A Technology-Driven Intervention to Improve Identification and Management of Chronic Kidney Disease in Primary Care
Short Title: CKD Wizard

National Clinical Trial (NCT) Identified Number: NCT03890588

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

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and the National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health Research Terms and Conditions of Award.

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

The study protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of the protocol, and the consent form(s) (or waiver of consent) will be obtained before any participant is enrolled. Any amendment to the protocol will be reviewed and approved by the IRB before the changes are implemented to the study. In addition, the IRB will determine whether a new consent is needed based on the approved protocol changes and make a determination regarding whether a recall needs to be obtained from participants who were previously waivered or provided consent.

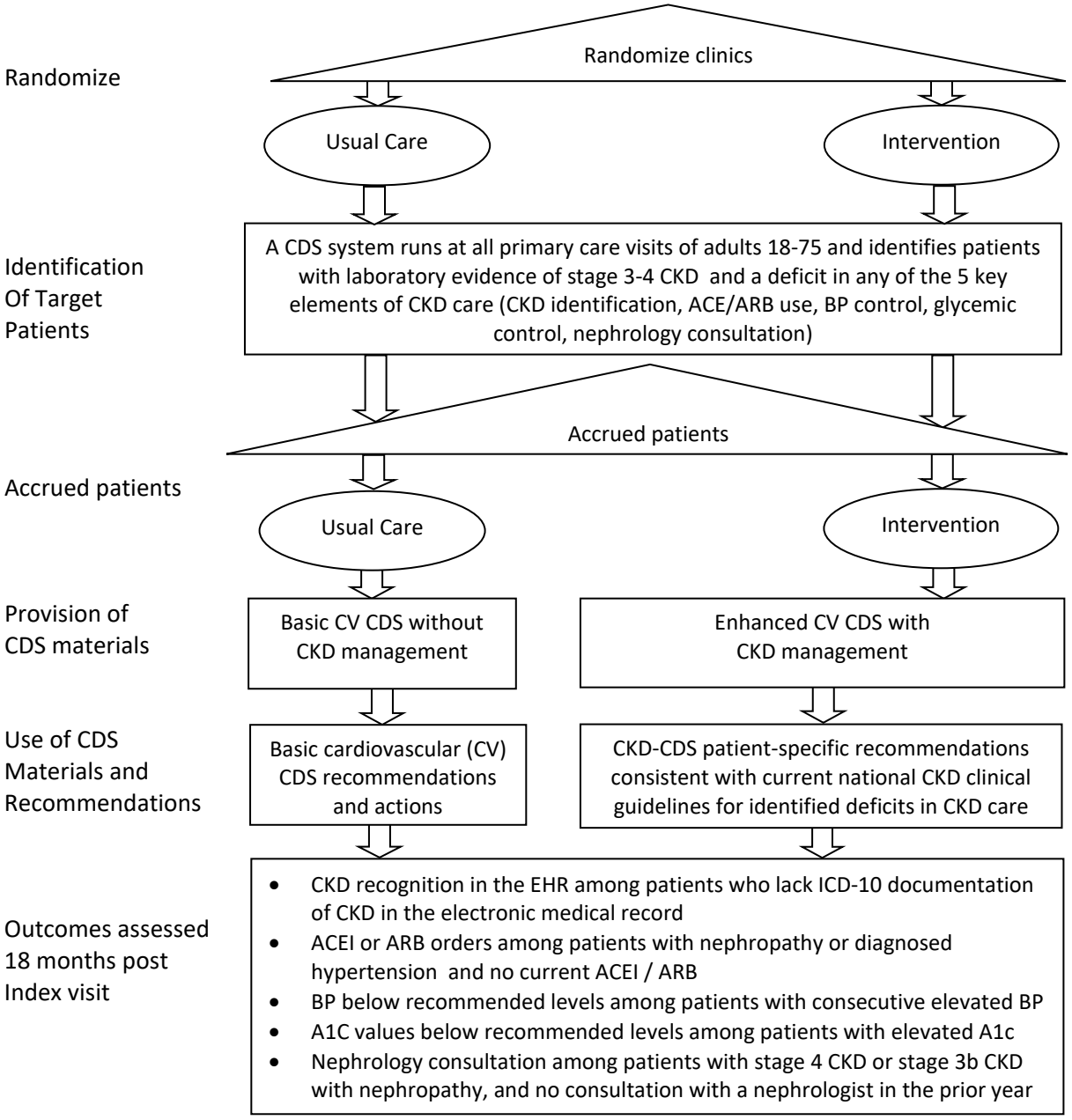
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Technology-Driven Intervention to Improve Identification and Management of Chronic Kidney Disease in Primary Care
Study Description:	To prevent serious chronic kidney disease (CKD) complications such as end-stage renal disease and cardiovascular (CV) events, better strategies are needed to identify, treat, and refer CKD patients seen in primary care clinics. This project expands an existing and successful web-based clinical decision support (CDS) system to include key elements of CKD care and rigorously assesses the impact of this intervention on quality of CKD care for patients seen in primary care settings, including better recognition of CKD, better management of blood pressure (BP) and glucose, and timelier referral to nephrologists when appropriate.
Objectives:	(1) Improve identification of adults with CKD at primary care encounters; (2) Increase appropriate use of renoprotective antihypertensive medications, improve BP control, and improve glycemic management in patients with diabetes through personalized evidence-based treatment options; and (3) Increase collaboration and consultation with nephrologists when advisable.
Endpoints:	Primary Endpoints: for patients with antecedent estimated glomerular filtration rate (eGFR) evidence of stage 3-4 CKD, 18 months after the index visit, rates of (1)provider-diagnosed CKD (2)angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) orders (3)recommended BP control (4)recommended blood glucose control; and (5)ordering consults with nephrology for patients with eGFR laboratory evidence of stage 3b CKD and urine micro-albumin creatinine ratio (UMACR) >30 mg/g or patients with stage 4 CKD.
Study Population:	The study includes adult patients aged 18-75 years from 32 HealthPartners (HP) and Park Nicollet (PN) clinics in Minnesota. This includes adult patients at study clinics with an encounter with a primary care provider (PCP) (general internist, family physician, adult-care nurse practitioner or physician assistant) that meet the inclusion and exclusion criteria described in Section 5 below. Patients are included in the analysis for each endpoint based on care deficits identified at the index visit.
Description of Facilities Enrolling Participants:	The study will take place at HP and PN primary care clinics that are part of a large integrated healthcare delivery system in Minnesota and Wisconsin. Clinics in the Twin Cities metropolitan area with primary care departments of adequate size will be enrolled in the study.
Description of Study Intervention:	The CKD-CDS intervention provides clinical recommendations at any primary care visit of patients with a deficit in any of the 5 key elements of CKD care. This presents patients and their PCPs multiple opportunities to consider timely, evidence-based treatment options to improve CKD care. At every primary care encounter, there will be: 1) Data exchange and evaluation where the electronic health record (EHR) exchanges data with the CKD-CDS web service; 2) Identification of study-eligible patients with CKD stage 3-4 with one or more specified care deficits (lack of CKD recognition, appropriate ACEI/ARB use, BP control, glucose control, or appropriate nephrology consultation) and alerting of rooming staff to print provider and patient CKD-CDS tools; 3) the patient and provider then use the tools and recommendations for shared decision-making
Study Duration:	29 months

Participant Duration: 18 months minimum of follow up after an index visit

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Pre-Index Visit	Index Visit – first study-eligible visit	18 months follow-up
Randomization of clinics to intervention or control	X		
Wizard runs in the background at the patient's primary care encounters. An encounter-based limited data set is collected and stored in a data repository (intervention & control).	X	X	X
Eligible patient is assigned a study identification (ID) for longitudinal follow up identification (intervention & control).		X	
Best Practice Advisory (BPA) occurs for rooming staff prompting CDS use for the eligible patient (intervention clinics)		X	
The eligible patient is exposed to CKD-CDS at a primary care encounter (intervention clinics)		X	
Shared decision making and action based on CKD-CDS recommendations (intervention clinics)		X	
Best Practice Advisory (BPA) occurs for rooming staff prompting CDS use for the eligible patient who previously received a BPA			X
The eligible patient who previously received a BPA is exposed to CKD-CDS at subsequent primary care encounter(s) (intervention clinics)			X
Shared decision making and action based on CKD-CDS recommendations (intervention clinics)			X
Safety monitoring per Data Safety Monitoring plan (intervention & control)		X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

CKD is a common and serious chronic disease that often leads to end-stage renal disease and major CV events. Although evidence-based CKD care can slow disease progression and avert complications, less than 10% of CKD patients currently receive major elements of CKD care in a timely fashion. The objective of this project is to develop, implement, and evaluate a technology-driven and team-based intervention to improve quality of care and clinical outcomes for patients with stage 3-4 CKD.

The proposed CKD-CDS intervention is rooted in the pragmatism of the primary care world, and is based on Wagner's established conceptual Chronic Care Model, which posits that optimal chronic disease care occurs when a "prepared practice team" encounters an "activated, motivated patient."[1] Without visit planning based on a priori organization of information, the complexity required to deliver evidence-based and appropriate stage-specific CKD (or other chronic disease) care in a timely way is an almost

superhuman task.[2-4] The intervention will provide patient-specific and stage-specific CKD treatment options in high- and low-literacy formats to the PCP and patients at each primary care encounter to facilitate shared decision making. This CKD-CDS will be implemented using previously successful methods that in previous CDS studies have achieved very high use rates with patients (>75% of targeted patient encounters) for diabetes and high cardiovascular risk. Scalability of this NIH-developed, non-commercialized intervention strategy is supported by its current use (without the CKD identification or specific recommendations) in care systems within 14 states that provide care to more than 2,000,000 patients in rural and urban areas in 2018.

The intervention is conceptually simple and accommodates the need for providing personalized, actionable health information to PCPs and their patients as a fundamental cornerstone of personalized medicine. We propose to extend an existing successful outpatient EHR-linked, Web-based CDS to include key aspects of care for adults with CKD stage 3-4. This is an ambitious goal for a 3-year project but is feasible due to the experience of our team and previous foundational CDS work funded by NIH grants.

If this intervention is effective, it is immediately scalable and could (a) improve quality of care for large numbers of CKD patients, thereby slowing progression of CKD and improving quality of life, (b) maximize the clinical return on massive public and private investments now being made in sophisticated outpatient EHR systems, and (c) provide a health informatics prototype that rapidly and consistently translates evolving evidence-based CKD clinical guidelines into delivery of personalized and coordinated CKD care within primary care settings.

2.2 BACKGROUND

Evidence-Based CKD Care Recommendations in Adults with Stage 3-4 CKD

There is substantial randomized trial evidence that key components of CKD care slow progression of renal disease and substantially reduce the occurrence of major adverse cardiovascular (CV) events. The strength of this evidence is reflected in evidence ratings of the recommendations found in a number of CKD clinical guidelines. Recommendations with strong ratings (grade B or higher) in multiple clinical guidelines[5-7] include: (a) Diagnostic classification of CKD based on eGFR and albuminuria category; (b) BP control to <140/90 mm Hg in adults with CKD and normal ACR <30 mg/g (or an equivalent albuminuria test) OR <130/80 mm Hg in adults with ACR >300 mg/g; (c) use of ACEI or ARB in adults with diabetes and ACR 30-300 mg/g OR all patients with ACR >300 mg/g. The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for blood pressure recommends that initial or add-on antihypertensive treatment should include an ACEI or ARB for the population aged 18 or older with CKD[8] ; and (d) Individualized glycated hemoglobin (A1C) targets of approximately 7% (or higher in patients with limited life expectancy or risk of hypoglycemia).

Selection of Key Elements of CKD Care

PCPs deal with a mean of 4+ problems per visit, and there are more than 400 evidence-based clinical recommendations that may apply to an adult primary care patient, depending on the patient's clinical status.[9,10] Thus, while in an ideal world, all CKD guideline recommendations would be included in a CDS

system, from a practical point of view, we have decided to strongly emphasize the CKD-related recommendations with the highest evidence rating and greatest potential to improve long-term health for large numbers of CKD patients. We argue that getting PCP buy-in and high use rates of a "good" CDS system is going to benefit many more patients than if PCPs decide not to use a "perfect" CDS system that is overly complicated and time consuming.[11-13]

Gaps in Key Elements of CKD Care of Adults with Stage 3-4 CKD in Primary Care Settings.

Causes of CKD Care Gaps. Across multiple clinical domains, it is clear that failure of providers to intensify treatment in a timely and appropriate way remains a major obstacle to care improvement.[14-21] Other obstacles to better CKD care include failure to evaluate a patient for CKD, failure to recognize CKD even when laboratory data substantiate the diagnosis, medication nonadherence, and lack of timely and appropriate referral to nephrology in certain clinical circumstances.[22]

Magnitude of CKD Care Gaps (Preliminary Data). Even in relatively high-performing primary care settings, there are remarkably large opportunities for improvement in CKD care. Table 1 shows data on basic elements of CKD care delivered to adults with CKD at HealthPartners Medical Group (HPMG) in Minnesota, where this study will be conducted. HPMG is a multispecialty medical group that partners with Park Nicollet (PN) in a care delivery organization that has been repeatedly recognized nationally for high-quality hypertension control, diabetes care, and excellent overall quality of care. However, recent data provide irrefutable proof that high percentages of adults with CKD fail to meet evidence-based BP, glucose, or ACEI/ARB treatment targets. This is related in part to low rates of CKD recognition and low rates of timely and appropriate referral to nephrology. These pilot data establish that sizeable gaps in quality of CKD care persist even in a well-organized care setting, and attention needs to be directed to specifically improving CKD care.

Table 1: Adults with chronic kidney disease (CKD) by glomerular filtration rate (GFR) stage with quality-of-care data at 17 HealthPartners Medical Group primary care clinics, 2015-2016.

		All eGFR 15-59	3a eGFR 45-59	3b eGFR 30-44	4 eGFR 15-29
A. 1+ eGFR 15-59 cc/min/1.73m^2 (N)	N	5766	3823	1559	384
CKD diagnosed	% of A	49.2	36.0	72.2	87.2
diagnosed hypertension	% of A	88.2	85.0	94.0	96.9
BP <140/90 mm Hg	% of A	67.1	69.2	63.5	60.8
BP <130/80 mm Hg	% of A	37.3	38.1	35.8	36.3
B. recognized hypertension or ACR ≥ 30 mg/g	N of A	5107	3263	1470	374
ACEI/ARB current	% of B	57.8	59.4	56.9	48.1
C. diagnosed diabetes or glycated hemoglobin (A1c) >=7%	N of A	2066	1232	638	196
last A1c <8%	% of C	76.7	78.9	72.7	76.0
last A1c <7%	% of C	50.3	51.9	46.2	54.1
D. ACR test rates in patients with GFR evidence of CKD	N of A % of A	1602 27.8	981 25.7	502 32.2	119 31.0
ACR test rates in patients with hypertension	N of B % of B	1398 24.2	861 22.5	433 27.8	104 27.0
E. Stage 4 GFR or stage 3b with ACR >30 mg/g	N of A	636	N/A	252	384
Nephrologist consultation within 2 years	% of E	45.6	N/A	42.5	47.7

Opportunities to Improve CKD Care in Primary Care Settings

This project identifies and exploits the current opportunity to bring the power of CDS to bear on the problem of suboptimal CKD identification, suboptimal CKD care, and delayed referral of CKD patients to nephrology for evaluation and needs related to disease progression. Widespread adoption of EHRs in primary care settings provides a recent opportunity to exploit EHR and integrated Web-based technology to improve CKD care. Time-motion studies suggest that a PCP using an EHR without CDS will need an estimated 30 clicks and at least 3 minutes to gather the information needed to confirm or confer a CKD diagnosis and current CKD stage of the patient; review electrolytes, eGFR, and albuminuria data; assess BP control, use of an ACEI/ARB, and glucose control; and assess the potential benefit of a nephrology referral.[23-28] Moreover, once uncontrolled BP or glucose is identified, PCPs using EHRs without CDS must click many times to locate and synthesize the clinical data needed to appropriately adjust therapy, which includes identification of current therapy and adherence to current therapy, identification of previous treatment, drug allergies or drug intolerances, consideration of possible dose adjustments due to impaired renal function, and consideration of various potential drug-drug and drug-condition interactions. Moreover, these myriad complex CKD-related issues that demand attention often constitute only one of several clinical issues that require attention at the current visit.[2, 13, 29-33] This clinical complexity often leads lack of recognition of CKD (or CKD progression) and deferral of necessary changes in treatment until the "next" visit, due to lack of time. At the next visit, this scenario is often repeated, such that the cumulative delay in CKD recognition, management, and/or appropriate nephrology referral often stretches to months or years.

Using CDS to Improve CKD Care in Primary Care Settings

CDS Has Rarely Been Used to Improve Outpatient CKD Care. Widespread use of EHRs offers new opportunities to improve CKD care. In reports issued 25 years ago, the Institute of Medicine asserted that EHR technology would lead to substantial improvements in quality of medical care in America.[34,35] Since that time, private and public investments in EHR systems have totaled hundreds of billions of dollars, with most CDS interventions unable to demonstrate improvements in chronic disease outcomes other than process measures until very recently.[36-43] Even so, technology specifically designed to improve CKD primary care has lagged behind, with few reports of success.[44-46]

Adapting Successful EHR-Linked Web-based CDS to Improve CKD Care. Much of what has been learned in the last 25 years about how to implement effective CDS in primary care settings for chronic diseases such as diabetes and hypertension can inform the design, implementation, and maintenance of CDS systems designed to address the multiple demands of CKD care. Key features of successful primary care CDS systems include the following: integrating the CDS at the appropriate point in the clinic workflow—usually near the beginning of the visit; engaging both office staff and clinicians in the CDS process; providing CDS that is more sophisticated than simple prompts and reminders; saving time for clinicians; providing the CDS in a simple and intuitive format; and providing CDS not only to the clinician but also to the patient.

Conceptual Model for this Technology-Focused, Team-Based Intervention to Improve Chronic Disease Care. Our previous work on using CDS to improve chronic disease care outcomes is guided by Wagner's well-vetted and much-used Chronic Care Model, which posits that optimal chronic disease care occurs when a "prepared practice team" encounters an "activated, motivated patient."[1] It is no surprise that Wagner suggests that innovative use of information systems and efficient visit planning are foundational elements of successful chronic disease care.[47,48] Without visit planning based on a priori organization of information, the complexity required to deliver evidence-based and appropriate stage-specific CKD (or other chronic disease) care in a timely way is an almost superhuman task.[2-4] CKD-CDS algorithms prepare the PCP for the visit, but they also are used to present the patient with a set of evidence-based treatment options related to CKD care. After the patient considers these options, the PCP can simply inquire about possible interest in one or more options and act on those the patient identifies, thus promoting both shared decision making and patient-centered care.

The CDS system we developed was also informed by extensive input from PCPs who would be users of the technology and by our careful analysis of numerous antecedent failed efforts to improve chronic disease care in primary care settings using CDS.[36-38,49-52] We deduced from this analysis that a successful chronic disease care CDS strategy must overcome the following barriers in order to be successful: (a) Decision support must be available at the point of care and be based on all available clinical data, including BP levels taken at the time of that visit;[43] (b) Decision support must be sophisticated (what drug, what dose) and not limited to general prompts or reminders (BP is too high);[36,38,53] (c) The tool must be integrated into the routine workflow of the primary care clinic; (d) CDS should be implemented in a way that engages patients and promotes shared decision making[54-56] and (e) Clinic training and feedback of clinic-specific and PCP-specific CDS use rates are needed to achieve and sustain CDS use rates high enough to have an effect on chronic disease outcomes.

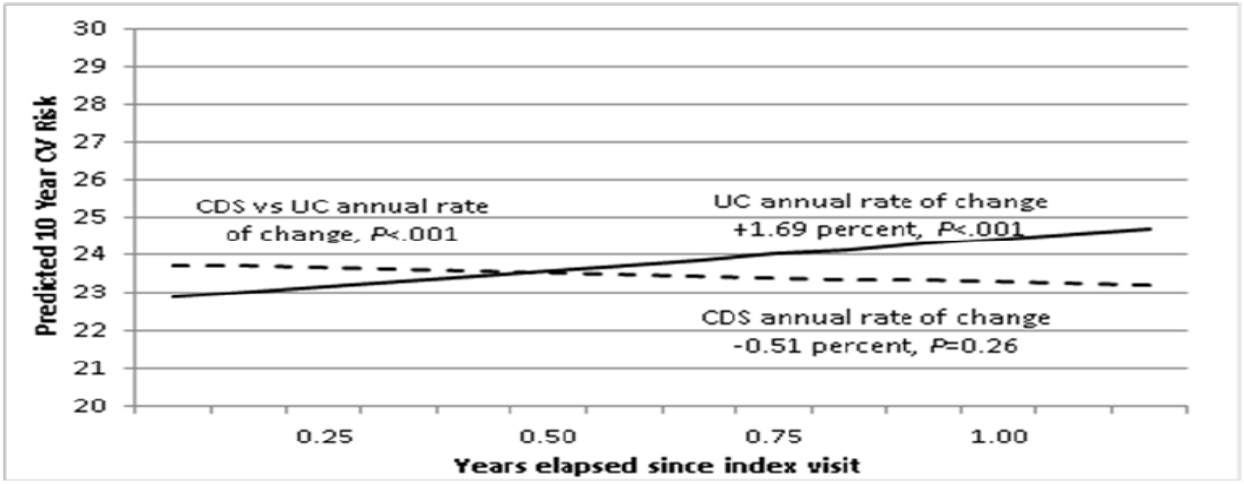
Previous Development of Successful Outpatient Chronic Disease Care CDS by our Research Team. This intervention is modelled on successful outpatient chronic disease care CDS systems that were part of 2 large NIH-funded projects that developed, implemented, and maintained high use rates of sophisticated CDS systems that address multiple clinical domains in adults, including glucose control, BP control, lipid management, aspirin use, smoking cessation, and weight management.

In the first of the completed projects, R01DK068650, the CDS significantly improved glucose and BP control in adults with diabetes and was very cost effective in a formal economic analysis.[57] In this trial, we randomized 11 clinics with 41 consenting PCPs and 2556 eligible diabetes patients and found that (a) the EHR-based CDS intervention was used at 62.6% of targeted intervention clinic visits, (b) the CDS system significantly improved glycated hemoglobin A1 (A1c) (intervention effect -0.26%, 95% CI: -0.06 to -0.47, P=.014) and systolic BP (intervention effect -2.64 mm Hg, 95% CI:- 0.19 to -5.10, P=.035) relative to control group diabetes patients, and (c) 95% of PCP users were satisfied or very satisfied with the CDS system.[43]

In the second completed project of CV Wizard CDS, we targeted adults without diagnosed diabetes or heart disease but with high CV risk and uncontrolled major CV risk factors and were able to achieve a

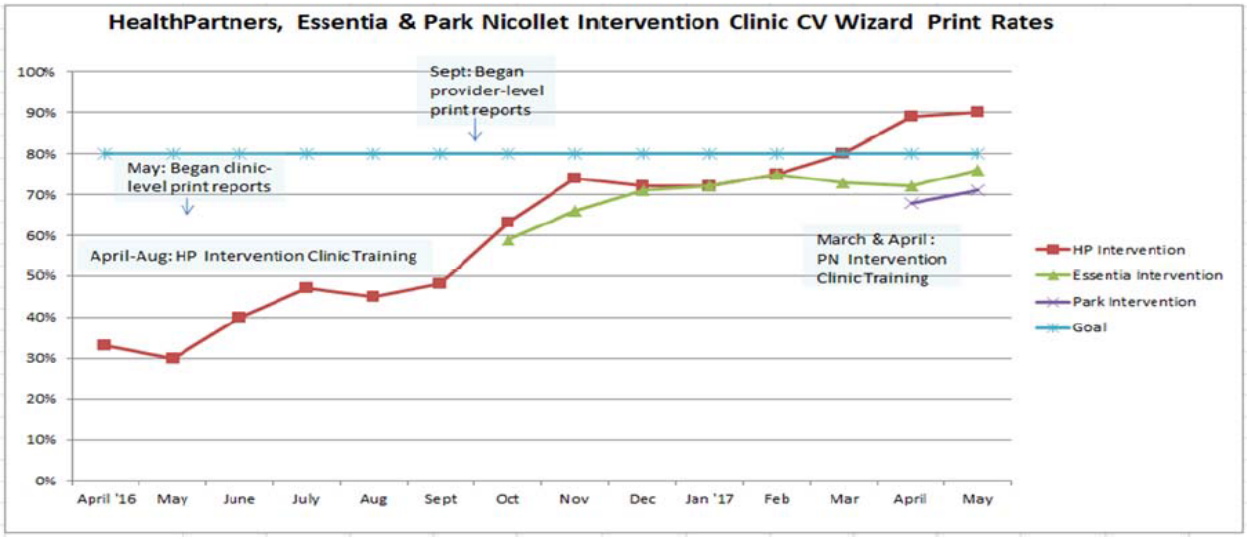
highly clinically significant absolute 2% reduction in 10-year ACC/AHA CV risk (22% vs 24% at end of study, P=.001), see Figure 1 below.

Figure 1: CV Wizard CDS Study Primary Outcome: - predicted 10 year CV Risk over the time elapsed since index visit by study arm



Further, the CDS significantly improved PCP-reported practice patterns, and PCP users of the CDS system reported 85%-98% satisfaction with the CDS system, with 94% recommending it for use by their peers.[58-61] In this study and subsequent implementation in other care systems, we have achieved sustained CDS use rates of 70%-80% at targeted visits, primarily by providing automated PCP-specific and clinic-specific feedback on CDS use rates at targeted visits (a strategy we will employ in this CKD project as well), see Figure 2 below.

Figure 2: Wizard CDS Use Rates in 3 Care Systems



The extension of this CDS system to include multiple key elements of care for adults with stage 3-4 CKD, with or without albuminuria, is a natural extension of the past work we have done with CDS in primary care settings. Happily, the Web service, algorithms, interfaces, data security arrangements, automated

feedback of use rates to PCPs and clinics, and other key features developed and implemented in prior projects are not only intact, the multi-channel Web service processes about 600,000 patient encounters per month, identifying selected subgroups of patients (about 150,000 patients per month) who may benefit from changes in treatment in order to achieve various evidence-based clinical goals at a processing time of 300 milliseconds per case. In this project, we propose adding CKD-CDS in a randomized fashion to primary care clinics to assess its impact on the key elements of CKD care targeted in this proposal. The CDS system is a non-commercialized system whose modest maintenance costs are currently shared among the participating medical groups.

Established Research Team. The research team includes expertise in primary care, nephrology, computer science, decision science, epidemiology, heath services research, statistics, and social sciences. In addition, we have an established and very talented team of programmers and analysts who are well acquainted with EHR and Web programming challenges, data security protocols, and other data-related issues, and we have the enthusiastic support of HealthPartners clinical leaders and nephrology department chairs that guarantee access to more than 30 primary care clinics for this clinic-randomized study.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS AND THEIR ASSESSMENT

Potential Risks. Risks to PCPs and patients are considered minimal. There could be risk that the CKD-CDS would recommend treatment that is not appropriate for an individual patient due to factors not present in the electronic health record data. Providers are well-trained about the limitations of the CDS and every CDS display contains a disclaimer that emphasizes that the CDS is not a substitute for clinical judgement as described in more detail below.

Risks could also involve violations of confidentiality. Because more than one nurse-PCP team uses the same printer, names on all printed CDS material is required to avoid mixing up the printed pages and giving personally identifiable health information (PHI) to the wrong patient (this is also true of the visit instructions/after visit summary that is provided as part of routine care). It is also desirable to have each patient's name on this sheet of paper to ensure the patient knows that the information on the paper is personalized and related to his or her own health state. The technical aspects of this system are also relevant. The CDS system includes a Web service that identifies eligible patients, computes CV and CKD risks, prioritizes clinical conditions, and provides treatment recommendations based on a complex set of evidence-based algorithms. Although the printout is displayed and printed from the EMR, the printout is controlled from the CDS Web site and, therefore, the Web site must have the patient's name and other PHI. Security measures to minimize risks in PHI violations are discussed in detail below.

Protection against Risk: The following measures will be taken to protect patients and PCPs from the risk of breach of confidentiality: The analytic database will be comprised of a Limited Data Set and maintained on a HealthPartners server within the HealthPartners firewalls, and only research team programmers and analysts on this project will have access to the password-protected analytic database.

The following measures will be taken to minimize the risk that a PCP will act wrongly on the basis of information provided through CDS tools developed for this study: Each project-related CDS

communication will include a written explanation, prominently placed, that no clinical action of any kind should be undertaken as a result of CDS suggestions without provider review of the patient's entire medical record and with due consideration given to all aspects of the patient's health, previous health care, current treatment, and other factors. Current CDS disclaimer as approved by HPMG and PN legal teams reads as follows: "The Wizard suggestions are based on electronically available data and are not intended to be a substitute for clinical judgment. Alternative actions to those that Wizard suggest may be indicated. Exercise independent clinical judgment, review allergies, and follow product labelling instructions before choosing Wizard prescribing suggestions." To date on CDS projects, no reports of PCPs acting wrongly on the basis of CDS problems have been reported. In general, the CDS is much more likely to prevent potential omissions in important care needed.

2.3.2 KNOWN POTENTIAL BENEFITS AND THEIR ASSESSMENT

No claim is made in communications with study subjects (whether providers or patients) that any personal benefit will accrue from participating in this project.

PCPs will have no defined benefits from participating in this project. However, the decision support designed to optimize CKD care may serve to familiarize some providers with new and potentially useful information that can be used to improve the clinical care they deliver in the present or the future. No providers or patients will receive monetary compensation for any aspect of the study unless specifically recruited and consented for interviews to assess the CDS design or experience.

As documented in this proposal, there are major existing deficits in the quality of CKD care delivered in primary care clinics nationally and internationally. Improved CKD care can reasonably be expected to reduce the burden of morbidity or mortality related to progressive renal disease and major cardiovascular events. If the interventions fail to improve CKD care, this knowledge will also be important since it will direct the attention of investigators to other, potentially more fruitful lines of investigation. Thus, regardless of specific findings, the results of this trial will provide important new knowledge that will ultimately contribute to improved care for adults with CKD.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES Impact of the intervention on:	ENDPOINTS	GUIDELINE JUSTIFICATION FOR ENDPOINTS*
Primary		
1. **provider-diagnosed CKD** for patients with no documented CKD diagnosis (recognition care gap)	1. **Provider-diagnosed CKD** in the 18-month period after an index visit	(a) **Diagnostic classification of CKD** based on eGFR and albuminuria category;
2. **ACEI/ARB orders** for patients with diagnosed hypertension or nephropathy and no current ACEI/ARB (ACEI/ARB care gap)	2. **ACEI/ARB orders** in the 18-month period after an index visit	(b) **use of ACEIs or ARBs** in adults with diabetes and UMACR 30-300 mg/g OR all patients with UMACR >300 mg/g;
3. **recommended BP control** for patients with consecutive elevated BP (BP care gap)	3. **Recommended BP control** by the end of the 18-month period after an index visit	(c) **BP control** to <140/90 mm Hg in adults with CKD and normal UMACR <30 mg/g OR <130/80 mm Hg in adults with ACR >300 mg/g;

OBJECTIVES Impact of the intervention on:	ENDPOINTS	GUIDELINE JUSTIFICATION FOR ENDPOINTS*
4. **recommended blood glucose control** for patients with elevated A1c (glucose care gap)	4. **Recommended blood glucose control** by the end of the 18-month period after an index visit	(d) **Glycemic control** using individualized A1C targets of less than 7% or less than 8% in patients with limited life expectancy, cognitive impairment, or increased risk of hypoglycemia;
5. **rates of consultation with nephrology** for patients with stage 4 CKD or stage 3b CKD and UMACR >30 mg/g and no recent consultation with a nephrologist (nephrology care gap)	5. **Nephrology consultation** in the 18-month period after an index visit	(e) Timely **nephrology care**
Secondary		
a) Use of non-steroidal anti-inflammatory drugs (NSAIDs) b) Medication adherence c) Treatment heterogeneity d) Treatment intensification among patients not at their BP or glucose goals e) CKD treatment patterns across PCPs f) safety issues, including hypotension, hypoglycemia, and electrolyte disturbances, emergency department (ED) visits, hospital admissions for renal and non-renal causes, major CV events, and mortality as deemed necessary per the data safety and monitoring plan g) Understand provider perspective in development of the prototype of the CDS	a) Rates of NSAID use b) Medication adherence scores to blood pressure and glycemia medications c) Treatment heterogeneity d) Rates of treatment intensification among patients not at their BP or glucose goals e) Variations in CKD treatment patterns across PCPs f) safety issues, including hypotension, hypoglycemia, and electrolyte disturbances, emergency department visits, hospital admissions for renal and non-renal causes, major CV events and mortality g) Provider experience with the CKD-CDS tools based on interview data	Rates of treatment intensification, variations of CKD care across PCPs and overall treatment heterogeneity are indicators of provider utilization of the CKD-CDS. On the patient side, treatment heterogeneity and care disparities are additional measures of overall quality of care. We have a data safety and monitoring plan that includes assessing safety issues like hypotension, hypoglycemia, electrolyte disturbances and ED visits among others. End user experience is important for future scaling up if the intervention is successful
* The endpoints for this study correlate with strongly rated recommendations for slowing progression of CKD in multiple clinical guidelines[5-7].		

4 STUDY DESIGN

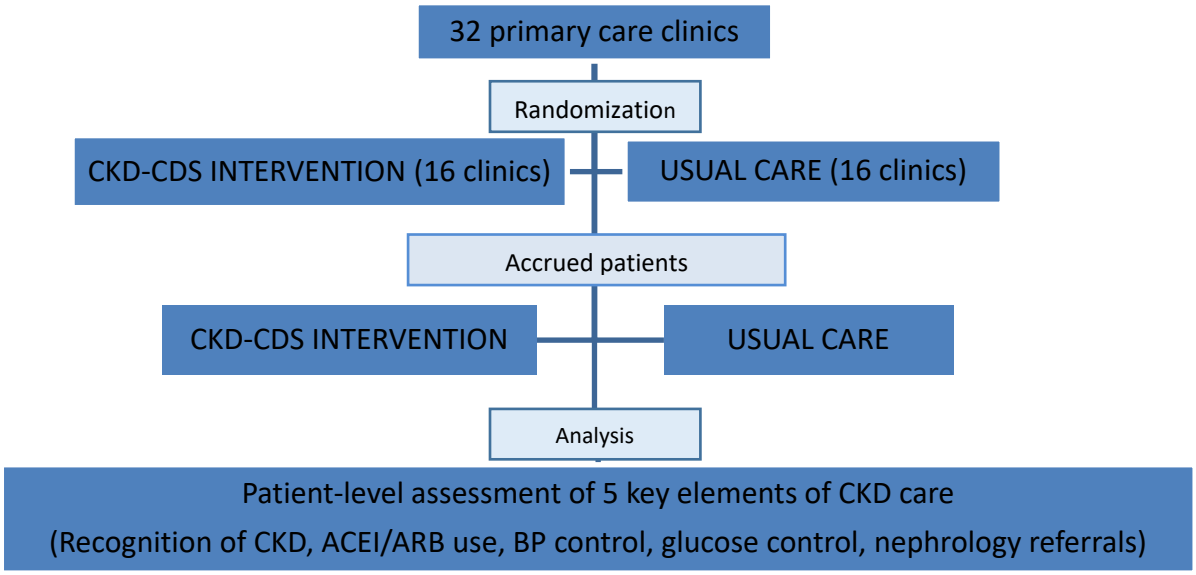
4.1 OVERALL DESIGN

- *A statement of the hypothesis*: CKD is a common and serious chronic disease that often leads to end-stage renal disease and major cardiovascular events. Although evidence-based CKD care can slow

disease progression and avert complications, less than 10% of CKD patients currently receive major elements of CKD care in a timely fashion. We hypothesize that the intervention will 1) Improve identification of adults with CKD at primary care encounters; (2) Increase the appropriate use of renoprotective antihypertensive medications, improve blood pressure control, and improve glycemic management in patients with diabetes through personalized evidence-based treatment options; and (3) Increase collaboration and consultation with nephrologists.

- *Phase of the trial*: 3
- *A description of the type/design of trial to be conducted*: This study is a prospective, 2-arm, cluster randomized trial, randomizing primary care clinics at HealthPartners and Park Nicollet to intervention and usual care arms. It is a single site study.

Figure 3: Study Design



- *A description of methods to be used to minimize bias*: Covariate-based constrained randomization using a computer-generated allocation scheme was used to enhance balance across study arms on key factors. This method enables multiple factors to be balanced between treatment groups and can increase statistical power beyond simple randomization.

- *Name of study intervention*: Chronic Kidney Disease Clinical Decision Support (CKD-CDS), also known as CKD Wizard
- *Name of sub-studies, if any, included in this protocol*: None

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The CKD-CDS intervention provides timely, data driven information to providers at primary care visits with patients who have CKD and a deficit in CKD care. Because it is common for patients to see more than one clinician over time, particularly in the same clinic, there is significant risk of contamination if the intervention were to be randomized at the patient or provider level. However, patients tend to receive most of their care over time at a single clinic, and clinicians tend to practice at a single clinic. For this reason, contamination risk across clinics is relatively low. The cluster-randomized trial design

randomizes primary care clinics to usual care or CKD clinical decision support to minimize risk of contamination.

Clinics were randomly allocated 1:1 to intervention or usual care based on the results of a computer-generated algorithm. From the time the CKD-CDS tool was implemented in April, 2019, through March, 2020, the CKD-CDS interface was programmed to display at eligible visits in clinics randomized to the CKD-CDS intervention group. As a result, intervention-eligible patients were exposed to the intended treatment at visits that took place in a clinic assigned to the same treatment group as their index visit clinic.

The care systems responded to the COVID-19 pandemic in March, 2020, by closing or realigning many of the randomized clinics, making significant changes to the clinics at which providers practiced and shifting from in-person to telehealth visits. The clinic closures and changes in provider locations disrupted what had been reliable correspondence between patients and clinic locations; and hence, made exposure to the intended treatment group unreliable. The shift in visit modality made it very difficult to access the CKD-CDS interface (i.e., the intervention) during visits. Index visits were suspended as of March, 2020, and the CKD-CDS interface was turned off between March and August, 2020, to prevent unreliable intervention delivery and technological challenges.

CKD-CDS delivery resumed in August, 2020 and included all patients who had an index visit at a randomized clinic through March, 2020. The clinic-randomized treatment group that was assigned at each patient's index visit followed each study-eligible patient to all of their post-index visits regardless of clinic location (intervention, control) or modality (in-person, phone, video). This programming change was made to preserve the patient-within-randomized-clinic structure, and maximize treatment fidelity. Programming treatment group assignment to follow the patient enabled the intended treatment to be delivered to patients at post-index visits, even when those visits take place with different providers or at different clinics.

Some provider contamination and learning effects are possible to the extent that intervention patients may have post-index visits with providers from control clinics. Because patients tend to continue seeing their index providers over time, control clinic providers' exposure to the intervention through seeing intervention patients is unlikely to be frequent enough for sustained learning.

The pragmatic study design improves generalizability to real world clinical settings.

4.3 JUSTIFICATION FOR DOSE

Not applicable

4.4 END OF STUDY DEFINITION

The end date for the study is defined as the date that corresponds to 18 months after the index visit of the last person enrolled at a study clinic during the 11 month patient accrual period. Note that the accrual period was shortened from 12 to 11 months due to the onset of the Covid-19 pandemic in March 2020. The pandemic also caused disruptions in care delivery and decreased volume of primary care encounters in mid-2020 which interrupted intervention delivery during this period. We extended the follow-up period from 12 months to 18 months to increase the number of patients with primary care encounters and follow-up measures needed to assess intervention impact.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Clinics are the primary unit of randomization. Medical group leaders at HPMG and PN agreed to enroll at least 30 primary care clinics in this study and provided letters of support. In order to be eligible for the study, a clinic was required to meet the following requirements:

1) Be a HealthPartners Medical Group or Park Nicollet care system clinic
2) Have an established adult primary care department within the clinic (family medicine, adult medicine, and/or combined pediatrics/internal medicine)
3) Have a minimum of 20 study eligible patients
4) Have access to a nephrologist or nephrology clinic within reasonable geographic proximity

Eligible Adult Patients:

Patients with an encounter with a primary care provider (general internist, family medicine physician, advanced practice nurse or physician assistant) at a study clinic were eligible for the CKD-CDS if the following criteria were met:

1) Aged 18 to 75 years, inclusive on their index date. The evidence-based guidelines on which the CDS intervention is based are not applicable outside this age range.[62]
2) Have laboratory evidence of CKD based on eGFR values <60 cc/min/1.73m^2, including the most recent eGFR value on or prior to index date, and the closest previous eGFR done at least one week prior
3) Have one or more CKD care components suboptimally managed at the time of the index visit.

		suboptimally managed if
CKD recognition care gap	1.1) CKD not documented in the electronic health record	1.1) ICD-10 codes N18.3, N18.4, N18.5, N18.6, N18.9 at <2 outpatient encounters, and not on the problem list, in the previous 2 years
ACEI / ARB care gap	2.1) stage 3 CKD; and 2.2a) diagnosed hypertension, or 2.2b) nephropathy; and 2.3) no evidence of hyperkalemia; and 2.4) ACEI / ARB not current at index	2.1) eGFR 30-<60 cc/min/1.72m^2; and 2.2a) ICD-10 codes I10, I11.x, I12.x, I13.xx, I15.x, I16.x at 1 inpatient or 2 outpatient encounters, or on the problem list, in the previous 2 years, or 2.2b) UMACR >= 30 mg albumin / g creatinine ; and 2.3) no ICD-10 code E87.5 or serum potassium >= 6.5 mg / dl in the previous 2 years; and 2.4) no ACEI / ARB orders with start date before or on index date, or end date on or after index date
BP care gap	3.1) 2 consecutive elevated BP	3.1) index BP and next most recent BP >= 130/80 mm Hg
Glucose care gap	4.1) diagnosed diabetes; and 4.2) A1c above goal	4.1) ICD-10 codes E10, E11 at 1 inpatient or 2 outpatient encounters, or on the problem list, in the previous 2 years; and 4.2) most recent A1c>=7 on or before index date
Nephrology care gap	5.1) Stage 3b or 4 CKD; and	5.1a) most recent eGFR15-<30 cc/min/1.72m^2, or

	5.2) nephrology referral needed	5.1b) eGFR30-<45 cc/min/1.72m^2 and UMACR >=30 mg/g; and 5.2) no completed nephrology visit in prior year

The index visit is defined as the first visit at any randomized clinic during the accrual period at which the patient met these CKD-CDS intervention eligibility criteria and none of the exclusion criteria. The patient accrual period (for index visits) was 11 months, followed by a 18-month observation period, so that patients will have 18 to 29 months of post-index follow up (estimated median, 24 months).

Each patient was assigned to the clinic where their index visit took place and by extension to the randomized treatment group of that clinic. Patients with index visits at clinics randomized to the CKD-CDS intervention (or usual care) group were considered CKD-CDS intervention (or usual care) patients. A patient could have post-index visits, that may or may not be intervention eligible, at clinics randomized to the other treatment group. Following intent to treat principles, the patient's treatment group assignment will not change as a result of the clinic treatment group assignment or patient intervention eligibility at the post-index visits. Additionally, the index visit marks the beginning of each patient's 18-month observation period.

Web-based eligibility algorithms assess eligibility at all visits in all randomized clinics for the duration of the intervention period. As a result, all patients who have visits during the intervention period will be universally and consistently screened for intervention eligibility without any action, or even awareness, from clinic staff. There is no consenting process for accruing patients into the study, except that patients who have requested to be excluded from all research will be excluded from the study analyses. In sum, neither the patients, clinicians nor study team can influence when a visit is identified as an index visit; and patients who exclude themselves from research are excluded from outcomes analyses. These factors combined minimize the risk of selection into the study denominator to the extent that virtually all intervention eligible patients are included.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from receiving the CKD-CDS:

1) Patients enrolled in hospice,
2) Patients with active cancer (3 or more diagnosis codes in last year) or undergoing parenteral chemotherapy
3) Patients with pregnancy in the last year
4) Patients with end stage renal disease

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

All visits at all randomized clinics are screened for intervention eligibility via the CKD-CDS eligibility algorithms for the duration of the study. The IRB waived written informed consent for patients so those who meet inclusion and exclusion criteria based on then-current electronic medical record data are said to have an index visit and included in the study. The only exception to universal eligibility screening is the rare occasion when a network-wide outage or other large-scale event prevents the algorithms from running. Such events are exceedingly rare, and we assume that unscreened yet eligible patients are equally distributed across treatment groups.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Based on endorsement and support for CDS by the medical leadership, the 32 largest clinics meeting the criteria for eligibility were included in the study with leadership approval. The CDS intervention was integrated into the routine care and workflow for patients in the clinics. Several strategies used successfully in previous studies were adopted to ensure high use rates of the CDS at the point of care. These include:

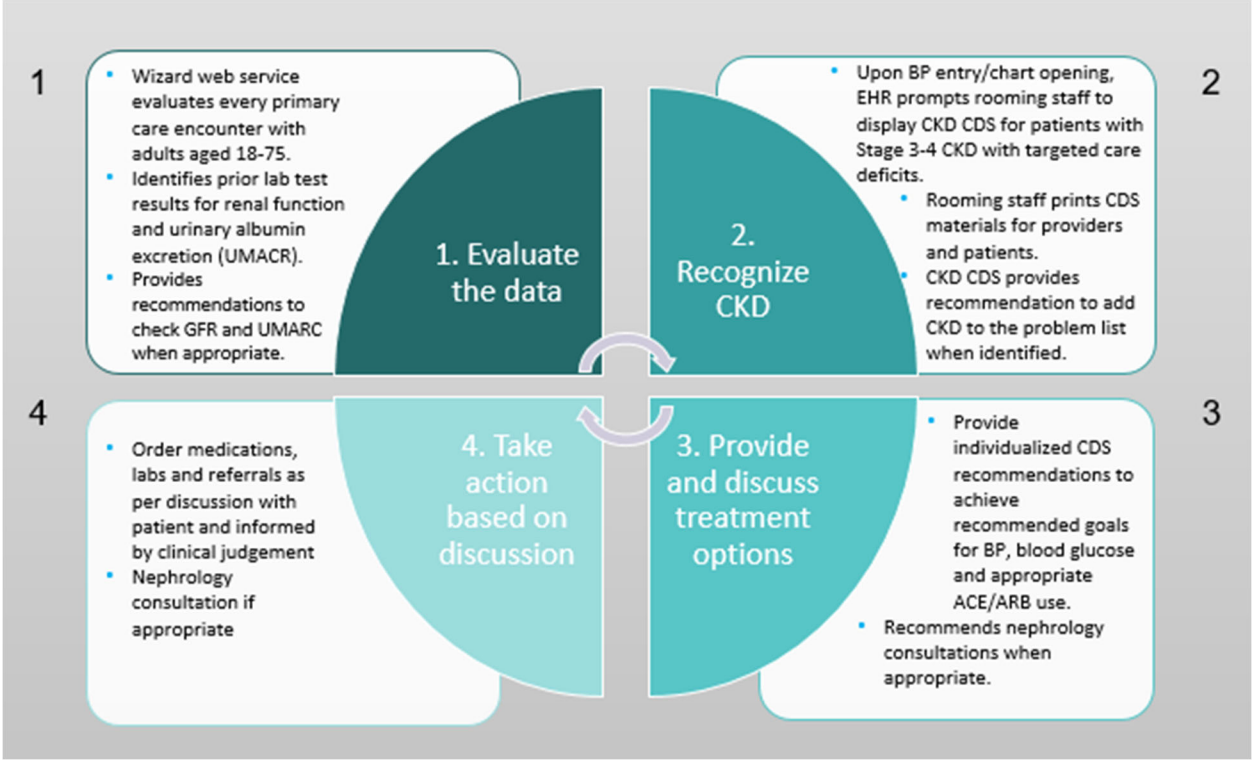
1. Training sessions for clinic staff either in-person or through live or taped webinars (with lunch provided) prior to the onset of the intervention to stress the importance of the intervention to patients and describe the recommended workflow.
2. Reliance on nursing staff rather than providers to print the CDS tools when a best practice advisory (BPA) pops up during the rooming process for patients who meet the study edibility criteria.
3. Setting a goal with providers and clinics staff to print the CDS tools at 75% or more of eligible encounters and sending clinic leaders frequent reports of CDS print rates at the clinic and provider levels.
4. Outreach phone calls and emails to clinic leaders if print rates at an intervention clinic drop below goal.
5. Assessing end user experience and collecting feedback throughout the intervention period and being responsive as needed to improve the CKD-CDS tools and intervention overall.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Intervention Clinics/Patients: The CKD-CDS intervention provides updated clinical recommendations at any primary care visit for study-eligible patients; at intervention clinics these are seen by PCPs and patients as described. At usual care clinics, the CDS output is not displayed or accessible to PCPs or patients but is archived electronically for analysis purposes. The CDS presents to patients and their PCP an evolving array of timely, evidence-based treatment options to improve CKD care (see Figure 2 below). Treatment options are patient specific, tailored to the patient's current clinical state, and evolve over time as the patient's clinical state evolves, or when evidence-based guidelines evolve. As described in detail above, the CKD-CDS intervention proposed in this project is rooted in a series of antecedent studies that developed more limited but successful forms of CDS.[40, 63, 64] From an operational point of view, implementing CKD-CDS at intervention clinics requires a series of 4 distinct steps that occur at every encounter as described in Figure 2 below.



Step 1: Data exchange and evaluation: The EHR securely exchanges data with the Web Service at every encounter of patients aged 18-75 triggered by BP entry or chart opening for video and phone visits.

Step 2: Recognition of CKD and presence of care deficits: Patients with stage 3-4 CKD are automatically identified by the Web Service and evaluated using algorithms maintained in the Web service for identification of CKD and for the 5 emphasized care gaps (identification of CKD, BP control, glucose control, ACEI/ARB use if appropriate, , and nephrology consultation if appropriate). If the patient has a care gap, the rooming staff receives an immediate BPA prompt to print CDS materials for the patient and the provider to review and use for shared decision making. Using a sequence of steps successfully implemented in previous studies, the rooming staff will print the materials and give the lay version to the patient to review while waiting for the provider. A professional version is left on the door for the provider to review before entering the exam room. This approach has been well-liked by our providers to help them be prepared and to engage patients in their care needs before the clinician-patient interaction. PCPs can also optionally view an electronic version of the CDS materials. The CDS can be viewed in real time for any patient by clicking on a button programmed in the EHR encounter display.

Step 3: Use of CKD-CDS recommendations as shared decision-making tools: The participating providers and all rooming staff in the intervention clinics will be trained in the use of the provider (professional) and patient (low-literacy) versions of the CKD-CDS. For this study, the CDS tool will be adapted to emphasize CKD and, for each identified deficit in CKD care, the CKD-CDS will display patient-specific recommendations consistent with then-current national CKD clinical guidelines; for example: (a) recognize CKD and ask the PCP to enter a CKD diagnosis on the problem list if indicated, and/or (b) specific considerations for how to modify BP control, glucose control, or ACEI/ARB therapy, and/or (c) refer certain patients to nephrology when referral criteria are met. The PCP assesses patient preference for any of the CKD-related treatment options. If the patient wants to act on 1 or more, the PCP can address it then or schedule a subsequent visit for that purpose. If the patient is not interested in any

option, no further action is needed at that day's visit. The decision support provided to the PCP is very specific and, if pharmacotherapy is indicated, decision support specifies either initiation or titration of specific drugs based on the drugs/doses the patient is currently taking, distance from goal, and other clinical considerations outlined above. The patient version of the CKD-CDS uses symbols to provide easy patient recognition of priority clinical areas and then suggests potential treatment options they can discuss with their provider. Presenting key CKD care recommendations when indicated (all of which are evidence based and capable of improving CKD care) allows the patient freedom to select his or her preferred treatment option from among several evidence-based potentially beneficial treatment options. Because patient preference for health-related actions varies across specific actions, offering several options improves the chance that a given patient may be interested in addressing at least 1 of the evidence-based options presented. Moreover, patient engagement is a key predictor of subsequent adherence and success of treatment, as we have previously shown in this patient population.[65-70] It is important to realize that the printed page the patient receives *is designed to direct discussion to a set of prioritized evidence-based treatment options with likely benefit to that patient.

Step 4. Take action based on the decisions made: After discussing with the patient, the provider can then go ahead and order the recommendations suggested by the CDS such as labs, medication, e-consults or referrals to nephrology or other specialists. All actions taken are governed by the provider's clinical judgement and the patient's preferences, not by the CKD-CDS.

Usual Care Clinics: All control clinics/patients will continue to use the basic EMR-linked CDS for CV risk factor management. This CDS system includes algorithmically derived identification of high CV risk patients and prioritized treatment suggestions for lipids, BP, glycemic control, weight, tobacco, and aspirin use based on distance from goal, current medications, comorbid conditions, labs, allergies, and safety considerations.[71-76] The basic CDS does not include information specific to CKD care. Important to note is that the CKD-CDS tool will be running silently (in the background) at all clinics randomized to the Usual Care arm of the study. However, only the results of algorithms run by the basic EMR-linked CDS for CV risk factor management will be displayed in the Usual Care clinics. Running CKD-CDS silently in Usual Care clinics ensures that identification of study-eligible patients, and collection of primary outcome data will be done identically across all randomized clinics. Our ability to control the display of the CKD-CDS tool by clinic ensures that patients in Usual Care clinics continue to receive current standard of care (CDS for CV risk) and prevents intervention contamination at Usual Care clinic visits.

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

The information exchange between the web service and electronic health record occurs automatically at each visit at the randomized clinics. Algorithms use the information extracted from the electronic health record to systematically assess care gaps, treatment opportunities and safety issues, and then assemble tailored intervention content that incorporates algorithm outputs. As a result, the intervention content made available to front end users is up to date, informed by all available and relevant data and consistent with treatment guidelines across all patients and encounters.

6.4 STUDY INTERVENTION COMPLIANCE

Achieving and maintaining high CKD-CDS use rates. The intervention relied on nursing staff rather than providers to print the CDS tools when a best practice advisory (BPA) pops up during the rooming process for patients who meet the study eligibility criteria. We set a goal with providers and clinics staff to print the CDS tools at 75% or more of eligible encounters and sent clinic leaders frequent reports of clinic and provider CDS print rates. We used outreach phone calls/emails to clinic leaders if print rates drop below goal.

PCP and clinic staff training. All training activities for intervention clinics were conducted collaboratively with HealthPartners and Park Nicollet, and the research team. We conducted training sessions either in-person or through live or taped webinars. Training focused on workflow and enhancements made to the existing CDS to address CKD. Training was modeled after successful training programs conducted in previous studies. We also provided information about the study and interventions in online newsletters and communications.

Mechanisms for collecting ongoing feedback from PCPs. Once the CKD-CDS tool was implemented in the intervention clinics, PCPs or clinic staff with questions or concerns about any of the recommendations that display for an individual patient, were able to provide immediate feedback to the research team through a tab on the online CDS display or through emailing the study team. The feedback was sent automatically through an encrypted email to the research staff for triage. This process was used infrequently but was useful to identify and correct minor coding bugs, especially during the pilot phase. It also enabled research team clinicians to answer questions for providers who were confused or not knowledgeable about current evidence-based CKD care recommendations. The research team provided a timely response to all providers who send feedback. The process was quite useful as a way to improve the accuracy of the CDS and to educate individual providers as needed.

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

This minimal risk study did not include specific halting rules. The CDS suggestions were evidence-based and guideline driven and providers are always advised to exercise their clinical judgement with any CDS suggestions. However, safety monitoring meetings were held regularly to assess frequency of possible adverse events related to overtreatment (severe hypoglycemia, documented hypotension, abnormal potassium values, etc.) in all randomized clinics.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Providers and patients exposed to the clinical decision support can ignore or disregard any component of the intervention at their discretion.
Patients who opt-out of participating in research were excluded from outcomes analyses.

7.3 LOST TO FOLLOW-UP

Unless they opted out of research, all patients who met study eligibility criteria and had an index visit in the accrual period were eligible for inclusion in the analysis; inclusion in specific outcome analyses varied by the clinical care gaps that were present at the index visit.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The data used to evaluate the effectiveness of CKD-CDS system on reducing 5 CKD care gaps will derive from the CKD-CDS tool itself (e.g., care gaps present at index visit) or the electronic health record (e.g., CKD diagnosis, ACEI / ARB orders). There are no scheduled assessment visits from accrued patients. Rather, data elements that document study eligibility and care gaps at the index visit, and outcome events that occur in the 18 months following the index visit, will be recorded in these electronic resources as care is delivered to patients, with the timing of care delivery driven by clinician and patient judgment. This clinic-based pragmatic trial will not direct the timing, manner or amount of care delivered to any accrued patient according to a pre-defined schedule.

8.2 SAFETY AND OTHER ASSESSMENTS

The CDS tool uses patient information in the electronic health record to apply evidence-based methods to identify eligible patients, compute CV risks, prioritize CV risk reduction, compute medication adherence, identify results of adherence assessments and action plans, and provide treatment recommendations based on a complex set of evidence-based algorithms. The study team has extensive experience in health services research and clinical research with human subjects, with procedures to safeguard privacy and personal information. See section 10.1.3 below on a detailed description of procedures put in place to assess and ensure safety of patient information.

Intervention adherence, defined as the rates at which CKD-CDS was opened and printed at study-eligible visits, was measured and monitored continuously during the study period and reported monthly to clinic leadership, as described above, despite a 6 month disruption due to the Covid-19 pandemic.

We used passive surveillance of electronic health record and administrative data sources maintained by HealthPartners to monitor the occurrence of safety events. These events included hypotension, hypoglycemia, electrolyte disturbances, emergency department visits, inpatient admissions for renal and non-renal causes, major cardiovascular events and mortality. Benefits to this approach are that safety events were ascertained identically for all accrued patients in all randomized clinics. Documentation of the safety events occurred in the course of delivering health care, ensuring that records are reasonably accurate and complete with minimal and randomly missing information. Missing information due to events for which patients do not seek care or care that escapes documentation in the EHR was assumed to occur rarely and equally across treatment groups.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An 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 severe hypoglycemia requiring intensive treatment in an emergency room or at home, hypotension, and electrolyte abnormalities.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity of AEs that the study team learns about outside of the passive surveillance system.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

AEs that the study team learns about outside of the passive surveillance system will have their relationship to study intervention assessed by the clinician who examines and evaluates the situation based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

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

8.3.3.3 EXPECTEDNESS

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.

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

We accessed the electronic health records and administrative data of all patients who accrued to this pragmatic trail in the course of preparing for regularly scheduled data safety monitoring meetings. We extracted data elements that documented the occurrence of any of the safety events (e.g., diagnosis codes, laboratory value, admission records) between 12 months prior to each accrued patient's index visit and 18 months after the index visit of the last-accrued patient. The rates at which each event occurred (e.g., events per 100 patient-years) were calculated in the pre- and post-index periods by randomized treatment group so that differential changes in event rates might be observed. Event rate summaries were presented at data safety monitoring meetings approximately thrice-yearly. By their very nature, the occurrence of these safety events had been documented by health care professionals in the course of delivering timely treatment and appropriate follow-up to the accrued patients.

The occurrence of an AE or serious adverse event (SAE) may also come to the attention of project team members during patient and provider survey results. These AEs not meeting the criteria for SAEs will be captured on the appropriate report forms. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (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 will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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. AEs characterized as intermittent require documentation of onset and duration of each episode.

The project manager, in collaboration with the PI will record all reportable events with start dates occurring any time after inclusion into the study population until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

According to the HealthPartners Institute IRB policies, investigators must report the specified adverse events or issues to the IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event. Investigators or the project team must report possible problems or issues with the research to the IRB Office in writing using the Unanticipated Problem/Serious Adverse Event Form. The written report should contain the following: Detailed information about the event or issue, including relevant dates; Any corrective and preventative actions, planned or already taken, to ensure that the issue or problem is corrected and will not occur again; An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any harm (e.g., physical, social, financial, legal or psychological) and any plan to address these consequences.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete a written report and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Participating clinics will be informed of AEs and SAEs through communication with the clinic and healthcare group leadership and providers. Although unlikely, if specific patients are affected or at risk, they will be contacted through their routine patient communication channels and through their providers.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Pregnancy is an exclusion criteria for the study. However, reporting is not warranted as there is no direct harm anticipated from the study.

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 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

The investigator will report UPs to the reviewing IRB and to HealthPartners Institute. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 5 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and the study sponsor within 10 working days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the OHRP within 1 month of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participating clinics will be informed of UPs through communication with the clinic and healthcare group leadership and providers. Although unlikely, if specific patients are affected or at risk, they will be contacted through their routine patient communication channels and through their providers.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Hypothesis 1: Among patients with antecedent eGFR evidence of stage 3-4 CKD, those with an index visit at a CKD-CDS intervention clinic will have significantly higher rates of provider-diagnosed CKD in the 18 months after the date of the index visit, compared with similar patients with an index visit at a UC clinic.

Hypothesis 2: Among patients with antecedent eGFR evidence of stage 3-4 CKD who also have diagnosed hypertension or UMACR >=30 mg/g, those with an index visit at a CKD-CDS intervention clinic will have significantly higher rates of ACEI or ARB use 18 months after the date of the index visit, compared with similar patients with an index visit at a UC clinic.

Hypothesis 3: Among patients with antecedent eGFR evidence of stage 3-4 CKD who have diagnosed hypertension, those with an index visit at a CKD-CDS intervention clinic will have significantly higher rates of recommended BP control 18 months after the index visit date, compared with similar patients with an index visit at a UC clinic.

Hypothesis 4: Among patients with antecedent eGFR evidence of stage 3-4 CKD who also have diagnosed diabetes at an index visit, those with an index visit at a CKD-CDS intervention clinics will have significantly higher rates of recommended glucose control 18 months after the date of the index visit, compared with similar patients with an index visit at a UC clinic.

Hypothesis 5: Among patients with eGFR laboratory evidence of stage 3b (eGFR 30-44 ml/min/1.73 m2) CKD and UMACR >30 mg/g, or patients with stage 4 (eGFR 15-29 ml/min/1.73 m2) CKD, those with an index visit at a CKD-CDS intervention clinic will have significantly higher rates of consultation with nephrology 18 months after index visit, compared with similar patients with an index visit at a UC clinic.

The operational definitions of the outcomes associated with Hypothesis 1-5 are summarized below.

outcome	description	operational definition
H1: CKD recognition	CKD documented in the electronic health record	ICD-10 codes N18.3, N18.4, N18.5, N18.6, N18.9 at an inpatient or outpatient encounter, or added to the problem list, on index date through 18 months post-index
H2: ACEI / ARB use	ACEI / ARB current post-index	ACEI / ARB orders with start date or end date on index date through 18 months post-index
H3: Blood pressure control	post-index BP at goal	in 18 months post-index, average of up to two most recent SBP<130; and average up to two most recent DBP<80
H4: Glucose control	post-index A1c at goal	most recent A1c<7% in 1 to 18 months post-index
H5: Nephrology referral	nephrology referral	referral to or completed visit with nephrologist, on index date through 18 months post-index

9.2 SAMPLE SIZE DETERMINATION

We conducted an a priori power analysis for each of the 5 outcome measures to estimate the minimum detectable difference in each given assumptions about analytic sample size, proportions of patients meeting outcome criteria, and intra-class correlations, all estimated from 2015-2016 HPMG pilot data of patients meeting categories for stage 3-4 CKD. The correlated sample of CKD patients within clinics was reduced to an equivalently sized independent patient sample by dividing the anticipated sample size by the design effect introduced by clustering within clinics [Neff pt = N / [1 + (nclus-1)ICCclin]. For the BP control outcome, the correlated BP sample size (M=Neff pt * m outcomes per patient) was adjusted to account for clustering within patients [Neff obs = M / [1+ (mclus-1)ICCpt]. Based on the effective sample sizes, we estimated the minimum proportion of CKD-CDS relative to UC patients meeting criteria for each outcome at 12 m that would be powered to reach statistical significance (power=.80, $\alpha 2$=.05).

Table 2 summarizes for each outcome the sample size, mean and intra-class correlation calculated from HPMG pilot data; the data-informed assumptions used in the power analyses; and the minimum

detectable and clinically meaningful differences among CKD-CDS versus UC patients. Power analysis assumptions were either consistent with or more conservative than pilot estimates. For each outcome, the minimum statistically detectable difference is smaller than the clinically meaningful difference, even under these relatively conservative assumptions. For example, the H1 analysis is powered to detect increases in diagnosis rates of 5.8%-11.1% among CKD-CDS relative to UC patients, a difference that is notably smaller than the 20% increase that would represent significant clinical improvement and should be attainable with the CKD-CDS intervention.

Table 2. Summary of descriptive statistics calculated from HPMG pilot data, key power analysis assumptions, and minimum detectable difference in 12-month post-index outcomes among CKD-CDS relative to UC patients for Hypothesis 1 to 5 outcomes.

	CKD Dx	ACEI / ARB	BP < 140/90	BP < 130/80	A1c <8	A1c <7	Neph referral
	HPMG pilot data estimates						
N[a]	10175	9012	8975	8975	3191	3191	1161
M (%)	52.9	54.6	70.4	43.3	79.7	48.7	37.8
ICC_{clin}	.027	.003	.004	.004	0	.003	0.063
ICC_{pt}			.28	.26			
	Power assumptions						
M (%)	50-60	50-60	70-80	40-50	75-85	40-50	30-40
ICC_{clin}	.01-.05	.001-.01	.001-.01	.001-.01	.001-.01	.001-.01	.05-.10
ICC_{pt}			.25-.35	.25-.35			
	Minimum detectable and clinically meaningful differences (%)						
detectable	5.8-11.1	3.4-5.7	3.2-7.1	4.3-8.4	3.5-5.9	5.2-7.0	13.5-17.9
meaningful	20	10	10	10	10	10	20

[a] estimated from number eligible in 17 HPMG clinics, prorated to 30 clinics assuming 13 similarly sized PN clinics

Pilot data from 2015-2016 primary care visits at 17 HPMG clinics found N=5766 adult patients aged 18-80 who had laboratory evidence of stage 3-4 CKD in 2015 and at least 1 post-index follow-up visit (median=5) before the end of 2016. PN primary clinics are similar in size and patient characteristics, suggesting a prorated N≈10,175 eligible CKD patients, including data from 13 additional PN clinics. We anticipate about 6% disenrollment from the medical group per year and about 2% per year to die. Very few patients switch from one clinic to another within HPMG or PN, and our algorithms accurately match over 95% of patients to a single PCP. In sum, we expect that data from a robust sample of patients with CKD will be available for testing Hypotheses 1-5. We will retrospectively retrieve the minimal necessary set of clinical information for conducting primary analyses as a limited dataset from the data repository that supports CKD-CDS operations.

9.3 POPULATIONS FOR ANALYSES

Individuals who meet all study wide inclusion and exclusion criteria at an index visit as described in Section 5 will be considered for inclusion in the primary analyses. Study-eligible patients will be included in the Hypothesis 1 through 5 according to the care gaps, defined in Section 5.1 , that are present at the time of their index visit.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All 5 hypotheses quantify the extent to which the CKD-CDS intervention relative to UC reduces deficits in measures of CKD care. Each will be defined as a single outcome based on data accrued in the 18 months after each patient's index visit. For all 5 measures, it is expected that the CKD-CDS intervention will positively impact the quality of care delivered to eligible patients with CKD.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

9.4.2.1. Analysis plan. All hypotheses will be tested using random coefficients models in which each binary post-index outcome (e.g., recognition in 18m) will be predicted via a link function from a fixed clinic-randomized treatment group predictor, Y_{10}; fixed clinic predictors for characteristics balanced at randomization, Y_{*0}; a fixed pre-index outcome status where appropriate, Y_{01}; and a random clinic intercept, V_j, such as:

$$\text{logit}(\text{BP<130/80 18m}_{ji}) = Y_{00} + Y_{10}\text{CKD-CDS}_j + Y_{*0}\text{balancing}_j + Y_{01}\,\text{SBP index}_i + [V_j].$$

Parameter Y_{10} is expected to be positive and statistically significant, indicating that patients in clinics randomly assigned to receive the CKD-CDS intervention are more likely to meet CKD recognition (H1), ACEI / ARB use (H2), BP control (H3), A1C control (H4) and nephrology referral (H5) thresholds in the 18 months post-index than patients in UC clinics, accounting for random variation across clinics and their own pre-index status on these outcomes.

The difference in predicted likelihoods of meeting each of the 5 outcomes through 18 months post-index will be estimated via planned contrasts and reported for ease of interpretation.

Secondary outcomes may be calculated using different thresholds (e.g., A1c<8) or treated as continuous variables (e.g., SBP in mm Hg) with adaptations made to the analysis models as necessary (e.g., identity link). Secondary analyses may include assessing (a) rates of treatment intensification among patients not at their BP or glucose goals, (b) variation in CKD treatment patterns across PCPs, (c) treatment effect heterogeneity, (d) intervention costs, (e) rate of occurrence and time to major CV events, and (e) rate of occurrence and time to hospital admissions or emergency department visits by eligible study subjects by treatment arm. We may also assess the impact of the CKD-CDS on NSAID use and medication adherence and treatment heterogeneity across demographic and racial groups.

9.4.2.2. Key Covariates. A key covariate in the H1-H5 hypothesis tests will be a binary indicator to denote whether the clinic in which the patient is seen was randomly assigned to the CKD-CDS intervention or the UC arm of the study. A second, pertinent to H3, quantifies the amount of time elapsed between the index visit and each measured BP. This covariate will be coded as (days since index/365) so that it quantifies the predicted annual change in BP control. Similarly, should the time elapsed between index and the last observed A1C differ by treatment group, log (time elapsed) may be included as an offset in the H4 analysis. Index CKD stage may be an important modifier of the CKD-CDS intervention. Stage 3-4 CKD will be defined based on the eGFR of 15-59 cc/min/1.73m^2 on the most recent eGFR test before the date of an index visit (stage 3a = 45-59, stage 3b = 30-44, stage 4 = 15-29), plus 1 or more antecedent eGFR values <60 cc/min/1.73m^2. Several other measures merit consideration as either secondary outcomes or as mediators or moderators of the primary analyses. These include (a) number of PCP patient encounters, (b) patient characteristics, including demographics and pre-intervention clinical

values and comorbidities (ICD-10 diagnosis codes and problem lists), and (c) PCP variation in baseline measures of CKD care.

9.4.2.3. Missing data. Data elements required for calculating the primary outcomes are extracted from EHR production tables. The absence of documentation of a care process, vital sign, or medication should not be interpreted as a missing value but rather as indicative of a care process or test not having been performed or medication not prescribed within the health system. Truly missing observations (eg, systolic BP measured, value not available) will be extremely rare, undetectable and assumed to be missing at random (MAR). The estimation techniques used in random coefficient models readily accommodate structural variation across observations in the amount of data present (eg, patients per clinic) and lead to unbiased parameter estimates and accurate standard errors when data are MAR.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Not applicable

9.4.4 SAFETY ANALYSES

Trends in safety concerns for subjects will also be followed as indicated by the Data Safety and Monitoring plan outlined in the safety oversight section below.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Patient Characteristics. For each study subject, we document the following from EHR and/or health plan data sources: demographics (e.g., age, gender, race, ethnicity, insurance type, primary language, use of interpreter), vital signs (e.g., all BP values), height, weight, body mass index (kg/m2), laboratory values (including all serum creatinine, eGFR, electrolyte, and other renal function-related tests), medications prescribed (based on EHR prescribing data), and medication prescriptions filled (based on claims data). We calculate the ACC/AHA 10-year CVD risk score at defined time points (pre-index visit, at index visit, at follow-up visits).[80] Adjustment for patient covariates may be necessary because randomization is done at the clinic level, and patient-level data may therefore exhibit random as well as selection-induced covariate imbalance. Because they are drawn from EHR and/or health plan records rather than patient surveys, these data elements will be of high quality and available for virtually all subjects.

Provider Characteristics. We will have complete data for a limited set of provider characteristics, including age, years since graduation, gender, full-time versus part-time work status, physician versus allied provider (eg, nurse practitioner), specialty board certification status, employment years, and number and proportion of patients with CKD by CKD stage. Provider characteristics may be considered covariates or moderators to estimate the differential strength of the intervention across different kinds of providers.

9.4.6 PLANNED INTERIM ANALYSES

Not Applicable

9.4.7 SUB-GROUP ANALYSES

Several measures merit consideration as mediators or moderators of the primary analyses. These include (a) number of PCP patient encounters, (b) patient characteristics, including demographics and pre-intervention clinical values and comorbidities (ICD-10 diagnosis codes and problem lists), and (c) PCP

variation in CKD care at baseline. Assessment of heterogeneity of treatment effects based on pre-specified subgroups of patients will incorporate a factor (e.g. sex) and its interaction with treatment arm in mixed models.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

We may examine the clinical impact of the CKD-CDS on the following: (1) non-aspirin NSAID use, (2) medication adherence, (3) provider behaviors such as treatment intensification among patients not at their BP or glucose goals, and CKD treatment patterns across primary care physicians (PCPs) (5) Rates of hypotension, hypoglycemia, electrolyte disturbances, emergency department visits, hospital admissions for renal and non-renal causes, major cardiovascular events, and mortality as deemed necessary per the data safety and monitoring plan.

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

A waiver of patient consent was requested and granted by the IRB for the following reasons:
a) All CKD-related treatment recommendations included in the CKD-CDS algorithms are evidence-based, as specified in national evidence-based clinical guidelines, and no care is advocated that is not evidence-based. Thus, the care recommendations conform to current standard of care and ought not represent any additional risk to patients beyond the routine risk that all patients assume whenever they have contact with the medical care system.
(b) The intervention identifies any current treatments that are potentially unsafe to the patient, which is of minimal risk to possible benefit to each patient at each visit during the study period.
(c) At intervention clinic training sessions and on every printed decision support screen and printed sheet, we emphasize that it is inappropriate for a PCP to implement suggested treatment recommendations without further checking the clinical status of a given patient.
(d) It would be impractical to consent patients (due to large numbers of patients and the intensity of clinic workflow) and impossible to answer the primary research questions (due to selection effects related to consent) if written informed consent of patients were required.

We are also received a waiver of informed consent for PCPs using the CKD-CDS tool for reasons (a), (b) and (c) above as well as the following reason(s): (d) the CDS tool, upon which the expansion to include CKD-CDS will be done for this study, is currently being used as part of standard care at HP and PN. Consent will be obtained from providers who agree to be interviewed as part of the evaluation of the CDS tools, and the consent form and consenting process was reviewed and approved by the IRB.

In addition to the internal HealthPartners Institute policies, Health Insurance Portability and Accountability Act (HIPAA) itself makes specific provision for waiver of authorization to use PHI for research recruitment purposes under some specific conditions, all of which this study meets[81].

At HealthPartners Medical Group, patients can opt out of use of their data for research. HealthPartners Institute keeps a record of the small number of individuals who have opted out to avoid use of their data or attempts to recruit them into studies. We will exclude patients who have declined permission for their medical records to be used in research.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Not-applicable.

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 participating clinics, investigators, study team members and the funding agency. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform participating clinics, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension.

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 and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

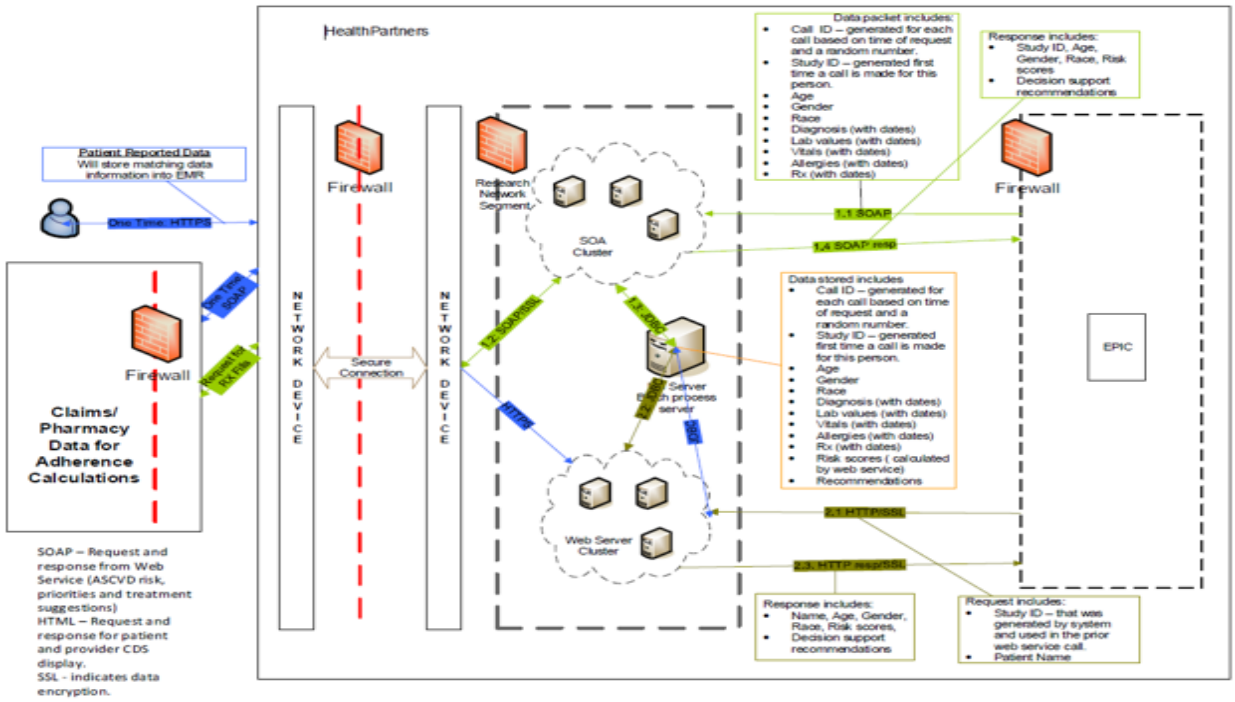
In order to ensure patient confidentiality, we need to print the name of the patient on the CDS tools that are printed and given to the patient and their PCP at the time of a clinic visit. Because more than one nurse-PCP team may use the same printer, names are required to avoid mixing up printed materials and giving PHI to the wrong patient. It is also desirable to have each patient's name on this sheet of paper to ensure the patient knows that the information on the paper is personalized and related to his or her own health state.

Although used for CDS display, patient names are scrubbed from the data nightly. The remaining data is retained in the operational data store for 2 weeks for immediate trouble shooting. Later, if needed for approved research, the data is moved to an analytic database with minimal access. With respect to the analytic databases, the following measures will be taken to protect PCPs and patients from the risk of breach of confidentiality: The patient name is not retained within the analytic database. A unique study ID code unrelated to the medical record number or other study subject-specific information will be assigned to each patient at the index visit (first visit in the intervention period). The study ID is used to link data from patient encounters over time and various data sources that are needed for analysis. A crosswalk table linking this code number to a PCP or patient name or medical record number will be destroyed within 12 months after completion of the linked databases needed to test study hypotheses.

Several measures are in place to ensure security of protected health information in the EHR-linked data repository (Web service), Figure 3. Data transfer to the Web service uses a Simple Object Access

Protocol (SOAP) with Secure Sockets Layer (SSL) encryption over a Hypertext Transfer Protocol Secure (HTTPS) computer network. There is a double firewall in the Web service so that, once the data flow through the initial Web service firewall, the data cross another firewall into a new secure pathway that once again employs SOAP, SSL, and HTTPS to process the data. This includes sending the data through a batch server for more efficient processing but all within the double-firewall Web service.

Figure 3: Data Flow for CKD-CDS intervention



In compliance with HIPAA regulations[81], no PHI will be shared outside of the affiliated covered entities (ACE) without obtaining a data use agreement or business associates agreement. As part of the ACE, researchers at the Institute are able to use HealthPartners medical records data for purposes such as those in this study in compliance with HIPAA regulations (i.e., following the concept of "minimally necessary" use of PHI).

The study team has extensive experience in health services research and clinical research with human subjects, with procedures to safeguard privacy and personal information. All study records are protected by:

- Locked storing all paper records in a secure location
- Use of untraceable study ID numbers instead of names wherever possible
- Password protection as well as firewalls
- Strong user login authentication on all electronic devices
- Physical security for all electronic devices containing personal information

Data will be retained in secure storage following the completion of the study in accordance with Minnesota and federal law. We guard against the potential for breach of subject confidentiality through a multi-layered system of data protection policies, processes, staff training, software safeguards and physical security measures for both paper and electronic data involved in research.

The following measures will be taken to protect subjects from the risk of breach of confidentiality:

- A unique person identifier unrelated to the medical record number or other study subject-specific information will be assigned to each patient study subject to protect patients from the risk of breach of confidentiality in the analytic datasets
- A file containing a link between the study ID and individually identifying information will be maintained at by a programmer who is member of the study team through the conclusion of the study.
- A cross-walk table linking the study ID to a patient identity will be destroyed within 12 months after the linked databases needed to test study hypotheses are completed.
- All electronic study data will be maintained in a computerized database residing on a username- and password-protected file-server to which only the researchers involved in the study will have access.
- All study-related paper documents containing individually identifiable information will be maintained in locked file cabinets.

Certificate of Confidentiality:
To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by 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

Data collected for this study will be analyzed and stored at the HealthPartners Institute. Data used by the CDS is stored at an operational data bank for 2 weeks for immediate trouble shooting. Later, if needed for approved research, the data is purged of patient names and moved to an analytic database with minimal access. After the study is completed, a completely de-identified, archived data set may be transmitted to and stored for use by other researchers outside of the study team.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Project Manager**
JoAnn M. Sperl-Hillen, MD *Senior Clinical Investigator*	*Kris Ohnsorg* *Research Project Manager*
HealthPartners Institute	*HealthPartners Institute*
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Other Team Members	
Co-Investigators	*Patrick O'Connor, Malini DeSilva*
Statistics and Data Management	*Lauren Crain*
Application Development	*Deepika Appana*

Consultants

Areef Ishani, MD, MS is the Director of Primary Care and Specialty Medicine at the Minneapolis Veterans Affairs HealthCare System Center and Professor of Medicine at the University of Minnesota. He is an active investigator in research involving CKD epidemiology, dialysis outcomes, and validity of the eGFR formula in populations based on race, gender, and age. He has experience implementing CDS systems within the primary care setting, specifically addressing the referral process between primary care and nephrology. As a consultant on this project, he will serve as member of Nephrology and Primary Care Advisory Group and will participate in regular meetings in all three years of the study.

James Wetmore, MD, MS is a general nephrologist practicing at Hennepin County Medical Center (HCMC), a level 1 trauma center based in Minneapolis, Minnesota, and the Medical Director at the HCMC Parkside Nephrology Clinic. His expertise includes CKD and maintenance dialysis with special emphasis on acute dialysis modalities such as continuous renal replacement therapy. He is also the Medical Director for Nephrology Research with the Chronic Disease Research Group at HCMC where he specializes in observational research utilizing large administrative databases to investigate the association of CV outcomes in chronic dialysis patients. As a consultant on this project, he will serve as member of Nephrology and Primary Care Advisory Group and will participate in regular meetings in all three years of the study.

Nephrology and Primary Care Advisory Group

The study has a team of nephrologists and primary care physicians as well as leaders from the HPMG who are involved in the oversight of the trial from the development phase all the way to the close of the trial and the analysis and publishing of findings. Their involvement is through email consultations as well as participating in meetings.

10.1.6 SAFETY OVERSIGHT

David Gilbertson, Ph.D is the safety officer for the study. Dr. Gilbertson is the co-director of the Chronic Disease Research Group and Director of Epidemiology and Biostatistics at Hennepin Healthcare Research Institute in Minneapolis, and an associate professor of Medicine at University of Minnesota. He has prior experience with renal research and Data Safety Monitoring Board (DSMB) work (he is on the DSMB for Technology Assisted Stepped Collaborative Care Intervention to Improve Patient-Centered Outcomes in Hemodialysis patients (TASCCI),” and has a long track record of important publications in the CKD field. Dr. Gilbertson was approved by our project officer for this position.

Meetings of the PI, the project team, and the safety officer will occur twice a year and follow NIH guidelines on conduct of such meetings, with a formal report describing the content of each meeting and the data reviewed. We will invite a representative of the funding agency, NIDDK, to participate via conference call at these formal meetings.

The safety officer will provide input and guidance on the study evaluation and intervention protocols, including quality assurance and safety issues related to the protocols and intervention strategy, as well as data handling activities. The safety officer will also provide periodic input and feedback related to study recruitment and retention rates, study eligibility determination issues, data completion rates, and adverse events via email, conference calls, and formal meetings every 6 months.

A special focus of interest will be the safety of patients exposed to the study intervention. The intervention supports more thorough identification of individual patients with stage 3-4 CKD and suggests to both patient and PCP evidence-based treatment options that have been shown in randomized trials to reduce progression of renal disease and/or reduce the occurrence of heart attacks and strokes. Any such care recommendations, if implemented, are delivered through usual care

channels using pharmacotherapies openly available in medical group formularies for FDA-approved indications only. Each study PCP has complete freedom to treat or not treat a given patient with whatever therapy the physician believes is best for that patient. Adverse-events information will be monitored using EHR data at a frequency determined by the safety officer and may include identification of electrolyte abnormalities and emergency department or hospital admissions related to syncope, hypotension, or hypoglycemia. Rates of monitored events will be compared in intervention and usual care clinics, and any significant differences will be promptly reported in writing to the NIH and to the HealthPartners IRB, consistent with NIH and HealthPartners IRB policy. We have budgeted funds for the safety officer but have not recruited a specific individual for this position. Consistent with NIH and HealthPartners Institute policy, the Safety Officer will not be affiliated with HealthPartners, HPMG, or PN.

10.1.7 CLINICAL MONITORING

Not applicable

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data capture system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to application and epic development team for clarification/resolution.
The HealthPartners Institute will provide direct access to all trial related clinics, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data Collection during the Development of the CKD CDS Tool

The development phase of the study will include an iterative process of developing the CKD-CDS tool and laying the groundwork for intervention implementation. This phase will involve algorithm development, programming, testing, feedback seeking and incorporation into the prototype and will culminate with pilot testing at 1-2 clinics. Part of the feedback seeking will involve in-depth video interviews with providers with the objective of qualitatively exploring how providers perceive the interface of the newly developed CKD-CDS and to determine which critical features, functions and evidence are needed to transform the CKD-CDS prototype into a functional tool. We will also do preliminary data pulls and chart reviews.

In-depth interviews

i. Process steps for identification of providers: We will use the providers currently involved in the study to get suggestions of providers that we can reach out to. We will also use the list of health care providers in the HPMG and PN provider databases who are current users of the CV Wizard.
ii. Recruitment: Using convenience sampling strategy, we will reach out to primary care providers and specialists involved in caring for patients with CKD in the HPMG and PN. We will initially target about 8 providers but will continue the interviews until saturation is reached[82].
iii. Consent: For providers to be interviewed to assess the CDS design or experience, written informed consent will be sought. IRB approved consent form and a cover letter will be sent by email/fax to potentially eligible PCPs, and they will have several weeks to study the forms, call research team

investigators (Dr. Kumar or Dr. Sperl-Hillen) with any questions or for clarifications, and sign and return the written informed consent form if they wish to voluntarily participate in the interviews. Providers who agree to participate in the video interviews will be given a gift card worth $100 via email or have $100 added to their paycheck after the interview.

iv. Interview process: An experienced interviewer and a user interface/ user experience engineer will facilitate the video interview using a GoPro camera and a semi-structured interview guide (attached). The interview guide will be pilot tested with 2 physicians and a project manager to ensure that the questions are clear and well understood. Each interview session will last approximately 30-45 minutes. We will first begin with a general discussion about the participants' baseline understanding of CDS tools and their perception on barriers and facilitators to using CDS tools in the context of their own practice. We believe that it would be helpful to get unbiased feedback about physician attitude towards use of CDS tools prior to introducing them to the CKD-CDS tool. After that, we will ask participants questions relating to the CKD-CDS tool. The programmer will take the provider through the tool using a test patient. The interviews will be audio or video recorded with the consent of the participants and transcribed verbatim. Analysis will involve a continuous iterative process whereby data from the interviews will be re-examined and identified concepts will be explored in subsequent interviews. The analysis will be cumulative and iterative building on the discussions from previous interviews (for example, interview questions and the CKD prototype design will be modified and refined for subsequent interviews) until themes reach saturation.

Preliminary data analysis and chart reviews

During the pilot test and throughout the patient accrual period of the intervention, we will perform preliminary data pulls and chart reviews of no more than 1% of the patients to assess the functioning of the CKD-CDS tool and the effect of the tool on patient care. We will also do chart audits in response to patient and provider feedback sent via the feedback tab found in the online version of the CKD-CDS tool to assess the problems and provide accurate feedback.

<u>Data Collection Following the Launch of the Intervention</u>

i. Process steps for identification of patients and patient records

Limited clinical data will be collected for adult study subjects for specified periods and will be used to: (a) identify eligibility (inclusion and exclusion criteria) for the study based on CKD care status at the time of an office visit, such as age, pregnancy, dementia, or active cancer therapy in the previous year; (b) identify any evidence-based deficits in CKD care based on currently accepted national CKD clinical guidelines; (c) provide a lay version of the evidence-based treatment recommendations for the patient and a professional version for the PCP; (d) assess the impact of study interventions on CKD care in eligible adults at intervention versus control clinics, and (e) assess the impact on outcomes of demographic characteristics such as gender, race, ethnicity, insurance type, primary language and use of interpreter

ii. Patient accrual

The index visit will be the first visit at any randomized clinic in the accrual period at which the patient was eligible for the CKD-CDS intervention. We anticipate that the patient accrual period (for index visits) will be a minimum of 11 months, followed by a minimum of 18-month observation period.

iii. Data sources

All necessary data to determine eligibility, implement and operate the intervention, and assess the impact of the intervention are derived from electronic health records (EHRs) or health plan or medical group administrative databases.

iv. Process steps for data acquisition

We will construct variable definitions and data extraction procedures for demographics, enrollment characteristics, vital signs, pharmacy, inpatient and outpatient encounters, and diagnoses. Data from all sources, including encounter data, claims, and EMR clarity data, will be restructured into a common format and data elements combined into uniform files. A unique identifier will link all person-level information. Data integrity will be assessed to ensure that observations are valid, reliable, and consistent. Each variable will be tested for completeness and out-of-range values. We will create Limited Data Sets that are consistent with human subject protection and HIPAA privacy regulations that will be kept at HealthPartners Institute, along with data dictionaries, coding manuals, and other documentation relevant to data collection or measurement issues. After this study, this resource may be available to the funding agency or to other approved investigators in accordance with then-current regulations about data privacy and data use.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last day of data collection.

10.1.10 PROTOCOL DEVIATIONS

The PI, Dr. JoAnn Sperl-Hillen, will lead weekly meetings of the investigator team to ensure that all project activities are conducted and completed in a timely fashion and exactly as specified in the study protocol. The team will identify and report any deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to NHLBI and the Program Official. Protocol deviations will also be sent to the reviewing Institutional Review Board (IRB) per their policies. In addition, the programmers will meet weekly to deal with operational issues related to development, implementation, and maintenance of the intervention tools and with data and analysis issues throughout the project.

10.1.11 PUBLICATION AND DATA SHARING POLICY

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. The project team plans to submit manuscripts to peer reviewed journals including, such as those devoted to primary care, quality improvement, or CKD. For HealthPartners, the team plans to share results through meetings and presentations to the relevant departments. Data from this study may be requested by other researchers 3 years after the completion of the primary endpoint or 2 years after the main paper of the trial has been published, whichever comes first, by contacting Dr. JoAnn Sperl-Hillen.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of

interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Institute of Diabetes and Digestive and Kidney Diseases has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

None

10.3 ABBREVIATIONS

A1c	glycated hemoglobin A1
ACC/AHA	American College of Cardiology/American Heart Association
ACE	affiliated covered entities
ACEI	angiotensin converting enzyme inhibitor
ACR	albumin to creatinine ratio
AE(s)	Adverse Event(s)
ARB	angiotensin receptor blocker
ASCVD	Athersosclerotic cardiovascular Disease
BP	Blood pressure
BPA	Best Practice Advisory
CDS	Clinical Decision Support
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CRF	Case Report Form
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
ED	Emergency Department
eGFR	estimated glomerular filtration rate
EHR	Electronic Health Record
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HP	HealthPartners
HPMG	HealthPartners Medical Group
HTTPS	Hypertext Transfer Protocol Secure
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
ICH	International Conference on Harmonisation
ID	Identification
IRB	Institutional Review Board
MAR	missing at random
MDH	Minnesota department of health
mg/dl	milligrams/deciliter
mm Hg	Millimeters of Mercury
NCT	National Clinical Trial
NIH	National Institutes of Health
NSAID(s)	non-steroidal anti-inflammatory drug(s)
OHRP	Office for Human Research Protections
PCP(s)	Primary Care Provider(s)
PEM	Patient education material(s)

PHI	personally identifiable health information
PI	Principal Investigator
PN	Park Nicollet
SAE(s)	serious adverse event(s)
SDM	Shared decision making
SOAP	Simple Object Access Protocol
SSL	Secure Sockets Layer
UC	usual care
UMACR	urine micro-albumin creatinine ratio
UP(s)	unanticipated problem(s)

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