ABSTRACT

DESCRIPTION (provided by applicant): Chronic kidney disease is steadily increasing in prevalence in the United States, causing significant morbidity and mortality. Stage 3 chronic kidney disease is associated with a 5-year all-cause mortality rate of 24.3% and a 5-year need for renal replacement of 1.3%. Stage 4 chronic kidney disease is associated with a 5-year 45.7% mortality rate and a 5-year 19.9% requirement for renal replacement. There is reasonable evidence that specific actions can be implemented by primary care physicians to delay chronic kidney disease progression and reduce mortality; however, chronic kidney disease is under-recognized and under-treated in primary care offices. The availability of computer decision support (CDS) for chronic kidney disease may help promote effective, evidence-based care, but evidence suggests that CDS alone may not be enough to improve quality of care. Studies have shown improvement in diabetes care from a combination of CDS plus practice facilitation. Studies of similar interventions for chronic kidney disease care have not been conducted. This group randomized controlled trial will test the extent to which CDS plus practice facilitation promotes evidence- based care and improves the clinical outcomes of reduced disease progression and mortality in primary care practices. The practice facilitation intervention is based on an effective approach for implementing the Chronic Care Model; it is a combination of CDS plus having practice facilitators work with on-site teams lead by a physician champion. In addition, each practice will be assigned an academic mentor and have routine audit and feedback of key elements of evidence-based chronic kidney disease care. Evaluation will include an intent-to-treat and process analysis between the CDS practices with facilitation versus the CDS-only practices of the clinical outcomes of chronic kidney disease progression and all-cause mortality. A cost- effectiveness analysis will compare the benefit of the intervention of CDS alone against the intervention of CDS plus practice facilitation in relationship to overall cost per quality adjusted years of life. This study will enroll 40 practices associated with the Distributed Ambulatory Research in Therapeutics Network (DARTNet), a federated network of organizations that use electronic health records.

IMPROVING EVIDENCE-BASED PRIMARY CARE FOR CHRONIC KIDNEY DISEASE

SPECIFIC AIMS

Chronic kidney disease (CKD) and end stage renal disease (ESRD) are steadily increasing in prevalence in the United States. There were 26 million American adults with CKD in 2000, a 30% increase over the past decade.[1] The annual incidence of ESRD is projected to increase from its 2007 level of 111,000 to 143,000 by 2020, when the prevalence of ESRD is expected be over 770,000 people.[2, 3] The aging of the population and the rising prevalence of obesity, hypertension, and type 2 diabetes--the major risk factors for CKD—contribute to this trend.[4] CKD is a serious condition; stage 3 CKD is associated with a 5-year all-cause mortality rate of 24.3% and a 5-year need for renal replacement of 1.3%. Stage 4 CKD is associated with a 5-year 45.7% mortality rate and a 5-year 19.9% requirement for transplant or dialysis.[5]

There is strong evidence that specific activities can be implemented by primary care physicians (PCPs) to delay CKD progression and reduce mortality. These include the use of angiotensin converting enzyme inhibitor (ACE) or angiotensin receptor blocker (ARB) [6, 7] medications; avoidance of non-steroidal anti-inflammatory drugs (NSAIDS)[8]; control of blood sugar in patients with diabetes[9] and control of blood pressure.[10] The use of statins in patients with CKD who were not on dialysis had a beneficial effect on cardiovascular mortality.[11] Other actions, such as early referral of Stage 4 patients to nephrology, can reduce mortality.[7, 12]

However, CKD is under-recognized and under-treated in primary care offices, and PCPs are generally not familiar with treatment guidelines.[13-15] Even when diagnosed, CKD is a chronic condition that, like diabetes, is frequently associated with co-morbidities, making effective treatment difficult due to the complexity. The availability of computer decision support (CDS) for CKD may help promote effective, evidence-based care, but evidence suggests that CDS alone may not be enough for quality improvement. However, interventions that include CDS *plus* practice facilitation have improved care for diabetic patients.[16-19]

The trial proposed in this application will test the extent to which CDS plus facilitation promotes evidence-based care and improves the clinical outcomes of reduced disease progression and mortality in primary care practices. We also propose to conduct an observational comparative effectiveness analysis of data from a larger database of electronic medical records in order to identify the most successful components of evidence-based care with respect to disease progression and all-cause mortality.

Specific Aim 1: Conduct a group randomized controlled trial of point-of-care computer decision support plus the full TRANSLATE model of practice change, versus computer decision support alone in promoting evidence-based care in primary care practices for all patients with an eGFR <60 and > 15 ml/min/1.73m^2 confirmed with repeat testing over three or more months. (CKD stages 3 and 4)

Hypothesis 1.1: CDS practices using the TRANSLATE model will provide a greater degree of evidence-based guideline-concordant care for CKD than CDS only practices.

Specific Aim 2: Conduct an intent-to-treat analysis between the CDS practices with facilitation versus the CDS only practices of the clinical outcomes of CDK progression and all-cause mortality.

Hypothesis 2.1: Patients with stage 3 and 4 CKD in facilitated practices will have slower CKD progression than patients in CDS only practices.

Hypothesis 2.2: Patients with stage 3 and 4 CKD in facilitated practices will have significantly lower all-cause mortality than stage 3 and 4 patients in CDS only practices.

Specific Aim 3: Conduct an as-treated analysis across all practices in the study as well as all practices within DARTNet that are willing to share data on patients with stage 3 and 4 CKD to determine the impact of greater guideline concordance on the progression of CKD and explore the impact of several individual intermediate outcomes on the rate of progression of CKD.

Hypothesis 3.1: Patients with greater guideline concordance will demonstrate less progression of disease.

Hypothesis 3.2: Lower systolic blood pressure at baseline and over time will delay the rate of CKD progression after controlling for other measured variables.

Hypothesis 3.3: Continued use of non-steroidal anti-inflammatory medications and use of an angiotensin converting enzyme inhibitor or an angiotensin receptor blockade agent will have independent and opposite effects on eGFR decline.

RESEARCH STRATEGY

A. SIGNIFICANCE

The NIH Roadmap provides a framework for the NIH to speed discovery and provide for its efficient translation to patient care. There are three major components to the roadmap: ‘‘New Pathways of Discovery,’’ ‘‘Research Teams of the Future,’’ and ‘‘Reengineering the Clinical Research Enterprise.’’[20] The Institute of Medicine's Clinical Research Roundtable described two "translational blocks" in the clinical research enterprise which some now label as T1 and T2. The first pathway (T1) was described by the roundtable as "the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans." The roundtable described the second pathway (T2) as "the translation of results from clinical studies into everyday clinical practice and health decision making."[21, 22] The following proposal describes a T2 clinical trial utilizing the Chronic Care Model to improve the detection and treatment of Chronic Kidney Disease in primary care offices. This trial will be supplemented by an Observational Comparative Effectiveness Research (OCER) study that will analyze a larger set of related electronic medical records data.

The Chronic Care Model has been widely accepted and utilized in primary care practices as a means of improving evidence-based care. [16] Peterson et. al. developed a nine-point action plan, including computer decision support (CDS) for implementing the Chronic Care Model. This plan is referred to as TRANSLATE. TRANSLATE stands for set your **T**arget, use **R**egistry and **R**eminder systems, get **A**dministrative buy-in, **N**etwork Information systems, **S**ite coordination, **L**ocal Physician Champion, **A**udit and feedback, **T**eam approach, and **E**ducation. Peterson successfully utilized this method in a large NIDDK-funded randomized controlled T2 trial for the treatment of diabetes.[18]

Chronic kidney disease (CKD) is a serious complex co-morbid condition that is increasing in prevalence[1] and costliness to the health care system.[23] It is, like diabetes, frequently associated with co-morbidities [24] and CKD expenditures now comprises over 24% of the entire Medicare budget.[25] There are known cost-effective treatments for the prevention of progression of CKD, such as the control of blood pressure, use of Angiotensin Converting Enzyme Inhibitors (ACE) or Angiotensin Receptor Blockers (ARB) [26-28], smoking cessation. [29, 30] Likewise there are measures that will reduce mortality if used in earlier stages of the condition (stage 3 and 4). This is defined as having an estimated glomerular filtration rate (eGFR) as calculated by the Modification of Diet in Renal Disease (MDRD) equation of between 15-60 ml/min/1.73m^2. Examples include earlier referral to nephrologists and placement of fistulas as opposed to intravenous catheters for hemodialysis. [7, 23, 31] But CKD is under- recognized and under-treated in primary care physician (PCP) offices, and PCPs are generally unfamiliar with treatment guidelines. Therefore, the uptake of evidence based interventions is low.[13, 14]

The Distributed Ambulatory Research in Therapeutics Network (DARTNet) is an Agency for Research and Quality (AHRQ)-funded network that is designed to create an infrastructure for conducting national comparative effectiveness research and T2 translational research in PCP offices.[32] It currently has over 140 primary care offices and 3 million patients available for translational research. All offices have electronic health records (EHRs - 10 different EHRs represented) with electronic data available for analysis following appropriate de-identification processes. DARTNet is growing rapidly with practices caring for an additional 1 million lives committed to joining soon. Each practice participating in DARTNet has a robust computer decision support system (CDS) that provides up-to-date point- of-care reminders to the clinician and office staff for a number of preventive services and chronic medical conditions, thereby making DARTNet an outstanding laboratory for both T2 translation and comparative effectiveness research involving patients in community PCP offices.

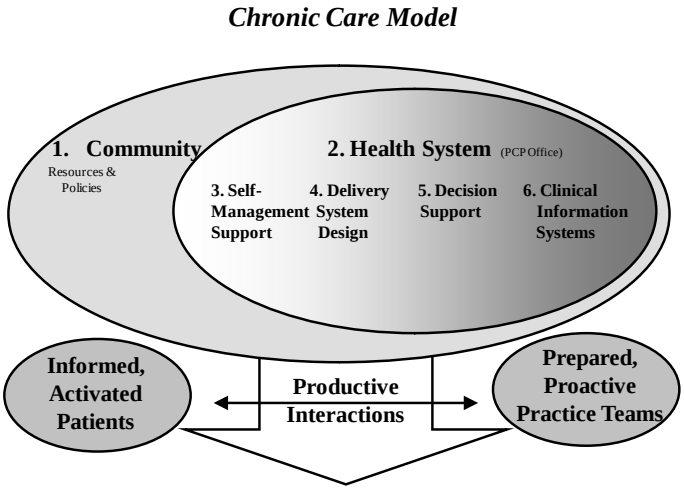
The key evidence-based elements that have been shown to reduce CKD progression or mortality are: 1) BP <130/80, 2) HbA1c < 7.0 3) LDL< 100 4) Use of ACE or ARB, 5) Referral to a nephrologist for GFR < 30 6) Smoking cessation and 7) Avoidance of the use of NSAIDS or COX-2 inhibitors. These are the intermediate outcome measures we will be testing. We therefore propose to carry out a large group block randomized controlled clinical trial comparing the effectiveness of CDS alone to CDS plus a fully facilitated TRANSLATE intervention to improve clinical outcomes in patients with Stage 3 and 4 CKD.

1. Computer Decision Support Alone vs. Computer Decision Support Plus Practice Facilitation

It has been repeatedly demonstrated that patients only receive approximately half the evidence-based care that they require. [33-36] The reasons for this are multi-factorial. Jaen et al. proposed a model of competing demands that prevented PCPs from devoting the time needed for preventive services.[37] They compared the requirements for both preventive and acute care management to those of a person at a dinner buffet with a full plate. In order to add something to the plate, something has to be removed. Their model was graphically confirmed by the time studies conducted by the Duke School of Public Health which demonstrated that providing the A and B grade evidence-based care recommended by the United States Preventive Service Task Force would require 7.4 hours per day,[38] and providing the necessary chronic disease management would require an additional 3.5 hours if the patient's disease were in stable condition and 10.6 hours if the disease were not controlled.[39] This critical need for improved efficiency of care and appropriate change in reimbursement strategies sparked the American Academy of Family Physicians, the American College of Physicians, the American Academy of Pediatrics and the American Osteopathic Association to issue a joint statement putting forth the principles of the Patient Centered Medical Home (PCMH) model.[40]

The key tenets of the PCMH are embodied in the Chronic Care Model (Figure 1), which has proven to be an effective theoretical framework for improving the implementation of evidence-based care in PCP offices.[16, 17]

Figure 1. The Chronic Care Model



One aspect of the Chronic Care Model - computer decision support - has demonstrated variable effectiveness in improving care. An evidence-based review by Garg et al. found that physician behavior was improved in 73% of the studies, but clinical markers were only improved 42% of the time. [41-45,46, 47], In contrast to this, the combined efforts of the TRANSLATE model were highly effective in improving diabetes care in a randomized controlled trial involving 24 practices and 8,405 diabetic patients. At 12 months, intervention practices had significantly greater improvement in achieving recommended clinical values for systolic blood pressure (SBP), Hemoglobin A1C (HbA1C), and LDL cholesterol than control practices. Control practices in this study were provided with a report of their process and outcome measures at baseline and were encouraged to continue usual quality improvement. All practices were instructed to target the same values.[18] The proposed study is intended to answer the question of whether the addition of practice facilitation, as was done in the TRANSLATE trial, compared to CDS alone will lead to improved evidence-based care for CKD in PCP offices.

2. The Need to Improve Evidence-Based Care for Pre-ESRD Patients

Some aspects of CKD care are solidly evidence based. These include: the use ACE or ARB[7, 28], the avoidance of non-steroidal anti-inflammatory drugs (NSAIDS)[8], control of blood sugar [9] and blood pressure[48] smoking cessation[30] and early recognition and referral of Stage 4 CKD patients [23]. A Cochrane systematic review concluded that the use of statins in patients with CKD who were not on dialysis had a beneficial effect on cardiovascular mortality and reduction of proteinuria, but did not delay progression of CKD.[49] Despite this

array of indicated interventions, only approximately 50% of CKD is recognized in early stages by PCPs.[13, 14] Therefore, there is a major opportunity to improve secondary prevention and complications of CKD prior to the need for renal replacement therapy. The TRANSLATE method was effective in improving diabetes care, thus it is reasonable to test whether it will be equally effective in the treatment of CKD.

B. INNOVATION

This study has 3 major innovations. They are:

1. TRANSLATE: Adapting the TRANSLATE method for implementing the Chronic Care Model that was effective in diabetes care to CKD. This generalization study will be described in more detail in the methods section.
2. Generalizable clinical decision support system: The point-of-care computerized decision support protocol engine is integrated with multiple EHRs. The Clinical Integration Networks of America, Inc. (CINA) system can be implemented against virtually any ambulatory EHR and is thus available to others.
3. DARTNET: Tracking in an efficient and longitudinal manner a very large population over a long period of time in real world practices through DARTNet allows both group level randomized RCTs as well as population-based OCER analyses to be conducted from the same study.

QED Clinical, Inc. (dba CINA):

CINA collects, standardizes and synthesizes data from multiple EMR vendors. CINA provides a set of tools for clinical decision support, quality improvement and data aggregation for reporting. These include point-of-care clinical decision support (CDS). CINA produces both cross-sectional and time-based reports that can demonstrate a change in both single and multiple variables over time. The point of care reminder system provides a synthesis of data for each patient including over 30 different algorithms based on the US Preventive Services Guidelines and evidence-based guidelines for multiple chronic diseases such as hypertension, diabetes, and congestive heart failure. The entire system promotes both goal based and process-based activities.

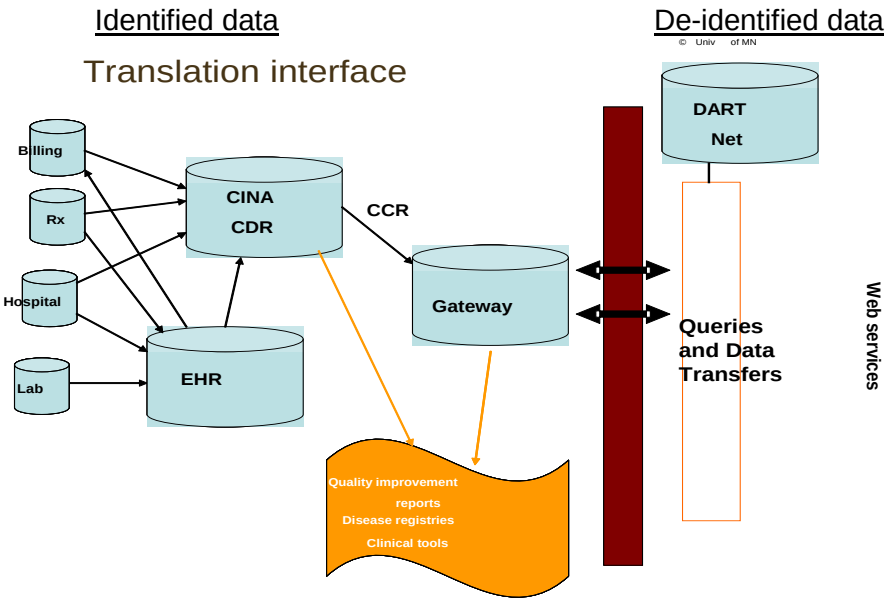
Distributed Ambulatory Research in Therapeutics Network (DARTNet):

DARTNet is a federated network of electronic health record (EHR) data from 24 organizations representing over 140 PCP practices and more than three million patients. The system captures and standardizes approximately 125 unique data elements per patient (e.g., all medications and all diagnoses represent two data elements) for up to the entire time period represented in each organization's EHR. DARTNet research partners seek to answer questions concerning the safety and effectiveness of medications and medical devices, to advance translational research activities and to create a learning community that seeks to improve clinical care in areas of interest to the group. DARTNet is also exploring its ability to fill gaps in routine clinical data when used for research purposes by using point-of-care data collection techniques.[32]

DARTNet uses the CINA Clinical Data Repository (CDR) to collect and standardize selected EHR data elements, which are then de-identified, transferred to a second database and presented for query access through a secure web-portal. Both of these databases reside within individual member organizations. A full dataset of identified or de-identified data never leaves the organization, though subsets of de-identified data can be transferred to the research team following local approval. The DARTNet system is expandable, utilizing local parallel processing and a two-stage data extraction and de-identification process. The DARTNet infrastructure as viewed from a single health care organization is depicted in Figure 2.

Current DARTNet practices are located in 10 states and utilize 10 different EHRs. DARTNet includes small, medium, and large practices. Some serve large Latino patient populations (mirroring their state's demographics) and another has a higher number of African Americans. The three largest groups have substantial Medicare populations. Since the US population has a CKD prevalence rate of 13%, it is expected that there will be approximately 300,000 CKD patients in DARTNet practices willing to participate in the OCER portion of this study (assumes 2 million patients with data from a 7 year time frame.)

Figure 2 - DARTNet as Viewed From a Single Organization



C. APPROACH

1. Overall Strategy, Methodology and Analyses

The proposed research consists of a group randomized controlled trial (RCT) followed by an observational comparative effectiveness research (OCER) study. Aims 1 and 2 will be addressed through the RCT, and Aim 3 will be completed through the OCER study. The RCT should enhance the number of individuals who receive guideline concordant care and the CDS system should increase the number of individuals with more complete data for OCER analysis across DARTNet.

Approach for Specific Aim 1: Conduct a group randomized controlled trial of point-of-care computer decision support plus the full TRANSLATE model of practice change, versus computer decision support alone in promoting evidence-based care in primary care practices for all patients with an eGFR >15 and <60 ml/min/1.73m^2 (stage 3 and 4) that has been confirmed with repeat testing over three or more months.

The elements of the full TRANSLATE method that are unique to the intervention group are: site coordination, local Physician champion, audit and feedback, team approach and education. The educational aspects will include participating in collaborative learning groups and having an Academic mentor.

Selection of Practices: This will be a group randomized controlled trial (RCT) comparing CDS alone to CDS plus practice facilitation. The unit of allocation will be the PCP practice. Candidate practices will be drawn from DARTNet members. To maximize baseline comparability across study conditions, prior to randomization offices will be stratified on practice size. There will be two practice sizes (< 4 providers versus > 4 providers). The mean and mode practice size for primary care practices in the USA is 4.5 clinicians. “Practices” will be defined as distinct office locations that belong to organizations with one or more practice sites. Only practices providing ambulatory primary care as their principal function, located in non-hospital settings, employing at least one primary care physician, with a minimum of 2,000 patients seen in the prior year, will be eligible for participation. If two or more selected practices are drawn from the same multi-practice organization, we will limit contamination by checking for clinician overlap and, based on random draw, retain only one practice from any set of practices within any organizations that share clinicians. Patients will not be randomized per se; they will be assigned to treatment conditions along with the medical practices in which they receive care. Given the

CKD national prevalence rate of 13% and we expect an average of 5,500 active patients per practice, we expect roughly 715 CKD patients per practice. A power analysis (presented below) shows this to be sufficient for the detection of moderate effect sizes in process and final outcomes. Patients will be considered to meet stage 3 CKD criteria if at least two consecutive eGFR measurements at least three months apart fell below 60 ml/min. At the inception of the study we will use data from the preceding 12 months to determine eligible patients with additional patients added to the analytical dataset as they meet study criteria after inception. We will also use these criteria to initiate the clinical decision support algorithms

TRANSLATE Method Elements: The first four elements of the TRANSLATE method will be implemented in both groups, while the remaining ones will apply to facilitation practices only. The CDS only practices will have the CKD decision support algorithms added to their CINA CDSS and will receive academic detailing concerning the bases for the algorithms. They will also be provided related technical support on request.

TRANSLATE Elements That Will Be Used in Both Arms:

Target: Common targets will be set for all practices and tracked through the CKD tool. The CDS only practices will receive a quick reference guide for the treatment of CKD, (Appendix A).

Registry and Reminder Systems: CINA will create a CKD registry and then maintain it throughout the study period. It will also provide point-of-care decision support to practice staff and physicians prior to patient visits.

Administrative Buy-in: We will obtain consent from each practice and work with all physicians in the intervention practices.

Network Information Systems: The information systems (EHRs and CINA) will be used to create system level reports across all intervention practices.

FULL TRANSLATE	PROVIDED BY
Target	CINA
Registry/Reminder	CINA
Administrative buy-in	Informed consent of practices
Network information systems	CINA
Site coordination	Practice Facilitation
Local Physician Champion	Practice Facilitation
Audit and Feedback	Practice Facilitation
Team approach	Practice Facilitation
Education	Practice Facilitation

TRANSLATE Elements that Will Be Used Only in Facilitated Practices:

Site Coordination: There will be a site coordinator at each practice who will assemble a quality improvement (QI) team that will meet monthly to review performance data regarding CKD. The site coordinator will also work with the clinicians and practice staff to implement workflow changes such as pre-visit planning, standing orders, and patient education materials to improve efficiency of disease management. In addition, the site coordinator will be in contact with the practice facilitator by videoconference for assistance and advice. There will be distance practice facilitators working with the AAFP NRN to support these practice level changes.

Local Physician Champion: This person will be the clinician leader and educator for other providers in each practice. Responsibilities will include supporting the site coordinator and the QI team. This physician will be in contact with the academic mentor for the practice regarding clinical questions about CKD and will participate in the two breakthrough learning collaboratives with the site coordinator.

Audit and Feedback: Practice, individual provider, and patient-level outcome reports for the intervention practices will be generated through CINA regarding the seven performance measures (BP, HbAIC, LDL, use of ACE/ARB, referral to a nephrologist, smoking cessation and avoidance of NSAID or Cox-2) and will be reviewed by the team. Reports will also be reviewed quarterly with the practice facilitator by videoconference. The videoconference will allow the facilitator to learn what worked in each practice and to share what other practices have implemented successfully.

Team Approach: A quality improvement (QI) team consisting of the local physician champion, site coordinator and nursing, front office, and administrative staff will meet monthly to review progress of the CKD project. Workflow changes will be recommended and tested.

Education: An educational program using academic detailing[50] practice facilitation[51], and collaborative learning through breakthrough collaboratives[52] and videoconferencing will be utilized to support the practices' efforts. Each practice will participate in two breakthrough learning collaboratives, one at the start of the

intervention and the other at 18 months. Two members from each practice will participate. In addition, all practices will be assigned an academic practice mentor. This mentor will be available to the office physician champion and practice coordinator to answer any questions and discuss plans. The academic mentor will review the practice's data and participate in a quarterly videoconference with either the study coordinator or the lead clinician to review progress on the project. The academic mentors will be Dr. Chester Fox (the PI), who has developed expertise in the recognition and treatment of CKD in PCP practices, and Dr. Joseph Vassalotti, a nephrologist who is Chief Medical Officer of the National Kidney Foundation. Successful implementation will be measured via process and clinical outcomes data extracted from the DARTNet database.

Data Collection:

Physiologic measurements: blood pressure, height, weight; lab values (LDL or Total non-HLD Cholesterol, Creatinine, HbA1c, microalbumin), basic demographic data: age, gender; smoking status, medication prescribed, co-morbidities will all be collected from practice EHRs. Race and ethnicity may be available in the EHR as some practices collect this data, where this data is not available it will be imputed using validated algorithms from RAND[53] Medication fulfillment data will be collected from Surescripts RxHub through CINA or the practice EHR. Death will be determined from information in practice EHRs or from linkages to the National Death Registry. CoreEvolution has developed a system whereby PHI is converted using a hash function and then matched to the death registry. We will use this system to check for deaths among patients who have not made any visits in the prior 12 months in the first two years of the intervention and in the prior 6 months in the final year of the intervention. We will use probability matches of .95 or higher as a positive match.

DATA ANALYSIS

General Approaches

Initially, descriptive statistics (mean, SD, proportions) will be computed for baseline patient and practice characteristics. In addition, chi-squares and t-tests will be used to determine whether there are differences between: (1) patients in practices randomized to different intervention conditions, and (2) dropouts and non-dropouts. Practices randomized to the two intervention groups (TRANSLATE, CDS only) will be compared on patient sociodemographic and clinical variables; these variables will be included as covariates in subsequent analyses if they differ between groups, are associated with outcomes, or are associated with dropout. In general, we will employ methods that utilize all available data, assuming ignorable missingness (MCAR or MAR).[54-59] For primary outcome variables that are continuous (or ordinal) we will explore whether these outcome variables are normally distributed prior to analysis. In the event that normality assumptions are not met, we will use transformations to normalize distributions, ordinal or Poisson regression where appropriate, or techniques using the appropriate link function (e.g. logit link for dichotomized measures).[60] We will employ intent to treat analyses using general (generalized) linear mixed model approaches (GLMMs) to incorporate data structures that are both hierarchical and longitudinal.[61] For time to event outcomes (e.g. death, ESRD), Cox proportional hazards models will be used to analyze the data. All hypothesis tests will be two-sided with alpha=.05 or p values reported). Goodness of fit statistics (e.g. AIC, deviance, -2 log likelihood and change in –2LL for nested models) and model fitting diagnostics to assess for influential points, outliers, overdispersion and heteroscedasticity will be used to evaluate alternative model specifications.[60] Covariates will be screened initially in bivariate analyses and included in multivariate analysis if they are related to the outcome at $p<.2$, differ between treatment arms, or are associated with dropout.

Because all data will be gathered from the practice EHRs, availability of data will not be dependent on participation in interventions, allowing robust estimates of effectiveness of interventions among those for whom they are intended as well as sub-analyses among those who participate. All statistical analyses will be performed using SAS version 9.2 (SAS Institute Inc., Cary, N.C.).

Specific Aim 1: Conduct a group randomized controlled trial of point-of-care computer decision support plus the full TRANSLATE mode of practice change, versus computer decision support alone in promoting evidence-based care in primary care practices for all patients with an eGFR <60 and > 15 ml/min/1.73m^2 (stage 3 and 4) confirmed with repeat testing over three or more months.

Power and Sample Size
With 20 practices per arm and a minimum of 200 patients per practice there will be a minimum of 4000 patients per arm. A sample size of 4000 per arm will provide >80% power to detect a .17 effect size difference between two arms at a single time point if the ICC is 3%. In terms of change over time, a sample size of 4000 will provide >80% power to detect a small linear trend effect (increasing from 0 at baseline to .2SD at final follow up) with four observations per person and an ICC of 3%, with a random effects structure with random intercept and random slope and 5% attrition over time.[62] If the ICC is higher (e.g. 10%) and attrition is higher (e.g. 20%) we will still have power to detect a medium linear trend effect (increasing from 0 at baseline up to .5SD difference at final follow up) with four observations per person.[62]

Patient Cohort for SA1 and SA2. Patients will be identified as eligible for this cohort if they meet criteria for stage three CKD at baseline; new patients will be added to the cohort up to *24 months* after initiation of the group-randomized trial to allow for potential minimum follow-up of 12 months. In the analyses described below, time will be coded individually for each patient, depending on when the patient is eligible to become part of the cohort. Diagnosis of stage 3 CKD requires two eGFRs<60 ml/min/1.73m^2 at least three months apart. For patients in the initial cohort time 0 is defined as the date of randomization; for patients added to the cohort time 0 is defined at date of the second eGFR<60. Therefore, baseline (time 0) will be defined as the date of randomization for patients who meet criteria for stage 3 CKD prior to study initiation or the *second* eGFR<60 with another eGFR <60 occurring a minimum of 3 months prior and no intervening eGFR>60 for patients who meet criteria for stage three CKD from baseline to 24 months after baseline. The rationale for choosing the latter definition for baseline for patients entering the cohort is based on the initial date when the physician would be expected to confirm the presence of stage 3 CKD and begin active clinical management to delay progression.

Hypothesis 1.1: CDS practices using the TRANSLATE model will provide a greater degree of evidence-based guideline-concordant care for CKD than CDS only practices.

The primary outcome for this analysis will be a patient-level score based on the percentage of goals achieved. Each goal will be assessed using EHR data for the *previous year (or part of the year in which the patient is eligible)* at baseline, 12 months, 24 months, and 36 months, as described in the table below. A composite guideline concordance score (GCS) will be created as the proportion of the number of applicable goals met. Secondary analyses will examine each outcome individually using all available data and continuous measures (e.g. systolic BP, HbA1c, LDL) or dichotomous measures (ACE/ARB, referral, smoking, NSAIDS).

TABLE 1: Evidence-Based Outcome Measures

Treatment Recommendation	Goal	Measurement
Control blood pressure	130/80	Means of last three systolic and diastolic BP; will be based on last one or two if fewer than three available
Control HbA1C	<7.0	Last HbA1c;
Control LDL	<100	Mean of last two LDL; last LDL if only one is available
Use ACE/ARB		Documentation in EHR/pharmacy of prescription; yes/no for each time period
Refer to Nephrologist (GFR < 30)		Referral documented, if applicable
Eliminate smoking		Yes/no for each time period
Eliminate NSAID/Cox-2 use		Yes/no for each time period

The structure of the data is hierarchical (patients nested within practices) and longitudinal (repeated assessments on patients at baseline, 12, 24, and 36 months).

Level 1 model. Repeated measures within each patient will be modeled as a time trend (linear growth curve shown below; quadratic trend will be tested) model. Time will be coded as days since baseline,

converted to months to aid interpretability. The guideline concordance score for patient i measured at time t in practice j is Y_{tij}

$$Y_{tij} = \pi_{0ij} + \pi_{1ij}\,(time)_{tij} + \varepsilon_{tij}$$

where π_{0ij} is the individual status at time 0, π_{1ij} is the linear growth rate for patient ij, and ε_{tij} is the term that represents the random deviation of observation t within patient ij from the predicted value.

Level 2 model. The patient level models specify the relationship between the patient-level coefficients and the coefficients in the Level 1 model. Fixed patient-level clinical and sociodemographic covariates (X_j) will be included at this level.

$$\pi_{tij} = \beta_{t0j} + \Sigma\beta_{tpj}\,(X_i) + r_{tij}$$

where β_{00j} represents the initial status of patient i within practice j, β_{10j} represents the linear growth rate for patient ij and r_{tij} is a patient-level random effect.

Level 3 model. The practice level models specify the relationship between the practice-level predictors and the coefficients in the Level 2 model. TRANSLATE will be coded 1 for facilitated practices and 0 for CDS only practices.

$$\beta_{00j} = \gamma_{000} + \gamma_{010}\,(\text{TRANSLATE}) + u_{00j}$$
$$\beta_{10j} = \gamma_{100} + \gamma_{110}\,(\text{TRANSLATE})$$

where γ000 is the intercept in the practice level model for β00j (i.e. mean initial status for usual care practices, adjusted for individual level covariates); γ010 represents the mean difference at baseline between usual care and facilitated practices; γ100 is the linear growth rate for usual care practices, γ110 is the *difference* in linear growth rate for usual care vs facilitated practices.The u's are practice-specific random effects that represent the deviation of practice j's coefficient from its predicted value and are independent of r_{tij} and assumed to have a bivariate normal distribution over practices. Thus, the primary hypotheses of intervention effectiveness on guideline concordance can be tested as H_0: γ_{110}=0. Other hypotheses of interest can be tested using a priori specified linear contrasts.

Specific Aim 2: Conduct an intent-to-treat analysis between the CDS practices with facilitation versus the CDS only practices of the clinical outcomes of CDK progression and all-cause mortality.

Hypothesis 2.1: Patients with stage 3 and 4 CKD in facilitated practices will have slower CKD progression than patients in CDS only practices.

The outcome for this analysis will be eGFR measurements over time. There will be multiple eGFR measures per patient over the duration of the study. We will use general linear mixed-effects models to estimate the rate of decline in eGFR and the degree to which the baseline covariates predict eGFR. Time for each observation will be coded as days since baseline, converted to months to aid interpretability. The statistical model will be the same as described above for hypothesis 1.1. The primary hypothesis of difference in slope between treatment groups will be tested as H_0: γ_{110}=0.

Hypothesis 2.2: Patients with stage 3 and 4 CKD in facilitated practices will have significantly lower all-cause mortality than stage 3 and 4 patients in CDS only practices.

All-cause mortality will be confirmed using the National Death Index to determine the exact date of death. The outcome for the analysis will be time from baseline to death. Patients who are alive at the end of the study period will be censored at the end of the follow-up time. Assumptions of the proportional hazards model will be checked for each variable. Covariates will include baseline eGFR, defined as the mean of the last two eGFRs prior to study entry, as well as sociodemographic and clinical characteristics. The Cox models will be adjusted for clustering of patients within practice. To assess discrimination, we will calculate the *c*-statistic from the Cox regression models using methods described previously.[63,64] The *c*-statistic is equivalent to the probability that the predicted risk is higher for a case than a non-case and has a maximum value of 1.

Specific Aim 3: Conduct an as-treated analysis across all practices in the study as well as all practices within DARTNet that are willing to share data on patients with stage 3 and 4 CKD to determine the impact of greater guideline concordance on the progression of CKD and explore the impact of several individual intermediate outcomes on the rate of progression of CKD. With de-identified EHR data on approximately

300,000 CKD patients, encompassing a minimum of 3 and a maximum of 7 years of follow up, we hope to identify which components of CKD care are most important in delaying progression and death.

Introduction to the OCER Study

Aim 3 will be achieved through the conduct of an observational comparative effectiveness research (OCER) analysis of data from a large database of electronic medical records (from DARTNet) in order to identify the most successful components of evidence-based care with respect to disease progression and all-cause mortality. We will be examining relevant data from all 40 DARTNet practices (and their respective patients) that participated in the randomized controlled trial as well as all practices in DARTNet who agree to share data. The OCER will examine data from four years before the RCT intervention and three years after it. We anticipate that over the seven years there will be 2 million DARTNet patients in participating practices and that approximately 300,000 will be eligible for analysis in the OCER study.

Patient Cohort for SA3. Patients will be identified as eligible for this cohort if they meet criteria for stage three CKD anytime during the DARTNet data collection period. In the analyses described below, time will be coded individually for each patient, depending on when the patient is eligible to become part of the cohort. For all patients, baseline (time 0) will be defined as the date of the *second* qualifying eGFR for diagnosis of stage three CKD.

Hypothesis 3.1: Patients with greater guideline concordance will demonstrate less progression of disease.

Guideline concordance relevant to CKD progression will include all elements from the treatment recommendations in TABLE 1 above for hypothesis 1.1 except LDL and referral to a nephrologist. The composite GCS score will be computed as defined for hypothesis 1.1 at baseline and every 12 months thereafter. Next, a time-weighted average (TWA) of GCS scores will be computed. The time weighted average will be calculated by dividing the area under the curve of all of the observed blood pressure measurements for a given patient by the duration of follow up for that patient. In the analysis described below this score will be the primary *patient-level* independent variable and will be centered at the overall mean to aid interpretability of model coefficients.

The outcome for this analysis will be eGFR measures over time, with multiple measures per patient over the duration of the study. Baseline (time 0) will be defined for individual patients as defined above. We will use general linear mixed-effects models, similar to those described above, to estimate the *rate of decline in eGFR,* the degree to which the baseline covariates predict eGFR, and the association between guideline concordance and rate of decline.

In the statistical model, level 1 will be the same as in hypothesis 1.1. The level 2 and level 3 models are shown below.

Level 2 model. The patient level model will include the patient's TWA guideline concordance score (GCS). Fixed patient-level clinical and sociodemographic covariates (not shown here) will be included at this level.

$$\pi_{0ij} = \beta_{00j} + \beta_{01j}\,(GCS_i) + r_{0ij}$$
$$\pi_{1ij} = \beta_{10j} + \beta_{11j}\,(GCS_i)$$

where β_{00j} represents the initial status of patient i within practice j, β_{01j} represents the effect of GCS on baseline eGFR, β_{10j} represents linear growth rate for patients at the mean GCS in practice j, β_{11j} represents the effect of one-unit increase in GCS on rate of change in eGFR, and r_{tij} is a patient-level random effect.

Level 3 model. The practice level models specify the relationship between the practice-level predictors and the coefficients in the Level 2 model.

$$\beta_{00j} = \gamma_{000} + u_{00j}$$
$$\beta_{01j} = \gamma_{010}$$

$\beta_{10j} = \gamma_{100}$

$\beta_{11j} = \gamma_{110}$

where γ000 is the intercept in the practice level model for β00j; γ010 represents the difference at baseline per unit of GCS; γ100 is the linear growth rate at the mean GCS, γ110 is the *difference* in linear growth rate per unit increase in GCS, and u_{00j} is the practice random effects. Thus, the primary hypotheses of association between GCS and rate of decline in eGFR can be tested as H_0: γ_{110}=0. Other hypotheses of interest can be tested using a priori specified linear contrasts.

Hypothesis 3.2*:* Lower systolic blood pressure at baseline and over time will delay the rate of CKD progression after controlling for other measured variables.

In order to assess the effect of longitudinal blood pressure measurements on eGFR decline, a time-weighted average (TWA) of systolic blood pressure (SBP) will be included as the primary independent variable (patient-level). The time weighted average will be calculated by dividing the area under the curve of all of the observed blood pressure measurements for a given patient by the duration of follow up for that patient. Time weighting of blood pressures in a series will utilize all SBP values in the data set and provide a more accurate overall assessment of blood pressure control during the entire observation period that is less sensitive than a simple average to frequent visits for elevated BP. Statistical models will be the same as for hypothesis 3.1.

Hypothesis 3.3: Continued use of non-steroidal anti-inflammatory medications and use of an angiotensin converting enzyme inhibitor or an angiotensin receptor blockade agent will have independent and opposite effects on eGFR decline .

The effects of continued use of non-steroidal anti-inflammatory medications and use of an angiotensin converting enzyme inhibitor or an angiotensin receptor blockade agent will be examined using duration of exposure to each as the primary independent patient-level variables that will be included simultaneously in the model. The statistical approach will be the same as for hypotheses 3.1 and 3.2.

Exploratory Analytic Approaches for Specific Aim 3 will include the use of time-varying covariates and partitioning between and within patient effects for longitudinal models.[65]

2. **Potential Problems, Alternative Strategies and Benchmarks:**
   Potential problems include the inability to recruit the required number of practices with the CINA protocol engine. Both Dr. Pace and Dr. Fox have extensive experience in recruiting practices for these kinds of studies, both regionally and nationally. It should take not more than 3 months to recruit all the practices. If recruitment goals are not met by the end of 3 months, practices that are just starting on CINA will be invited into the study.
   Practice upheaval that requires a practice to drop out of the study. This is expected to be a rare occurrence, but if it occurs within the first 2 years of the study, another practice will be invited in provided there can be at least 18 months of data collected

   Alternative strategies for recruitment and drop-outs are presented above.

   Benchmarks for success:
   - Recruit 40 practices for specific aim 1 and 2
   - Have over 300,000 patient records for analysis for specific aim 3
   - Have all 20 intervention practices participate in the 2 collaborative learning groups with at least 2 attendees
   - By the end of the first year, show improvement in the process measures of on ACE/ARB, off NSAIDS, and referral to Nephrologists for patients with eGFR < 30

3. **Procedures, Situations or Materials that May Be Hazardous to Personnel:** None.

Time Line

Grant Activities	Pre Award	Year 1				Year 2				Year 3				Year 4				Year 5			
Pre-Award Preparations																					
Finalize CKD computer decision support																					
Finalize IRB approvals																					
Recruit eligible study-site sample frame from DARTNet																					
T2 Translational Activities																					
Study Site Selection																					
Randomly select 40 study sites from DARTNet																					
Randomize (20 each) into CDSS only (Arm 1) & TRANSLATE groups (Arm 2)																					
TRANSLATE activities																					
Breakthrough Collaborative Group for TRANSLATE practices																					
Limited learning collaborative by videoconference																					
Quarterly reports of CKD performance																					
Video or telephone conference with Academic mentor																					
Site coordinator conference with practice facilitator																					
EMR data extraction through CINA into DARTNet																					
Outcome Ascertainment (Aims 1 and 2)																					
Conduct intent to treat analysis of process measures																					
Conduct intent to treat analysis of outcome measures																					
Observational comparative analysis																					
Prepare analytic plan																					
Finalize analysis																					
Dissemination Plan																					
Manuscript preparation-																					
Publication submissions																					
National Presentations (AHRQ PBRN; Practice improvement; Nephrology spring clinical meetings; NAPCRG)																					

Preliminary Studies

The Principal Investigator, Chester Fox, MD, Professor of Clinical Family Medicine at the State University of New York at Buffalo, is a member of the KDOQI Education Committee, an Expert Consultant for the New York State Quality Improvement Office for the Prevention of Chronic Kidney Disease, a member of the Vascular Access Steering Committee of the IPRO End State Renal Disease Network of New York, and a member of the New York State Department of Health Task Force on Chronic Kidney Disease and a member of the CMS technical expert panel for the Fistula First Breakthrough Initiative. He is also a member of the Steering Committee of the National Federation of Practice-Based Research Networks and Director of UNYNET, the Upstate New York Practice-Based Research Network.

Most recently Dr. Fox has focused his work on improving Primary Care Physicians' (PCPs) care of patients with CKD. In 2008 he published a guide to evidence-based CKD care for PCPs.[66] This guide synthesizes the key evidence-based behaviors and a clinical action plan that PCPs can implement to treat CKD and its complications. One of the guide's co-authors was Joseph Vassalotti, MD, a Co-Investigator on the present application.

In a (2006) qualitative study, Dr. Fox explored common PCPs' practices and knowledge regarding CKD. Semi-structured interviews and exit surveys were conducted with ten PCPs from randomly selected UNYNET practices. Three reviewers conducted content analysis using the immersion-crystallization approach. Five general themes emerged: 1) a lack of awareness of CKD guidelines, 2) a desire for more guidance, 3) a

persistence of traditional, less accurate, diagnostic procedures, 4) variability in treating complications, and 5) uncertainty about when to refer to a nephrologist.

In a 2008 study funded by AHRQ, Dr. Fox and colleagues sought to increase PCPs' awareness of and quality of care for CKD patients. The intervention used three modalities: practice enhancement assistants, computer decision-making support, and academic detailing. This study used all the elements of TRANSLATE except site coordination and local physician champion. Recognition of CKD, mean glomerular filtration rate and diagnosis of anemia increased significantly, while angiotensin-converting enzyme inhibitor and aspirin use showed no significant change. Medications that did not show significant change were metformin and non-steroidal anti-inflammatory drug use. [67]

Two year follow-up data were collected in one of the practices that show minor erosion in gains when the support of the practice enhancement assistants and the computer-guided support systems were removed. The diagnosis of CKD went from 20% at baseline to 90% at the end of intervention and was 70% two years later. Some long-term benefits were maintained suggesting that the intervention provided education and re-enforcement necessary to effect long-term change in behavior.

DARTNet Studies

DARTNet has a number of studies underway including a trial of the management of Community Acquired Methicillin Resistant Staph Infections in ambulatory care, a randomized trial of peer mentoring for diabetes mellitus and a trial focused on measurement-based depression care. The system has demonstrated the ability to develop and support new clinical decision support algorithms, to support point of care data collection from patients and clinicians and to aggregate data across millions of patients.

Other Research Team Members: We have assembled a multidisciplinary team of investigators whose collective knowledge and expertise comprise the skills needed to conduct the proposed study. It includes:

Joseph Vassalotti, MD: Associate Professor, Division of Nephrology, Mount Sinai Medical Center. Dr. Vassalotti is Chief Medical Officer of the National Kidney Foundation and a member of the NIH Coordinating Panel of the National Kidney Disease Education Program.

Wilson Pace, MD: Director of the American Academy of Family Physicians National Research Network (AAFP NRN). Dr. Pace is a family physician specialized in practice reorganization, practice-based research methodology, and the use of electronic data collection techniques to improve clinical decision support and patient safety.

James Galliher, PhD: Research Director of the AAFP NRN. Dr. Galliher is a social psychologist with expertise in practice-based research, protocol design, national sample surveys, sampling strategies measurement and analysis, and secondary data analysis.

Miriam Dickinson, PhD: Dr. Dickinson is the AAFP NRN's Senior Scientist and Biostatistician. She has extensive experience with randomized controlled effectiveness trials and expertise in applying complex statistical methodology to analytic challenges associated with multilevel analytic modeling.

TBA: We will recruit a PhD-level researcher with expertise in data collection and analysis.

Experience Using DARTNet: All members of the AAFP NRN have experience conducting research using data from DARTNet, and in 2009 Dr. Pace and colleagues published an article describing DARTNet in detail and elucidating its value for comparative effectiveness research.[32]

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