PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL

Electronic Tools to Increase Recognition and Improve Primary Care Management for Hypertension in Chronic Kidney Disease

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I. BACKGROUND AND SIGNIFIGANCE

Prevalence, Outcomes and Cost of Chronic Kidney Disease: Chronic kidney disease (CKD) is prevalent, afflicting 26 million Americans, and is a condition associated with high morbidity and mortality. In addition, CKD is costly. The average cost per person per year is about $20,000 and Medicare costs for ESRD total $26.8 billion. CKD Diagnosis, Monitoring, and Treatment Must Be Improved in Primary Care Clinics: There are effective approaches to monitoring and treatment that must be disseminated broadly in order to cut costs and to save lives. Dissemination efforts must focus on primary care clinics because 95% of patients with CKD have early disease and are cared for by primary care physicians (PCPs). Only 15% of patients whose estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73m^2 are aware that they have CKD, so it is especially important that PCPs become aware of the diagnosis early.[5-9] Furthermore, there is evidence that CKD is under-diagnosed by PCPs. Data from our 15 primary care clinics showed that only 15% of patients with CKD had a documented diagnosis of CKD and only 40% had a urine albumin test. Hypertension Control in CKD Improves Outcomes: Hypertension (HTN) is one of the most, if not the most, important risk factor for long-term outcomes such as kidney failure, cardiovascular events, and death. A met analysis of three large cohorts of CKD patients without diabetes concluded that maintaining blood pressure below 140/90 mmHg decreases risk of these outcomes significantly.[11] Several guidelines have been issued to emphasize the importance of HTN control in CKD. Evidence-based Management by PCPs for HTN in CKD: Many effective approaches for recognition of CKD and treatment of uncontrolled HTN in CKD are appropriate for the primary care setting. Lifestyle Change Counseling: Lifestyle change is recommended for all patients with uncontrolled HTN. The role of the PCP as counselor for lifestyle change is accepted and welcomed by both patients and PCPs.[15,16] Lack of time is a common barrier, but when PCPs perform brief counseling it tends to be successful, as shown in the literature on tobacco cessation. Anti-hypertensive Medication Initiation and Intensification: Evidence-based guidelines recommend certain anti-hypertensive agents in CKD, either an angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACE/ARB). The UK NICE guidelines specify a protocol for initiation and intensification of medications based on demographic characteristics.[20] Efforts to simplify patients' medication regimens and provide patient education are proven to be effective in reducing blood pressure HTN in CKD Is Under-recognized and Suboptimally Managed, but CDS Has Shown Potential in Clinical Trials of the Non-CKD HTN Population**:** Nationally representative data show that 52% of CKD patients have diagnosed HTN, 19% have preHTN, and 16% have undiagnosed HTN. Treatment rates are suboptimal given the fact that less than 40% of CKD patients with uncontrolled HTN are prescribed anti-hypertensive medications. HTN control rates, cited as 48% to 72% across studies, are also suboptimal. A large meta-analysis of clinical decision support (CDS) for HTN in a non-CKD population showed a positive result, but with a small

average effect size of just 1 mmHg.[26] An intervention in a managed care organization that incorporated CDS improved HTN control rates with an institution-wide adoption of a titration protocol and follow-up visits with a medical assistant. A multi-arm study combined CDS that recommended specific medication titration and quarterly performance reports with nurse counseling. BP control and SBP improved in all groups, but there was no significant difference between intervention groups and the control group. Another study in a non-CKD population showed a strongly positive result. The investigators tested CDS that synthesized data on the patient's current anti-hypertensive regimen and made a recommendation to intensify treatment. There was a positive result in mean BP in the arm which combined CDS with provider education and patient education (138/75 mmHg), as compared to CDS plus provider education (146/76 mmHg), and as compared to provider education alone (145/78 mmHg). Several recent trials of CDS have shown improvement in urine albumin monitoring and ACE/ARB prescription rates in CKD. However, no studies of CDS have shown an improvement in HTN management in CKD. In one pre-post study in which provider education was delivered along with multiple EHR-delivered recommendations, a flowsheet containing CKD-relevant data, and a registry, there were significant effects on diagnosis and monitoring, but no significant change in BP. [31] Another study used CDS for PCPs and nephrologists in conjunction with patient education letters and the option of a self-management outreach support program. There was no impact on BP outcomes. [Sequist, personal communication] Another study compared CDS alone to CDS along with a practice improvement effort to implement the Chronic Care Model. The study found no significant effect on BP outcomes, [Fox, personal communication] The proposed study, if successful, would be the first to improve HTN in CKD patients through an intervention that incorporates CDS.

II. SPECIFIC AIMS

Hypothesis: The mean systolic blood pressure of the CKD population can be decreased by an intervention with three innovative features: 1) methods to synthesize EHR data in order to identify under-diagnosed chronic conditions, 2) iterative improvement in CDS content through human factors methods to maximize the "informativeness" of the CDS, and 3) the use of behavioral economic principles to create behavioral "nudges" internal and external to the CDS.

Specific Aim 1: To develop and validate the intervention.

Specific Aim 1a: To develop and validate the CDS that will: 1) synthesize existing laboratory tests, medication orders, and vital sign data; 2) increase recognition of CKD, 3) increase recognition of uncontrolled HTN in CKD patients; and 4) deliver evidence-based CKD and HTN management recommendations.

Specific Aim 1b: To improve the design and content of the CDS using human factors methods, specifically usability testing.

Specific Aim 1c: To develop a "wrap-around" intervention including two behavioral "nudges": 1) pre-checked default orders, and 2) an email to obtain commitment from PCPs to obtain their commitment to follow the CDS recommendations.

Specific Aim 2: To test the effectiveness of the intervention.

Specific Aim 2a: To evaluate whether the intervention developed in Aim 1 significantly decreases mean systolic blood pressure in a population of CKD patients with blood pressure > 140/90, N=2,350 (N derived from EHR data about primary care patients at 15 clinics). We will evaluate the effectiveness of the intervention in a pragmatic, cluster-randomized controlled trial, randomized at the level of the physician (185 PCPs). Secondary outcomes will include hypertension-specific process measures, such as treatment intensification.

Specific Aim 2b: To evaluate whether the intervention improves process measures for quality of CKD care including: documented CKD diagnosis, annual serum creatinine test, and annual urine albumin test. We will also examine process measures related to CKD care. We will use multivariable logistic regression to account for clustering by PCP using a multilevel statistical regression model, as implemented in the SAS package through the GLIMMIX procedure.

Specific Aim 2c: To perform a cross-over study in order to evaluate the effect of the intervention on PCP behavior and PCPs' intention to change behavior, as measured by a validated 12-item questionnaire.

III. SUBJECT SELECTION

Subjects: All patients over the age of 18 who have a visit with a PCP at one of the intervention practices during the 2 years preceding the study period will be eligible. We are able to utilize data from the past 2 years stored in the EHR to identify CKD patients with uncontrolled HTN. The first inclusion criteria will be CKD, defined as two prior eGFR 16-59 mL/min/1.73m2 separated by 90 days, as calculated by CKD-EPI, or two prior UACR >30mg/g. The second inclusion criteria will be uncontrolled hypertension, defined as at least one SBP >140 mmHg within the 2 years preceding the enrollment visit, as well as SBP >140 mmHg at the enrollment visit. Our objective was to include PCPs who have a consistent panel of primary care patients. We obtained a list of currently employed physicians, physicians assistants and nurse practitioners in our primary care network of 15 practices. We excluded residents in training, as well as physicians who were only seeing urgent care and walk-in patients.

Inclusion of Women and Minorities
Women will be represented in this study, reflecting the patient population of the BWH primary care practices and the physician population of BWH; women comprise over 50% of patients in these practices. Minorities also are fully represented in this study in proportion to their presence in these primary care practices and in proportion to their presence in the BWH physician and specialist community. The practices serve an ethnically and socioeconomically diverse patient population. Approximately 16% percent of BWH patients are Latino and 29% are Black. About 1.5% of BWH patients are Asian. Definitions of patients' race and ethnicity will be based on self-report at the time of hospital registration. By promoting uniformly high standards of patient care, our interventions may lessen disparities in care.

IV. SUBJECT ENROLLMENT

Randomization and Enrollment: This study will utilize a matched-pair cluster randomized design with the intervention on the cluster level, and the main outcome (6 month minus baseline change in SBP) measured at the patient level. We will have 174 clusters (made up of 185 clinicians) in the study. We will match pairs of clusters with similar number of patients and prior year mean blood pressure of patients in the cluster. One cluster in each pair with be randomized to the intervention and unit one to usual care. Patients will be electronically identified and included in the study over the course of 12 months. Patients seen by PCPs during the pilot study will be excluded. Retrospective data indicates that 70% of patients have a follow-up around 6 months. Outcomes assessment will occur at 180 days (+/- 60 days). After the 12-month enrollment period ends, data collection will continue for 6 months so that those enrolled toward the end of the enrollment period will have a full 6 months to complete any interventions ordered by the PCP. A small subset of PCPs will be enrolled in a pilot study for approximately one month, as described below in study procedures Aim 1b. Clinical outcomes will be recorded and reviewed every month over the course of the trial.

V. STUDY PROCEDURES

Aim 1, and 1a Study Procedures:

Modify Rules for Automated Diagnosis of CKD and Uncontrolled HTN: Dr. Samal is a participant in the NKDEP Health Information Technology care plan working group.[80] She has contributed to their efforts to new national standards for diagnosis of patients with CKD using EHR data. We will modify the rules from the MAPLE study in order to align them with this new national standard. Then, we will create rules for automated diagnosis of uncontrolled hypertension. We will implement the BPA in “silent mode” for the control arm. This means that we will identify control patients in real time according to the same inclusion criteria as intervention patients, excluding all patients who are pregnant.

Develop Rules for Evidence-based Recommendations for HTN in CKD: We will leverage past work that we have done in a study that delivered recommendations based on JNC7.[73] An example of one of the rules is to determine whether anti-hypertensive agents have been prescribed but are not at highest potency. If so, the CDS will deliver a recommendation to increase the dosage. Or, if multiple agents have been prescribed at maximum potency, the CDS will access the patient’s refill record. If the patient has not been refilling medications on schedule, the tool will recommend a medication adherence discussion. We will also include one-click access to documentation and orders relevant for CKD. For example, a message that gives a specific diagnosis, “This patient has stage 3b CKD with unknown level of albuminuria”), as well as an actionable order, “Click here to order a urine microalbumin to creatinine ratio test.” The BPA will include a BP entry field in which a PCP can record a repeat BP reading.[83,84] If the PCP enters a BP reading, it will automatically be recorded in the vital signs flowsheet and vice versa. We will include appropriate laboratory monitoring test orders. Confirmatory testing is appropriate for an abnormal urine albumin level, so we will include an order if the prior result was abnormal.[85] We will also provide one-click access to print patient handouts. In order to minimize cognitive overload and improve self-efficacy we will only deliver three messages at one time. We will develop a ranked list to drive the choice of recommendations. For example, in patients with CKD and HTN who smoke, tobacco cessation would be the highest priority.

Implementation of CDS in Epic: The next step is implementation in Epic as a BPA. Each of the rules will be added to the Epic database. The BPAs appear in an area of the screen that is visible when orders are being entered. Currently, there are several cancer screening BPAs and a seasonal influenza BPA. The CDS will be moved to the Production environment in "silent mode" before the scheduled start date of the trial, where it will record when it would fire, but it will not be displayed to the user. This step will allow us to validate that the rules are accurately identifying patients and producing the correct recommendations through a chart review. We will review 10 charts of patients with CKD and uncontrolled HTN per clinic for a total of 150 charts. The CDS will be activated in the Production environment on the start date of the clinical trial in Aim 2.

Validation of Hypertension-specific Process Measures: In preparation for the clinical trial in Aim 2, we will validate three process measures. Two of the measures will reflect treatment intensification by the PCP, 1) an increase in dosage or 2) addition of a new anti-hypertensive agent. The third measure will reflect medication adherence by the patient using data from a pharmacy benefits manager. We will perform a retrospective chart review of 150 charts to calculate the sensitivity and specificity of each rule.

Aim 1b Procedure:

Task Scenario Development and Pilot Test: Usability testing clinical scenarios will be developed by two subject matter experts (Dr. Samal and Dr. Bates). Tasks will include adding CKD to the problem list, placing lab and/or medication orders, and printing patient education handouts. We will also include a test scenario that could lead the PCP to decide not to follow the CDS recommendation and we will see if they are able to enter a justification without assistance (see "accountable justification" section below). The scenarios will be reviewed by the research team to ensure that the content, format, and presentation are representative of real expected use and address the major components of the CDS. Then we will pre-load test patients with the data necessary for these scenarios and prepare the usability test procedure (described below). The usability test will be piloted with a PCP and we will ask for feedback on the usability test process, as well as content and wording of test scenarios.

Usability Test Procedure: A usability test plan will be developed that includes details on the testing procedure, tasks, usability metrics, usability goals, and appendices containing the test scenarios, pre-test instructions, and post-test interview questions. A moderator and observer from the research team will both attend each session. First, the moderator will describe the usability test procedure using scripted pre-test instructions to ensure that all participants receive the same instruction. The participant will be informed of the goal of evaluating the CDS and that the session will be video-taped. The moderator will describe the "think-aloud" process, asking the participant to share their thought process and expectations while completing the tasks.[87] An example of think aloud will be demonstrated. Then, the moderator will begin recording the session using Morae software. The participant will read each task aloud, attempt the task, and inform the moderator when the task is complete. The moderator will record task success or failure based on the intended outcome as described in the test plan. If a participant is having trouble completing a task, he or she will be given an assist at the moderator's discretion. The observer will make note of assists and other usability or comprehension issues that arise. After all tasks are complete, the moderator will administer a verbal post-test interview. The moderator will ask questions like, "How did you interpret this?", "Why did

you do X?" and "What would you change about the content of the CDS?" The moderator and observer will manually record observations during the testing session. In addition to the comments and data recorded during the session, usability metrics will be coded after the session using Morae software. Usability metrics are measurements collected to determine to what extent usability goals have been met. The metrics will include task completion success rates, time-on-task, error rates, and assists by the moderator. We will be able to compare these measurements to those gathered from subsequent tests to determine whether iterative changes to the CDS have improved the usability of the CDS. Qualitative analysis: Qualitative methods will be employed to analyze the data. The research assistant will review the video recordings to identify usability issues based on observations of the participants during the task and the participants' think-aloud comments. Video recordings will be transcribed verbatim, and subject identifiers will be removed from the transcripts. The transcripts will be organized by task and participant and then quotes will be identified that illustrate a user expectation, frustration, or misinterpretation of content or functionality.

Pilot Study: Prior to the clinical trial, a pilot study will be conducted in live clinical settings. A subgroup of PCPs will be selected an the BPAs will be turned on for approximately one month. Interaction with the BPAs will be monitored. Each time a BPA fires the research team will contact the PCP by email to gather feedback through surveys and/or interviews. Iterative refinement of BPAs may be undertaken.

Aim 1c Procedure:
1) Pre-checked, no-action default: The first nudge will be part of the CDS. We will display the CDS with certain options pre-selected. We plan to include addition of the CKD diagnosis to the problem list and addition of a patient education handout to the after-visit summary.

2) Pledge email to obtain commitment from PCPs to follow the CDS recommendations: As a starting point, we need to ensure that PCPs are aware of the clinical practice guidelines. At the beginning of the study, we will send an advertisement email to all PCPs in the network. In addition, as part of the intervention, we will ask PCPs to commit to following the recommendations presented to them in the BPA, or writing their rationale in the CDS if they choose not to. The PI will send an email via REDCap to intervention PCPs giving a brief overview of the CDS content. By clicking a link in the email, the intervention PCP will come to a REDCap survey asking them to type their name to pledge to consider the CDS recommendations provided in our BPAs. The control PCPs will receive a similar email without the specific details about our study and without the REDCap link.

Behavioral Science Methods Review Committee: Though the research team does include co-investigators with expertise in behavioral science methods, we have decided to convene an advisory group consisting of three experts in behavioral science as applied in interventions for both PCPs and patients. We have chosen the members of this committee based upon their familiarity with chronic disease management interventions and EHR-based interventions. We have limited the group to three members because we plan to meet on a monthly basis during the first two years of the study. This group will give advice to the research team on elements of
Aim 1 and the roll-out of the clinical trial.

Specific Aim 2 & 2a Procedures:
Setting: The Brigham and Women's Primary Care Practice-Based Research Network (BWPC PBRN) is one of 155 PBRNs nationally certified by the Agency for Healthcare Research and Quality (AHRQ). The BWPC PBRN is a network of 15 practices which includes hospital-based practices, community-based practices, and community health centers affiliated with Brigham and Women's Hospital. The network includes 185 primary care physicians that care for approximately 150,000 patients.

Subjects: All patients over the age of 18 who have a visit with a PCP at one of the intervention practices during the 2 years preceding the study period will be eligible. We are able to utilize data from the past five years stored in the EHR to identify CKD patients with uncontrolled HTN. The first inclusion criteria will be CKD, defined as two prior eGFR 16-59 mL/min/1.73m$_2$ separated by 90 days, as calculated by CKD-EPI, or two prior UACR >30mg/g. The second inclusion criteria will be uncontrolled hypertension, defined as at least two SBP >140 mmHg within the 2 years preceding the study period. We will exclude all patients who are currently pregnant. The CDS will review lab data starting five years before the visit to determine whether the patient has CKD using the logic described above. If the patient has CKD, the CDS will search BP data starting one year before the visit to determine whether the patient has had at least two SBP > 140 mmHg.

Specific Aim 2b Procedure:
Outcomes: We will analyze the actual use of the CDS, defined as interaction with the BPA, signing of orders, or accountable justification documentation within the BPA.

VI. BIOSTATISTICAL ANALYSIS

Data collected during the pilot study will not be included in the final analysis. Patients enrolled in the pilot study will not be enrolled in the final analysis. However, PCPs in the pilot study will be included in the intervention arm of the main clinical trial. A subgroup analysis will be performed on patients of these PCPs.

Table 1. Outcome Variables and Measures for Both Arms

Measurement Variable	**Form of Variable**	**Analysis Metric**	**Time Point**
Primary			
Mean SBP	Continuous	Change from baseline	6 months, 12 months, 18 months
Secondary			
Controlled SBP Rate	Dichotomous	Proportion of patients with controlled SBP rate	6 months, 12 months, 18 months
Urine Albumin to Creatinine Ratio	Continuous	Urine Albumin to Creatinine Ratio	6 months, 12 months, 18 months
Serum Creatinine > 2.0	Dichotomous	Proportion of patients with Creatinine > 2.0	Monthly
eGFR	Continuous	eGFR	6 months, 12 months, 18 months

Medication ordered	Dichotomous	Proportion of patients with recommended medication ordered	6 months
Basic metabolic panel ordered	Dichotomous	Proportion of patients with basic metabolic panel ordered	6 months
Referral to e-consults	Dichotomous	Proportion of patients with referral to e-consults	6 months
BPA acceptance	Dichotomous	Proportion of patients where BPA was accepted	6 months
Mean SBP of less than 110	Dichotomous	Proportion of patients with mean SBP of less than 110	Monthly
Newly documented allergy	Dichotomous	Proportion of patients with newly documented allergy due to adverse drug events	Monthly
K+ > 5.2	Dichotomous	Proportion of patients with K+ > 5.2	Monthly
K+ < 3.6	Dichotomous	Proportion of patients with K+ < 3.6	Monthly
Mean SBP intent-to-intervene analysis with imputation of missing 6-month BP measurement	Dichotomous	Proportion of patients with missing 6-month BP measurement	6 months
Controlled SBP Rate intent-to-intervene analysis with imputation of missing 6-month BP measurement	Dichotomous	Proportion of patients with missing 6-month BP measurement	6 months

Table 2. Outcome Variables and Measures for Intervention Arm Only

Measurement Variable	**Form of Variable**	**Analysis Metric**	**Time Point**
Acknowledgment reason entered	Dichotomous	Proportion of patients with acknowledgment reason entered	6 months
Feedback button clicked	Dichotomous	Proportion of patients with feedback button clicked	6 months
PCP participation on pledge email survey	Dichotomous	Proportion of patients whose PCPs participated in pledge email survey	6 months
Guideline accessed	Dichotomous	Proportion of patients with guideline accessed	6 months

VII. RISKS AND DISCOMFORTS

There are minimal risks to physicians or patients as a result of the intervention. For clinicians, there is a risk that the decision support and other tools could have unexpected adverse consequences such as creation of more work, unfavorable workflow issues, and overdependence on technology. Although important to consider, these risks are balanced by evidence suggesting the effectiveness of computerized clinical decision support to improve the quality of patient care. For patients, the risks are those that are typically undertaken in the receipt of general medical care. That is, it is conceivable that the intervention could result in a change in management (e.g., ordering more tests, referral), but in the case of chronic kidney disease this may in fact lead to a clinical benefit. There also is the possibility of psychological risk to patients associated with being labeled as having chronic kidney disease; however, this risk is outweighed by the potential benefits associated with better evaluation and treatment of the disease. Finally, there is a risk of overtreatment of hypertension which may cause hypotension or an acute decrease in kidney function. The intervention is delivered to the primary care physician, who will weigh the risk and benefit of treatment intensification. However, this risk is expected to be low since we only recommend treatment intensification within consensus guidelines.

VIII. POTENTIAL BENEFITS

This research has the potential benefit of improving the quality of care for patients in the intervention practices, which ultimately could prevent disease progression and death. There are no potential benefits to the control subjects, who will receive current standard of care.

IX. MONITORING AND QUALITY ASSURANCE

The investigators will establish an independent Data Safety Monitoring Board (DSMB), which will serve as an independent group to monitor participant safety, study burden and scientific validity of the clinical data. The PI will ensure that the research is conducted in an ethical manner in accordance with good clinical practice and meets all applicable regulatory laws and policies. In addition to meeting the responsibilities for protecting the rights, safety, and welfare of the subjects enrolled in the research, the PI will review safety data, study conduct, procedural safety enrollment, adverse events, and other study-related information. The PI and co-investigators will review enrollment, adverse events and any recent literature that may be relevant to the research on a quarterly basis. Formal minutes with discussion points and remediation/actions plans (e.g. changes to protocol and consent documents) will be created, maintained, and relayed to the DSMB. The DSMB will convene in person or by teleconference once per year. At this meeting, the board will review any cases where systolic blood pressure was found to be below 110 mmHg, any reported adverse events, and deaths of enrolled patients.

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