below, and separate sub-studies are noted, where applicable.

Aim 1: Optimize the process of delivering a provider-led, coach-supported patient education intervention prior to using it in a cluster-randomized controlled trial. We will use CQI and systems improvement methods, with input from multi-disciplinary teams, to streamline how the provider-delivered EDI will be integrated into clinics. [This aim and its activities are covered with a separate but related QI IRB approved study – HUM00152989.] We hypothesize that: **H1.** CQI and systems approaches will facilitate resource and process efficiency comparing intervention and control groups.

Aim 2: Identify the impact of a provider-led, coach-supported patient education intervention on patient clinical and self-reported outcomes over one year using a cluster-randomized controlled trial. The primary outcome is change in systolic blood pressure between T0 and T3, and the secondary outcomes are slope of systolic BP between all timepoints, change and slope in diastolic blood pressure between all timepoints, estimated glomerular filtration rate (EgfR), urine protein:urine creatinine, serum creatinine, medication adherence, patient knowledge, self-efficacy, motivation, and satisfaction. We hypothesize that, compared to patients in the control group, patients in the intervention group will: **H2.** Have lower blood pressure. **H3.** Experience higher EgfR, greater reductions in urine protein, and higher medication adherence. **H4.** Have greater knowledge about CKD, and higher self-efficacy, motivation, and satisfaction with CKD care.

Aim 3: Identify whether and to what extent implementation outcomes (provider adoption, fidelity, perceived usefulness) are associated with clinical and patient-reported outcomes. We hypothesize that: **H5.** Within intervention clinics, provider adoption, perceived usefulness of, and fidelity to the provider-delivered Intervention-EDI will be high and positively associated with clinical and patient-reported outcomes. **H6.** Providers will perceive the intervention as beneficial and feasible for future translation into community settings.

9.2 SAMPLE SIZE DETERMINATION

The primary outcome is systolic BP. A conservative difference of systolic BP between intervention and control groups ranges from 3–5 mmHg.[72-76] It is assumed that each patient will have BP checked at least four times in person. Additional clinical BPs in the EMRs, including those used by various specialties within the health system, will be recorded as available. Sample size calculations are based on a comparison of intervention and control groups in baseline minus 12 month differences in a cluster-

Difference (mmHG) Between Groups	Intraclass Correlation	Standard Deviation	Patients per clinic	# clinics needed
3	0.05	7	30	10.3
3	0.05	7	50	8.9
3	0.05	7	100	7.8
3	0.1	7	30	15.9
4	**0.1**	**7**	**30**	**9.4**
4	0.1	7	50	8.6
4	0.15	7	30	12.5
5	0.15	7	30	8.3
5	0.15	7	50	7.9

randomized controlled trial. A significance level of 0.05, power of 0.90, and a standard deviation of 7 for the between-patient variation in baseline minus 12 month differences were assumed in all calculations.[77] Based on prior studies, the intraclass correlation coefficient (ICC) for clinics is likely to be 0.10 or lower.[78] The table above gives the total number of clinics required to detect a difference between groups of 3–5 mmHg with 90% power for ICCs of 0.05, 0.10, and 0.15, and 30, 50, or 100 patients per clinic. Based on these power calculations, balancing rigor and efficiency, 9.4 clinics (rounded to 10) are needed if we recruit 30 patients at each clinic, to detect a difference of 4 mmHg between the intervention and control group clinics with an ICC of 0.10. Recruiting up to 50 or even 100 patients does not significantly change the number of clinics needed. We have commitment from 10 participating clinics, allowing an equal number in each treatment group and giving us ample power to detect differences in the primary outcome. Enrolling 30 patients per clinic in 10 clinics yields a total patient enrollment of 300. However, prior similar studies show there may be patient withdraws of up to 10-15%.[11] We will increase the target enrollment number for the participating clinics (for up to 10 participants per clinic) where we are able to recruit more and if/when there is higher than 10-15% drop out. We will also add clinics (for up to 5 clinics) as supplementing clinics for clinics that are not on track of enrolling at least 15 participants. As such we will increase enrollment targets to a total of 450 patients.

9.3 POPULATIONS FOR ANALYSES

For the primary outcome (12-month systolic BP), an intention-to-treat analysis will be used, with treatment (intervention) effects tested in the initial models described for cluster-randomized trials with pre-planned covariates.[79] If a clinic drops out of the study prior to patient enrollment, we will consider asking other clinics at study sites to participate as alternatives. If a clinic drops out after study enrollment commences (which we do not expect, as shown in letters of support), they will be analyzed as intention-to-treat. Clinical trial analyses often are limited to those patients with complete data. However, this strategy may yield overly optimistic effect size estimates since problems adhering to the protocol or worse health status often are associated with missing data. Although we will conduct an initial analysis using only observed data, we will conduct a second analysis that imputes missing data for patients using the method described by Lavori, Dawson, and Shera.[80] In brief, we will use logistic regression to model patients' or clinics' likelihood of having outcome data and define strata within which outcome values are missing at random. We will then stratify according to these propensities, randomly sample from the observed outcome distribution, and impute these values for missing data within each stratum. When data are missing for items within survey scales, we will use recommended imputation procedures rather than deleting patients list-wise from the analysis.[81]

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will follow international guidelines for analysis and reporting of cluster-randomized clinical trials.[79] We will first examine the distributions of all study variables to assess missing data, possible coding errors, and distributional form, including skewness, variance, and extreme values. Next, we will explore bivariate associations between study variables. We will examine baseline data for clinically important differences between treatment groups for demographics and clinical data, including BP and other potential prognostic indicators, at the patient level.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For the primary outcome (12-month systolic BP), an intention-to-treat analysis will be used, with treatment (intervention) effects tested in the initial models described for cluster-randomized trials with pre-planned covariates.[79] Systolic BP is continuous and analysis requires accommodating correlation within clinics, so we will use linear mixed models with a random effect for clinic implemented using the MIXED procedure in SAS. The baseline systolic BP will be included as a covariate. Two secondary analyses will be performed. First, the within-person slope of systolic BP over time will be modeled, using all time points including baseline as outcomes, with an interaction between intervention and control groups and time included to test for different slopes between intervention and control groups. Second, baseline covariates that significantly differ between treatment groups will be included as covariates in models comparing treatment groups. Diastolic BP is inherently measured with systolic BP and is also a continuous measure. We will examine differences in diastolic BP in secondary analyses, similarly as described for systolic BP.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Although the study was not powered specifically for secondary outcomes, the majority of the secondary outcomes are continuous variables (time patients spend in clinic visit at t(0), EgfR, urine protein, as well as most survey measures, including but not limited to: patient knowledge, medication adherence, self-efficacy, motivation, and satisfaction. For more details, please see Appendix 1.) for which power can be calculated based on effect sizes (multiples of the standard deviation) for any specific outcome. With the original target, a total of 350 patients (175 in the intervention and control group each), we have a 90% power to detect an effect size of 0.4 assuming an ICC of 0.10 within cluster. This is a small to moderate effect on Cohen's scale where approximately 0.25 is a small effect and 0.50 is moderate. We will try to achieve the same overall power by adding patients at clinics where we are able to recruit more and if/when there is higher than 10-15% drop out. We will also add clinics (for up to 5 clinics) as supplementing clinics for clinics that are not on track of enrolling at least 15 participants.
As above, for continuous data, analysis requires accommodating correlation within clinics, so we will use linear mixed models with a random effect for clinic implemented using the MIXED procedure in SAS to test the treatment (intervention) impact on outcome. The respective baseline continuous measure will be included as a covariate in each model. For Aim 1 hypothesis testing (whether delivery of EDI is efficient), the time patients spend in clinic at visit t(0), is only a one-time, baseline comparison.

9.4.4 SAFETY AND INTERIM ANALYSES

Safety monitoring, classification of events and reporting are described in section 8. There are no planned interim analyses other than what is done for study data safety and monitoring along enrollment for the study. When enrollment is 25% complete, 50% complete, and 100% complete, the following will be collected and analyzed descriptively and reviewed by the study DSMB:

- Number screened, number enrolled, number withdrawn.
- Demographics for patients enrolled in control and intervention clinics.
- Adverse events analysis which will include descriptive analyses of the adverse event, severity, whether unexpected or expected, whether or not there were associated hospitalizations.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

For outcomes that are categorical (e.g. provider adoption of, and fidelity to, the EDI, EMR medication refills and exploratory analyses related to patient behaviors in the past week), we will test intervention effects using logistic regression for longitudinal data (SAS Genmod or Glimmix procedure). When examining whether provider adoption and fidelity to the EDI are associated with clinical (systolic BP,

EgfR, Urine protein) and patient-reported (patient knowledge, medication adherence, self-efficacy, motivation, and satisfaction) outcomes, analysis will be limited to the clinics assigned to intervention. We will use surveys that are previously validated where able (e.g. CKD knowledge survey by Wright et al.[25]). For surveys that are new or adapted for this study, we will examine for evidence of reliability and validity. Specifically, Cronbach's alpha (or Kuder Richardson-20) will be used to quantify internal consistency among items. We will use principal component factor analysis to characterize clustering of items and potential sub-scales.[82] We will evaluate for evidence of validity comparing correlation to original scales when surveys are adapted, or to examine for expected associations with measured characteristics when no prior scales have been developed. To detect associations between the survey scales and measured characteristics (e.g. patient sex, age) chi-square tests, t-tests, and Kruskal-Wallis tests will be used depending on the variables compared.

9.4.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed by measure and time point except for safety monitoring and interval DSMB reporting— and then only as aggregate and not identifiable, as outlined in section 8 and included in the MOP.

9.4.7 EXPLORATORY ANALYSES

Cost-effectiveness of coaching: A key to the sustainability of our intervention is to understand the cost of the intervention versus potential cost saving from lowering the rate of use of other resources (e.g. ER or hospital visits). A formal cost-effectiveness modeling exercise is beyond the scope of this study, but we will examine annual costs of coaches' actual clinical work, so that a formal cost-effectiveness assessment can be performed in future next steps. We will do this by tracking the hours necessary for coaches' clinical work (i.e. time spent coaching patients, not research-related activities) using time logs. We will then estimate the annual patient volume for each coach and account for the costs of the coach using their pay scale broken down into an hourly wage. In next steps, cost savings will be estimated by examining the differential in use in patient resources (e.g. inpatient hospitalizations, ER visits) between groups. Similar approaches have been used previously.[83]

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent will be obtained through one of two methods: The preferred method is in-person, with a signature obtained on a paper version of the informed consent. If the patient cannot stay after their appointment, they will be given the option to complete the consent process through phone. Instead of a signature, they will be asked if they agree to be in the study. Answering "yes" to that question indicates consent to enroll in the study. If the patient is consented on the phone, they will be given a copy of the consent form (hard copy) for their personal records. The consent form describes in detail the study intervention, study procedures, risks and benefits, and contact information for the study team. Copy of

the consent forms (one for patients enrolled to serve as controls and other for patients enrolled to receive intervention) are uploaded in eResearch.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The preferred method of informed consent is in-person. However, if the patient cannot stay after their appointment, we will give them the option to consent over the phone.

In-person consent:
Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The study team member will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

Phone consent:
A study team member will go through the Institutional Review Board (IRB)-approved consent form content on the phone with the patient. The study team member will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to ask questions prior to verbally consenting. The patient will be given a copy of the consent form (hard copy) for their personal records.

The participant will sign/say yes to and complete the informed consent process prior to any procedures being done specifically for this study and activities that are not unregulated. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without negative impact to them (without prejudice). A copy of the informed consent document will be given or sent to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be emphasized and consent will include a specific statement that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.1.3 AIM 3 CONSENT PROCEDURES

In Aim 3, participating primary care providers will receive a provider survey accompanied by an informed consent cover letter, available in electronic or paper format. This cover letter will explain the purpose of the study, the voluntary nature of participation, confidentiality measures, and contact information for the study team. Providers will provide consent by proceeding with the survey after reading this letter.

Similarly, health coaches will receive an open-ended survey to share their perceptions of the intervention. An information sheet at the beginning of the survey will explain its purpose, the voluntary nature of participation, confidentiality measures, and contact information for the study team. Health coaches will indicate their consent by proceeding with the survey after reviewing this information.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, DSMB and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples, patient-reported measures (either during coaches or study surveys) and clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private areas. Coach calls will be direct to patients and arranged with patients prior, as appointments, so that patients are allowed to ensure they are available and in an appropriate setting to receive coach calls.

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

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

The database that contains survey results and clinical data will only be identified by study ID's. A separate file will be created to link the participant's name and other identifiable data to the study ID. Only the core study team (e.g. PI and research assistants) will have access to the password protected linking file. We do not anticipate any information to be identifiable without the linking file. Only health coaches and core study team key study personnel will be able to have access to identifiable information

on patients receiving health coaching and that would only be in the case of logging into the secure password protected coach consul for study purposes and/or coaching (in cases for coaches).

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Michigan. All transferred data will abide by local and UM policies regarding sharing data and encryption. The study data entry and study management systems used by clinical sites and by University of Michigan research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Michigan.

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Biochemistry: serum creatinine will be collected at the time of enrollment and at time of study completion (12 months post enrollment). This equates to 2 serum creatinine measurements per patient in total for the study. A total of about 8 tablespoons of blood will be collected from each participant (4 tablespoons once at enrollment plus 4 tablespoons at completion of the study). This equates to a total of about 120 ML of blood collected. This will be collected using existing local UM and DMC/WSU laboratory facilities for collection and processing, using their standardized assays. Previously established and local laboratory practices will be followed.

Urine testing: a urine protein measurement and a urine creatinine measurement will be collected at the time of enrollment and at study completion for the patient. This is to calculate urine protein to urine creatinine ratio. At least 10 ml will be collected and no more than 200 ml (it is difficult for patients to urinate a specific amount because the sample is collected into a small cup). This will be collected using existing local UM and DMC/WSU laboratory facilities for collection and processing, using their standardized assays. Previously established and local laboratory practices will be followed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. The DSMB will consist of selected members who are external to the study and who have no conflicts of interest or scientific involvement with the study. The DSMB will be lead / chaired by a Dr. T. Alp Ikizler M.D. He has served on other DSMBs and is both a clinical leader and well-established researcher. As needed, the PI and study biostatistician will be available to provide input and/or attend the DSMB's meetings, at request of DSMB. The DSMB will approve initiation of the proposed study for enrollment of human subjects, evaluate the progress of the study at initiation, when enrollment is 25% complete, 50% complete, and 100% complete. Additionally, if the study is slow to recruit, the DSMB will meet at least yearly. In addition, urgent or emergent meetings of the DSMB may be called at any time by the chair of the DSMB or NIH project officer in event of any issues regarding patient safety. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. DSMB reports will be included in status reports (RPPR reporting) to the NIH yearly.

10.1.7 CLINICAL MONITORING

To assure adequate protection of the rights of human subjects, Dr. T. Alp Ikizler, Professor of Medicine and Chief of the Division of Nephrology at Vanderbilt will chair the Data Safety Monitoring Board that will conduct monitoring of the study per a monitoring agreement to be included in the MOP. The established monitoring plan will ensure the quality and integrity of the data through pre-investigation visits, periodic site visits, review of adverse events/subject records, with recording of study progress in enrollment, demographics, and adverse events analyses in regularly scheduled reports.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

To ensure consistent delivery of the intervention and uniform application of enrollment and data collection protocols, we hosted a kick-off meeting in Year 1 attended by investigators, research staff, project support and representatives from each site. Goals of the study were discussed along with design and procedures. Study team members have been split into teams and assigned aspects of the study to develop and give input on study materials development. In addition, we brought in experts in quality improvement (through UM Quality and Innovation Program) and leaders on the study team in continuous quality improvement (CQI). With study team member input, we have developed a study team communication plan for study personnel, staff, co-investigators, as well as providers and staff in involved clinics. We are working with staff at UM to develop an online project website, and there will be an additional secure/password protected feature for providers from involved clinics to sign in and learn more about the study. Descriptions of the study will be produced in a variety of formats for distribution via group emails and as handouts in clinic.

In addition, for specific study procedures, we will produce data collection manuals with detailed instructions for issues such as how to note missing data, how to make changes on data collection forms, and how to adjudicate decisions when survey response options are unclear and have this reviewed by our colleague experts in CQI. In addition, once enrollment begins, data quality issues will be discussed at weekly meetings between project staff and the PI. Data integrity and completeness will be checked periodically by research personnel and reported at biweekly team meetings as described previously in section 8.2.

Quality control (QC) procedures will be implemented beginning with the data entry systems and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Rigor and reproducibility will be maximized by quality control of all study protocols and procedures and by using a robust experimental design for the intervention. This study applies high standards in its methodology and its analysis plan which will be continued through interpretation and results reporting. We will be transparent in reporting experimental details so that others may reproduce and extend the findings in the future.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

Clinical data (including adverse events (Aes), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the University of Michigan. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

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

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations will be addressed in study source documents, reported to the NIH NIDDK Program Official and University of Michigan Institutional Review Board (IRB). The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

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

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

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers years after the completion of the primary endpoint by contacting Julie Wright, MD, MPH.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. This study protocol however does not involve the collection and sharing of genomic data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical 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 design and conduct of this trial. The study leadership in conjunction with the NIH NIDDK and UM and DMC/WSU have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AE	Adverse Event
BP	Blood pressure
CFR	Code of Federal Regulations
CHECK-D	Controlling Hypertension through Education and Coaching in Kidney Disease
CKD	Chronic kidney disease
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CQI	Continuous quality improvement
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMC/WSU	Detroit Medical Center/Wayne State University
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
EcrF	Electronic Case Report Forms
EDI	Encounter decision intervention
EGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HTN	Hypertension
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
PI	Principal Investigator
QC	Quality Control
QI	Quality improvement
RA	Research assistant / research associate
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UM	University of Michigan
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
V.0.2	03/14/2019	V.0.1 submitted to UM-IRB on January 4, 2019. After initial review, IRB requested multiple revisions including: 1) Educational worksheet/tool is now referred to as the Control-EDI or Intervention-EDI 2) Health coaching website is now referred to as the portal 3) Removed mentioning of HUM 155950 – study team was advised by IRB to not submit EDI as a QI project, but rather part of this study – HUM00136011 4) We are no longer using the Central Biorepository	Requested by IRB and to keep terminology consistent. V.0.2 approved by IRB on 03/27/2019.
V.1.0	06/19/2019	1) Expanded criteria for early withdrawal/discontinuation of patient-participants 2) Added "terminal illness" as exclusion criteria 3) Addition of PI signature page 4) Minor text corrections	1) To more precisely define events that would warrant ending subject participation 2) It is not the intent of the study to recruit terminally ill patients 3) To meet GCP requirements V.1.0 approved by IRB on 08/05/2019.
V1.1	10/04/2019	1) Updated outcome measures to reflect changes made during ClinicalTrials.gov review (see Sections 1.1, 3, 6.1, 9.1, 9.4.3, and 10.5) 2) Added information to amendment history in Section 10.4 3) Specified "language barrier" as exclusion criteria in Section 5.2 4) Minor formatting corrections	1) To reflect changes made during ClinicalTrials.gov review 2) To meet GCP requirements 3) All health coaching and health education are available in English only

V1.2	05/20/2020	1) Included new section "TELEMEDICINE PROCEDURES/PROCESSES AS DEEMED NECESSARY DUE TO COVID-19" 2) Modified table in 1.3 Schedule of Activities (SOA) to expand timeframe of T0 measurements 3) Updated inclusion criteria for Systolic BP from ">140" to "≥140" 4) Updated inclusion criteria for EgfR lookback period from 12 months to 18 months 5) Specified "pregnant" exclusion criteria 6) Specified that Dr. Resnicow is leading training (see Section 6.4) 7) Clarified information provided on DSMB's roster (see Sections 8.2 & 10.1.6) 8) Minor formatting/text corrections	1) Remote procedures now included to adhere to COVID-19 related restrictions on in-person study activities 2) To accommodate time needed for remote procedures 3) Systolic BP criterion was intended to be "greater than or equal to 140" 4) Patient's annual return visits may be scheduled more than 12 months out from their last EgfR test 5) Being pregnant is an exclusion criterion, whether a patient self-identifies as pregnant or if their medical record indicates pregnancy. 6) Dr. Fagerlin is now at the University of Utah and unable to co-lead training sessions with Dr. Resnicow 7) The study biostatistician may attend the DSMB's meetings, but will not be a DSMB member
V1.3	10/15/2020	**1) Specified "Patient Numeracy (SNS)" in Appendix 1: Outcome Measures** **2) Removed reference of Section 8.3.5 from Section 10.1.10.** **3) Added S-TOHFLA as method of measuring Health Literacy in Appendix 1: Outcome Measures** 4) **Add "Schedule of Activities" information to Section 11.**	**1) To clarify the instrument used for this variable (SNS)** **2) Section 8.3.5 describes AE reporting, not deviations** **3) The REALM-SF measure can only be used during in-person study visits. Due to the need to measure health literacy remotely, the S-TOHFLA has been added to the T0 survey.** **4) Expands upon protocol's flexibility regarding visit tolerance windows due to newly adapted remote processes.**
V1.4	02/03/2022	**1) Increase target enrollment number** **2) Allow more contacts/in-person contacts** **3) Allow using EMR lab results for missing labs**	**1) In order to achieve the same overall power for statistical analysis.** **2) To extend protocol's flexibility regarding contact numbers and methods to retain participants**

			3) Using EMR lab results can supplement missing labs data affected by Covid-19 pandemic
V1.5	8/18/2022	**1) Change the blood pressure eligibility criteria** **2) Add some conditions to "Expected" list of adverse events**	**1) Per recommendation from the Data and Safety Monitoring Board (DSMB) of the study, we will lower the blood pressure eligibility criteria from 140/90 to 130/80 in order to include more potential patients and to be consistent with the more recent blood pressure targets in guidelines.** **2) We have found some adverse events that should be added to the "expected" adverse events list**
V1.6	2/2/2023	**1) Modify "An investigator may discontinue or withdraw a participant from the study for the following reasons" to include "If the participant changes their primary care provider to be outside of the health system"**	**1) All patient participants' PCPs are involved in the study, and we communicate with them throughout the study. This includes sharing recordings of intervention participants' health coach calls and notifying the PCP if lab values or blood pressure readings are outside of the "normal" range. If a participant gets a PCP outside of the study's health systems, we cannot communicate with them to share this information.**
V 1.7	3/20/2023	1) Provide references to survey answers to participants who request it, but only at the end of their participation 2) Clarify that on-site follow up may occur at any scheduled appointment within the health system 3) Clarify that blood pressure readings can be collected from the EMR	1) The visit survey contains some questions with right and wrong answers. On occasion, participants request the correct answers. While it is not our intention to send out mass communications, we will provide references to where they can get answers to some of the surveys as appropriate. 2) Section 11 states "study team will also try to make in-person contacts with participants prior to or after their other on-site medical appointments." We have added the text in section 8.1 to mirror this and explain we may approach participants at scheduled appointments within the health

			system. In clinic, researchers will find a quiet, private area to talk to the participants. 3) Adding this to match the text in section 9.2 stating "Additional clinical BPs in the EMR will be recorded as available."
V 1.8	5/13/2024	1) Introduce primary care providers as a subgroup of the study population (Aim 3) 2) Update information on the PI and Co-Is 3) Clarify that EMRs/medical records include those used by specialties within the health system	1) Aim 3 of the study will assess the adoption, fidelity, and perceived usefulness of the intervention among primary care providers once their patients have completed Aim 2. Additional details on measurement methods and consent procedures have been included. 2) Updates the PI's change in academic rank and contact information and removes Co-Is who are no longer part of the study team. 3) Clarifies that we will collect data (lab results, blood pressure readings, and AEs) from all electronic medical records (EMRs) within the health system, including those used by various specialties.
V 1.9	3/17/2025	1) Specify health coach perceptions of the intervention in the implementation outcome assessment 2) Describe the consent procedure for health coach survey 3) Update endpoints to include updated secondary endpoints/outcomes 4) Revise the schema to reflect updates to enrollment and study visit processes implemented since COVID-19 5) Add a footnote noting the larger tolerance windows for study visits 6) Update Appendix 1: Outcome Measures	1) Add details on assessing health coach perceptions of the intervention as an exploratory outcome via an open-ended survey 2) Outlines procedures for obtaining informed consent from health coaches prior to survey participation 3) Clarify protocol language to align with the outcome measures listed on ClinicalTrials.gov 4) Clarify that enrollment occurred by phone; study visit data (surveys and blood pressure) are collected via phone, email, mail, or in person, and biospecimens are collected at the clinic lab at patients' convenience 5) Clarify that data-collection tolerance windows have been extended from 7-14 days to a few months 6) Update secondary outcomes, reclassify EMR-based medication adherence as an exploratory outcome, and revise time points for the provider survey and coach perception assessment

10.5 APPENDICES

APPENDIX 1: OUTCOME MEASURES

Variable	Time point(s)	Variable type	Outcome type
Demographics/patient characteristics (age, sex, gender, race, ethnicity, education, income, general health status)	t(0)	continuous, categorical	N/A
Co-morbid conditions (cardiovascular dz, liver dz, diabetes, CHF, cerebrovascular dz)	t(0)	categorical	N/A
Health Literacy (REALM-SF/S-TOHFLA)	t(0)	continuous	N/A
Medications of interest (BP, diuretics, and statins)	t(0)	categorical	N/A
Patient Numeracy (SNS)	t(0)	continuous	N/A
Change in systolic BP between baseline and 12 months	t(0), t(3)	continuous	primary
Change in diastolic BP between baseline and 12 months	t(0), t(3)	continuous	secondary
Change in EMR-recorded BP between baseline and 12 months	t(0), t(3)	continuous	secondary
Change in study visit BP supplemented with EMR BP if missing	t(0), t(3)	continuous	secondary
Change in BP using the combined dataset using all study visit and EMR BP values	t(0), t(3)	continuous	secondary
Slope of systolic BP between baseline and 12 months using all available BP values	t(0), t(1), t(2), t(3)	continuous	secondary
Slope of diastolic BP between baseline and 12 months using all available BP values	t(0), t(1), t(2), t(3)	continuous	secondary
BMI (weight in kg/height in meters squared)	t(0), t(1), t(2), t(3)	continuous	N/A
Estimated Glomerular Filtration Rate (EgfR)	t(0), t(3)	continuous	secondary
Serum creatinine	t(0), t(3)	continuous	secondary
Urine protein-creatinine ratio	t(0), t(3)	continuous	secondary
Medication adherence (MMAS-8)	t(0), t(1), t(2), t(3)	continuous	secondary
Medication adherence from electronic medical record	t(0), t(1), t(2), t(3)	continuous	exploratory
CKD knowledge (KiKS)	t(0), t(1), t(2), t(3)	continuous	secondary
Self-efficacy for med adherence (MASES-R)	t(0), t(1), t(2), t(3)	continuous	secondary
Self-efficacy for disease self-management (PKDSMS)	t(0), t(1), t(2), t(3)	continuous	secondary
Patient motivation (TSRQ)	t(0), t(1), t(2), t(3)	continuous	secondary
Satisfaction with CKD care (CAT)	t(0), t(1), t(2), t(3)	continuous	secondary
Satisfaction with CKD care (CCM)	t(0), t(1), t(2), t(3)	continuous	secondary
Self-report BP-related behaviors (sodium, activity)	t(0), t(1), t(2), t(3)	continuous	secondary
Patient plans to revisit EDI	t(0)	categorical	exploratory

Variable	Time point(s)	Variable type	Outcome type
Patient portal use	t(0), t(1), t(2), t(3)	categorical	exploratory
Patient review of coaching educational materials	t(1), t(2), t(3)	categorical	exploratory
Provider discipline	t(0)	categorical	N/A
Provider years in practice	t(0)	continuous	N/A
Provider gender	t(0)	categorical	N/A
Provider race	t(0)	categorical	N/A
Provider adoption based on EMR query and patient survey	t(0)	categorical	secondary
Perception of usefulness by provider survey	after all patient follow-ups, up to one year	continuous, categorical	secondary
Provider fidelity measured by EMR query	t(0)	categorical	secondary
Provider practice size (number of patients yearly)	t(0)	continuous	N/A
Provider affiliated health system	t(0)	categorical	N/A
Clinic ‘'Discipline’'	t(0)	categorical	N/A
Geographic location (patient home and clinic 5-digit zip codes) and income data	t(0)	categorical	N/A
Clinic characteristics	t(0)	categorical	N/A
Visit time with provider	t(0)	continuous	secondary
Total time in clinic	t(0)	continuous	secondary
Coach perceptions of coach intervention	after all patient follow-ups, up to one year	categorical	exploratory
Number of calls, number completed on time, length of time, coach content of calls	across study duration	continuous	N/A
Coach call survey - online questions coach asks at follow up calls	across study duration	categorical	exploratory
Coach baseline survey - patient values report cared, grades of behaviors	t(0)	categorical	exploratory
Goal reminder questions	across study duration	categorical	exploratory
Patient perceptions of health coaching	t(3)	continuous	secondary
Cost and efficiency of coaching related to intervention	t(3)	continuous	exploratory

11 TELEMEDICINE PROCEDURES AS DEEMED NECESSARY DUE TO COVID-19

Due to the COVID-19 pandemic, the CHECK-D study is adding the following remote procedures and policies in order to adhere to any restrictions put in place throughout the intervention period of the study. Recruitment, enrollment, study visits, and data collection will occur in-person only when deemed safe for participants and staff. These changes apply to all participants and will remain in effect post-pandemic.

Telehealth PCP Appointments now eligible for screening and recruitment: All patients scheduled for telehealth appointments (such as, phone visits, video visits) with their PCPs at participating clinics will be screened for eligibility, and their healthcare providers will be prompted to review the EDI with eligible patients. After patients check out, a study team member will approach patients over the phone for recruitment.

Screening and Recruiting Patients Not Scheduled for Upcoming Appointments: In the event that recruitment is slowed due to any of the participating clinics ceasing or significantly reducing the amount of in-person and telehealth appointments on their schedules, the study team will screen these clinics for eligible patients that may or may not have an upcoming appointment with their healthcare provider. The study team will make every effort to work with the healthcare providers for recruitment and review of the EDI, as originally intended. The study team will send patients an introductory letter before approaching them over the phone for recruitment.

Electronic Consent: Consent can now be obtained using HIPAA complaint, cloud-based electronic signature technology (e.g., SignNow), where an electronic signature is obtained on a digital version of the informed consent. If the patient is consented electronically, they will be given a copy of the consent form (hard copy) for their personal records. Consent can still be obtained in-person and over the phone.

Surveys: All enrolled participants will be able to complete surveys remotely. Participants will be able to complete a paper survey to mail back to the study team, or receive an electronic version of the survey via email distribution.

At Home Blood Pressure Monitors: Each participant will receive an at-home blood pressure monitor from the study team. These monitors will be used by participants to check blood pressure after enrollment and at 1, 6, and 12 months after enrollment. Whenever it is possible, in-person BP readings will also be taken by research staff. Blood pressure readings from the medical records, including those used by specialties within the health system, may also be collected when readings are within the study-determined visit windows.

Blood/Urine Tests: Lab orders will continue to be placed by the study team after the enrollment visit and 12 months after enrollment. Lab completion will be done as close to study time-points as stay-at-home orders and patient availability allows. However, if labs are not complete but there are equivalent test results available in the medical records, including those used by specialties within the health system, we will collect data using the existing results. This will apply to both Intervention and Control groups.

EDI Distribution: The study team will work with each participating clinic to make sure that enrolled participants receive the EDI.

Schedule of Activities: During the new and unprecedented times brought on by the COVID-19 pandemic, the CHECK-D study team has made great strides to adapt and add processes aligned with restrictions in research activities and contact with participants. The tremendous changes required demands flexibility as we interact with participants and collect data. We will continue to collect all data for patient study visits (t0-t3) with every effort to align with the "schedule of activities" in our original IRB protocols. However, because of patient activity that is now virtual, may rely on mail and acknowledges participant needs for flexibility, the collection dates for study measures may fall outside of the original "schedule of activities" visit tolerance windows. Thus from this point forward, data collection events that fall outside of the visit tolerance windows will not be considered protocol deviations and not be reported as such. Exact time points of data collection will be documented in study logs, and accounted for in our analytic plan.

Number of Contacts: Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, no less than 3 contact attempts). The contacts may include telephone calls, emails, in-person* contacts and a lost to follow up reminder letter to the participant's last known mailing address or local equivalent methods.

*Sometimes patients come back to clinic for follow-ups. We have found that in person contact may be a better or the only way to follow up with patients with limited resources (e.g., due to no internet, inconsistent phones). In order to reduce the rate of lost-to follow-up, the study team will also try to make in-person contacts with participants prior to or after their other on-site medical appointments if we cannot reach them by phone or email.

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13 PROTOCOL SIGNATURE PAGE

Protocol Title: Controlling Hypertension through Education and Coaching in Kidney Disease (CHECK-D)

Protocol Number: Version 1.9

Protocol Version/ Date: _____

Sponsor Name: Health and Human Services, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____