Improving Chronic Disease Management with Pieces (ICD-Pieces)

Sponsor National Institutes of Health/National Institute of Diabetes in Digestive and Kidney Diseases

NIDDK Funding Mechanism: Exploratory/Development Cooperative Agreement

Study Protocol Version 1.8

October 31, 2018

Statement of Compliance

This study will be carried out in accordance with good clinical practice (GCP). This study will be conducted in accordance to NIH clinical terms of award.

All key personnel (all individuals responsible for the design and conduct of this study) have completed human subjects protection training.

Table of Contents

List of Abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitor
ACO	Accountable Care Organization
AKI	Acute Kidney Injury
ARB	Angiotensin II Receptor Blockers
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CV	Cardiovascular
DFW	Dallas Fort Worth
DM	Diabetes Mellitus
DSMB	Data Safety Monitoring Board
eGFR	estimated Glomerular Filtration Rate
EHR	Electronic Health Record
ICD-10	International Classification of Diabetes 10
ICD-9	International Classification of Diabetes 9
ICD-Pieces	Improving Chronic Disease Management with Pieces
MCC	Multiple Chronic Conditions
NKDEP	National Kidney Disease Education Program
NLP	National Language Processing
PCCI	Parkland Center Clinical Innovation
PCP	Primary Care Providers
PHHS	Parkland Health and Hospital System
Pieces	Parkland Intelligent e-Coordination and Evaluation System
PROs	Patient Reported Outcomes
SUNY	State University of New York
THR	Texas Health Resources
UTSW	University of Texas Southwestern Medical Center
VA	Veterans Administration

PROTOCOL SUMMARY

Improving Chronic Disease Management with Pieces (ICD-Pieces)

Objectives

The overall goal of the study, Improving Chronic Disease Management with Pieces (ICD-Pieces) is to improve the care of patients who have the triad of coexistent chronic kidney disease, diabetes and hypertension. The ***primary objective*** of the study is to test the hypothesis that patients who receive care with a collaborative model of primary care and subspecialty care interventions enhanced by novel information technology and practice facilitators to leverage data from the electronic health records will allow accurate identification of patients with a triad of CKD, diabetes and hypertension using objective and reproducible criteria, and provide clinician support for implementation of best practices of care, monitoring clinical measures, adjusting treatments and reduce 12-month all-cause unplanned hospitalization rate for CKD, diabetes and hypertension.

Secondary objectives as follows:

a) To test if implementation of the collaborative model of primary care-subspecialty care interventions will reduce 30-day readmissions (for patients who have an index hospitalization), emergency room visits, cardiovascular events or deaths from any cause and disease-specific hospitalizations pre-specified in this study as cardiovascular complications, congestive heart failure, volume overload, accelerated/malignant/uncontrolled hypertension, acute coronary syndromes, myocardial infarction, coronary/peripheral revascularization, stroke, limb ischemia/amputations, diabetes complications, uncontrolled diabetes or hypoglycemia, acute kidney injury, hyperkalemia, electrolyte disturbances, drug toxicity, medication errors and infections.

b) To develop and validate predictive models for risks of disease-specific hospitalizations, all-cause hospitalizations, 30-day readmissions, emergency room visits, cardiovascular events and deaths for all patients with coexistent CKD, diabetes and hypertension.

c) To collect demographic data and clinical descriptive data to assist phenotyping patients with a triad of CKD, diabetes and hypertension.

d) To obtain important safety data for patients with CKD, diabetes and hypertension including acute kidney injury, progression of chronic kidney disease (changes in eGFR), development of electrolyte disturbances and medication errors and drug toxicity (even if not leading to hospitalization).

e) To collect information on resource utilization including not only hospitalizations but emergency room visits, outpatient visits and procedures completed (both diagnostic or therapeutic).

Design and Outcomes

The study will employ a prospective stratified cluster randomization design. The stratum is each of the four large healthcare systems participating in the study. The unit of randomization will be primary care clinics. In some healthcare systems several primary care clinics share the same geographic location and personnel and they will be randomized as a single unit.

The primary outcome of this trial is all cause hospitalizations for patients with a triad of CKD, diabetes and hypertension. Specifically, the outcome will be hospitalization rates at 12 months for all study participants. We will capture all cause unplanned hospitalizations including both regular hospitalizations as currently defined by CMS and observation status overnight (to avoid uncertainties related to variations in applications of definitions based on the recent implementation of the two midnight rule). Hospitalizations will be ascertained from electronic healthcare records with assistance of electronic tools in each of the participating healthcare system. To maximize completeness of outcome data acquisition we will also track study patients with outcome data from the Dallas Fort Worth Hospital Council which is a cooperative regional-sharing initiative that allows to match patients with any hospitalizations in any hospital in Dallas Fort Worth. Patients in ProHealth in Connecticut are part of an accountable care organization (ACO) and outcomes are also captured in a database from reports received by ACO. There will be also special attention to capture outcome information from VA database patients followed at the VA of North Texas who may not be part of the group identified through the Dallas Fort Worth Hospital Council.

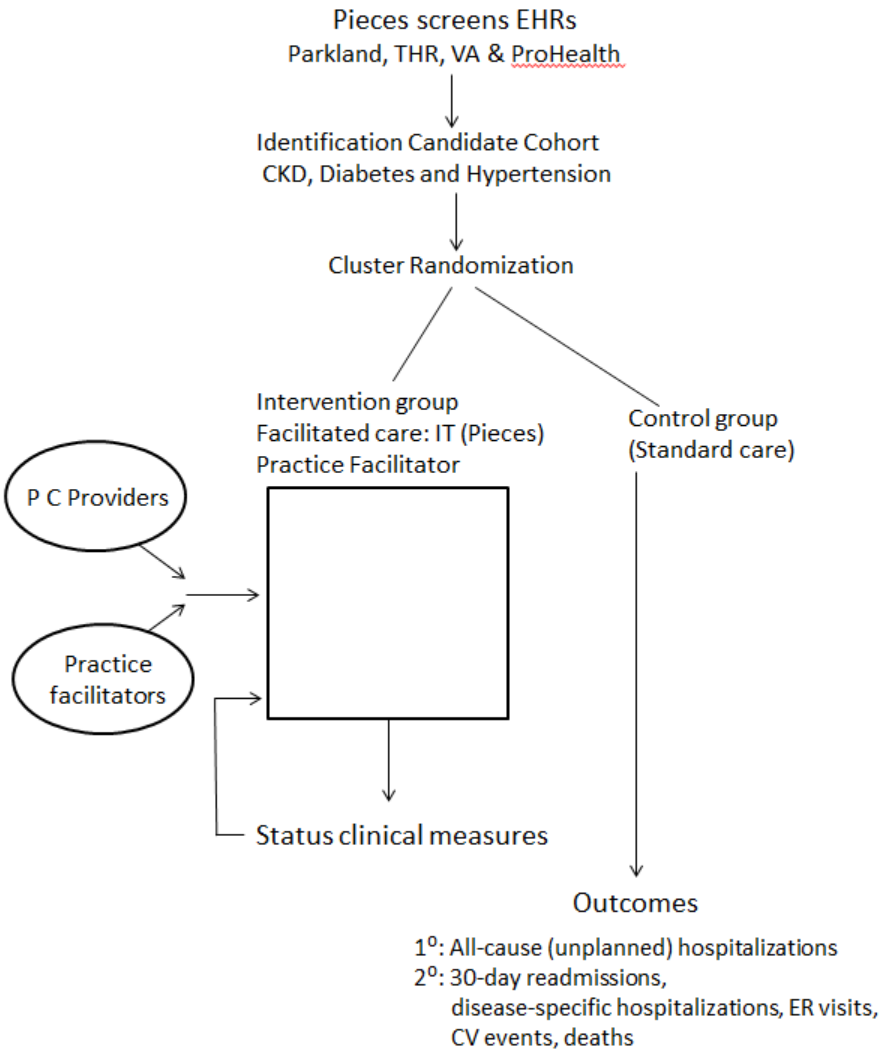
Secondary outcomes captured in the study will include 30-day all cause readmissions (for those patients who have an index hospitalization), emergency room visits, cardiovascular events and deaths, and disease-specific hospitalizations for cardiovascular complications, congestive heart failure, volume overload, hypertension complications, acute coronary syndrome, myocardial infarction, coronary/peripheral revascularization, stroke, amputation/limb ischemia, uncontrolled diabetes, hypoglycemia, diabetes complications, acute kidney injury, hyperkalemia, electrolyte disturbances, medication errors, drug toxicity and infections.. Data for secondary outcomes will be obtained as outlined above with the primary outcomes. In addition, we will verify if enrolled patients who do not have an encounter in our systems within two years of study participation are classified as dead or alive using the Social Security Index.

Other secondary outcomes captured from the electronic health records will include descriptive patient characteristics including demographic and clinical data from patients with CKD, diabetes and hypertension as well as information on patient comorbidities, changes in renal function (eGFR), episodes of acute kidney injury as well as safety/adverse events. Resource utilization will be captured from careful evaluation of hospitalization events, clinic visits and diagnostic and therapeutic procedures completed.

Interventions and Duration

Figure: Schematic Design ICD-Pieces Trial summarizes main components of the study

Schematic Design ICD-Pieces Trial



There will be two study groups: An active intervention group randomized to the collaborative model of care facilitated by information technology and practice facilitators and a group randomized to standard/usual care. Pieces will screen electronic health records of participating healthcare systems to detect patients with a triad of CKD, type 2 diabetes and hypertension according to established inclusion criteria for the study. The candidate cohort of potential sites will then be randomized to active intervention (collaborative care model enhanced by Pieces) or control group (standard of care). Interventions available for implementation in the active group include maintaining blood pressure less than 140/90mmHg, use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), treatment with statins, aiming for hemoglobin A1C at recommended target for coexistent comorbidities, avoidance of nephrotoxic medications including nonsteroidal anti-inflammatory drugs (NSAID). Other interventions available include education on CKD for both primary care providers and for patients. There will also be available material on lifestyle modification and immunizations.

After a patient is enrolled, the primary care practitioner activates the CKD, diabetes and hypertension collaborative model of care. Primary care practitioners will have the option to

initiate protocols for CKD management, hypertension management, lipid management and diabetes management. Protocols can be initiated via smart sets in the electronic health record. Practice facilitators working together with primary care practitioners can also assist with activation of protocols, smart sets, responses to information on clinical measures and overall implementation of the collaborative model.

Sample Size and Population

The sample size for this study is 10,991 patients. The stratum will be healthcare systems and unit of randomization is primary care/practice site. Men and women ages 18-85 years will be study participants.

Study Duration

Enrollment of study participants from selected clinics will occur over a period of 2 years. The study duration for each participating subject will be 12 months.

1. Key Roles

1.1 Principal Investigator

Miguel A. Vazquez, MD
Professor of Internal Medicine
UT Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, TX 75390-8856

1.2 See Appendix for a list of co-Investigators and Study Staff

1.3 Collaborating Institutions

University of Texas Southwestern Medical Center (Central Academic Partner)
5323 Harry Hines Boulevard
Dallas, TX 75390-8856
Cheryl L. Anderson
214.648.4494

The State University of New York at Buffalo
Sponsored Projects Services
402 Crofts Hall
Buffalo, NY
Jeffrey Schieder
716.645.4408

Dallas VA Research Corporation
4500 South Lancaster Road, Bldg. 43, Suite 124
Dallas, TX 75216
Phyllis A. Bilbrey
214.857.2090

Texas Health Resources
Texas Health Resources
612 E. Lamar Blvd. Pavillion 3
Arlington, TX 76011
Ferdinand Velasco, MD
682-236-6061

PCCI
8435 Stemmons Freeway Suite 1150
Dallas, Texas 75247
Ruben Amarasingham, MD, MBA
214.590.1168

Parkland Health and Hospital Systems (PHHS)
5200 Harry Hines Blvd
Dallas, TX 75235
Liz McMullen
214.590.4128

Connecticut Center for Primary Care, Inc.
P.O. Box 762
Farmington CT 06034
Tom Meehan, MD
860-284-5288

2. Background and Rationale

2.1 Background on Condition

Chronic kidney disease (CKD), diabetes and hypertension are three common chronic medical conditions in the general population. It is estimated that 31% of US adults have hypertension, 14% have CKD, and almost 10% have diabetes[1-4]. Diabetes and hypertension are among the most prevalent chronic medical conditions in adults of all ages[1,5]. Diabetes and hypertension are the two leading causes of CKD in the United States, which has now become a major public health problem[77]. The triad of CKD, diabetes and hypertension conspires to promote particularly adverse outcomes[9,10,16,18,17]. Moreover, CKD disproportionately affects vulnerable populations including the elderly, Hispanics, African-Americans and those who reside in socioeconomically deprived areas[1,2,3].

In patients with CKD, the kidneys are not able to filter blood normally and have reduced glomerular filtration rate (GFR) and/or abnormal leakage of albumin in the urine. Compelling data indicates that graded reductions in GFR are strongly associated with higher risks of death, cardiovascular events, and hospitalizations, independent of traditional cardiovascular risk factors [5,12]. Premature death, both from cardiovascular disease and from all causes, is higher in adults with CKD compared to adults without CKD[6,7].

Multimorbidity or the coexistence of multiple chronic conditions (MCC) is especially significant for patients with the triad of CKD, diabetes, and hypertension. Specifically, the coexistence of kidney disease and diabetes is associated with considerably higher mortality than the excess risk with either risk factor alone[10] (***Figure 2.1***). Similar relationships are observed with CKD and hypertension and with diabetes and hypertension[11,12]. While risk prediction models for progression from CKD to ESRD among those with CKD, diabetes and hypertension are clinically useful, they are very limited in predicting cardiovascular events and mortality[13,20,50].

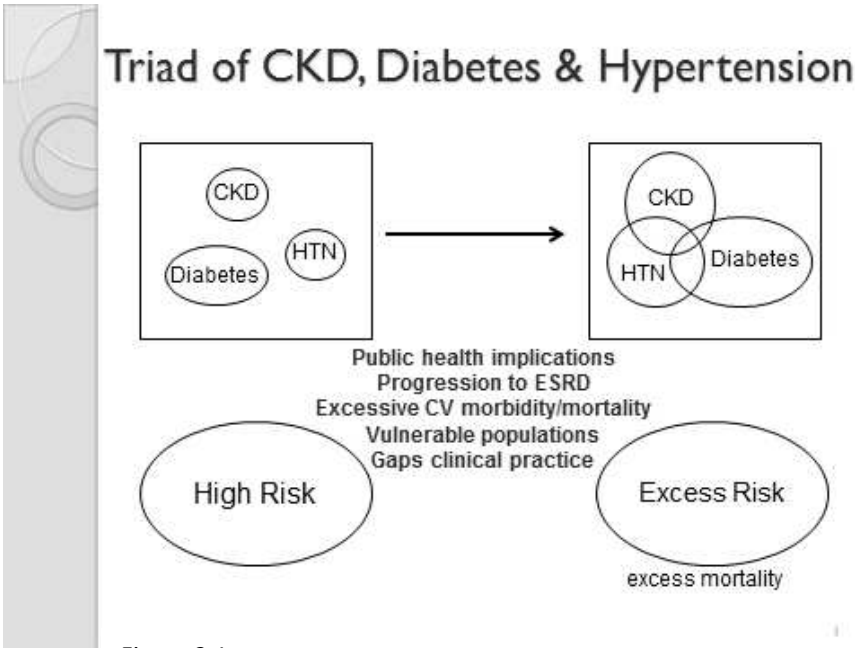


Figure 2.1

Given the increasing prevalence of the triad of CKD, diabetes and hypertension, and the excessive risk for cardiovascular morbidity and mortality, there is an urgent need to deeply phenotype this group of patients, identify risks for adverse outcomes, and develop and implement best practices to care for these patients.

Challenges in the care of CKD, diabetes and hypertension

Care for patients with multi-morbidities is challenging and often suboptimal. Appropriate care for patients with CKD, diabetes and hypertension includes early detection and institution of strategies to slow progression and treat associated complications and cardiovascular risks [5,77].

Early diagnosis of CKD allows for the institution of effective therapies that can prevent the onset and progression of irreversible kidney damage. Detection of CKD can be accomplished with relatively simple tests, such as serum creatinine and urine for protein and/or albumin. Unfortunately, a large proportion of patients with high risk conditions for CKD, such as diabetes and/or hypertension, do not have basic tests of kidney function or urine albumin performed.[14] Progressive CKD is a catastrophic condition that leads to end-stage kidney disease requiring very expensive therapies including dialysis and transplantation. These patients suffer from excessive rates of depression, catastrophic cardiovascular events such as stroke, heart attack and heart failure and other comorbidities that are difficult and expensive to manage.[1,2,4,48,49,47,46,45] CKD detection and documentation is low even across health care systems with sophisticated electronic health records (EHR) [83].

Catastrophic consequences result from lack of detection of CKD, diabetes and hypertension

More than 25% of adults with Type II diabetes are undiagnosed. Moreover, based on fasting glucose or hemoglobin A1C values, around 35% of adults in the US have pre-diabetes, and a large proportion are not aware of the risk[56]. Among adults with hypertension, about 22% are not aware of their condition[1,21]. The consequence of missed detection of CKD, diabetes and hypertension is higher morbidity, mortality and financial cost to our healthcare system.

Failure of implementation of strategies to treat CKD, diabetes and hypertension and associated complications

Several strategies are proven effective to treat CKD, diabetes, and hypertension. Recent guidelines from medical groups have included specific recommendations for patients who have CKD coexisting with diabetes and/or hypertension.[5,25,24,65,67-71,31,34,11] Appropriate interventions, including treatment of hypertension, blocking the renin-angiotensin-aldosterone system, improving glycemic control and managing dyslipidemia can slow the progression of CKD and reduce the risk of cardiovascular disease for most patients with CKD, hypertension, and diabetes.[26,27,28,29,30,32,33,22,23,19,57,58,59,60,62,63]

Unfortunately, many of these strategies are not implemented in patients with CKD, diabetes and hypertension. Less than half of adults with CKD have blood pressure values within recommended targets[14]. About one half of patients with diabetes do not meet targets for glycemic control, BP or LDL cholesterol levels [35]. The use of recommended medications and achievement of targets for risk factor management are also unacceptably low for patients with CKD [1,2,5,14]. Furthermore, patients with CKD, diabetes and hypertension suffer from excessive morbidity and mortality from adverse safety events.[76,79,80,81]

2.2 Study Rationale

The need for new strategies to improve care for patients with CKD, diabetes and hypertension

There are some effective ways to treat chronic medical conditions, but implementation of recommended treatments is a major challenge.

Surveys have revealed that most primary care physicians and subspecialists (e.g., nephrologists) favor collaborative care for patients with CKD[36]. However, implementation of care for those with CKD, diabetes and hypertension among practitioners remains fragmented, and delayed care is common. Education and efforts to facilitate communication among patients and providers about chronic disease management are effective in removing patient-related and physician-related barriers to CKD care. Health services research suggests that the design of the care system is a primary determinant of the quality of care in most chronic conditions[84,85].

Some large health care systems have reported success identifying large numbers of patients with CKD and providing comprehensive CKD care[37,38,83]. The most promising strategies to improve CKD care emphasize multidisciplinary care models[39,40,41,42]. Integration of nephrology care and diabetes care in the chronic care model within existing health care systems has achieved some success in vulnerable populations with CKD, including those served by the Indian Health Service[43,44]. Low recognition of CKD, limited resources, and lack of familiarity with CKD care have limited wider application of these approaches.

Recent studies have reinforced the need for new strategies to improve care for patients with CKD. The introduction of automated eGFR reporting has led to higher detection of CKD in some healthcare systems but limited improvements in CKD care.[83] Electronic CKD checklists have improved adherence to some CKD guidelines but limited in scope.[75] Ongoing studies are evaluating the role of novel interventions including implementation strategies to promote patient safety through care transitions, patient-directed education and self-management tools, utilization of patient navigators, utilization of clinician decision support models and patient-decision support for selection of modalities of renal replacement therapy[74].

2.2.1 Implementing a new model of care for multiple chronic conditions

At Parkland Health and Hospital System, we have had the opportunity to address the challenge of caring for patients with CKD in and underserved safety-net hospital system by putting in place a collaboratory model of primary care and subspecialty interventions using a novel technology platform (Pieces) in a pilot study supported by NIDDK [74]. *(see figure 2.2.1 CKD Implementation Study)*

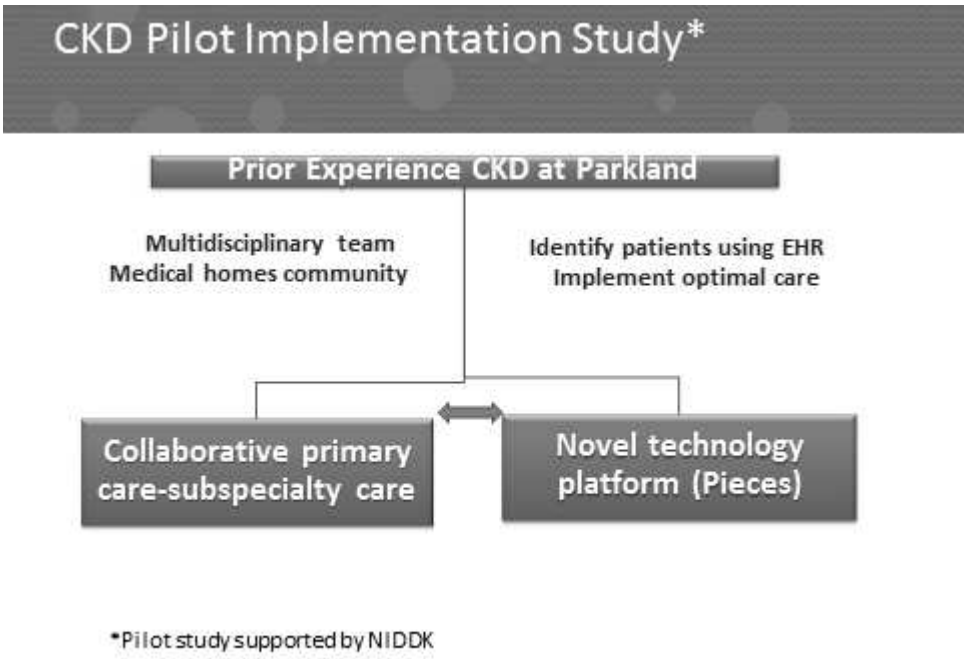
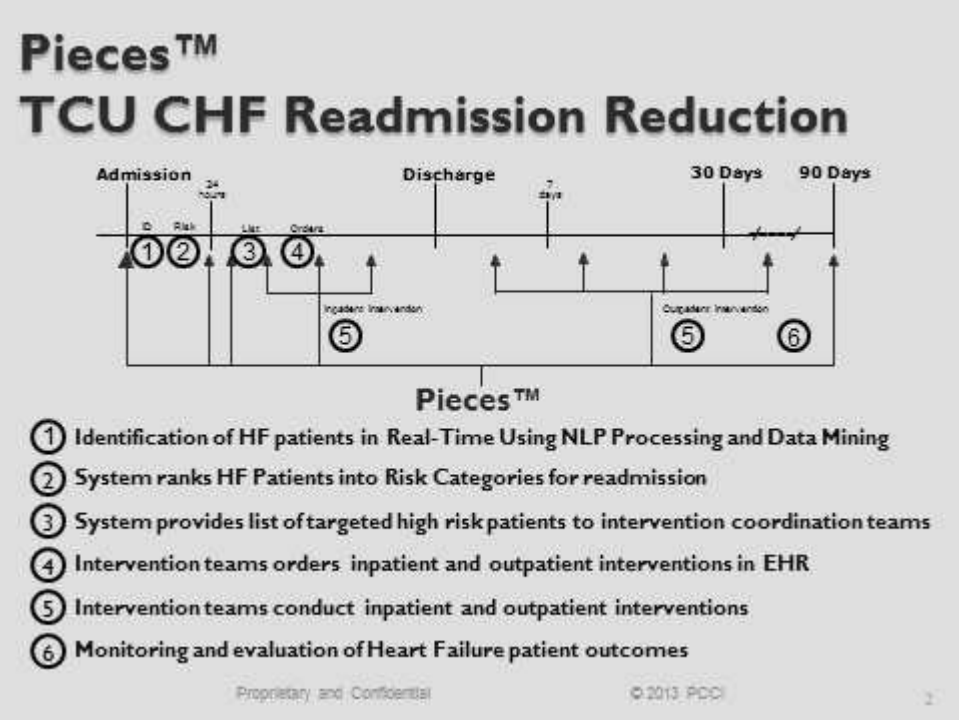


Figure 2.2.1

2.2.2 Using a novel information technology to improve care of patients with multiple chronic conditions

PIECES (Parkland Intelligent e-Coordination Evaluation System) is an IT-enabled e-monitoring and coordination software platform that sits on top of the electronic health record. Pieces has been developed and assembled by Dr. Ruben Amarasingham who is a co-investigator in our study. Pieces™ is comprehensive and can identify patients with specific clinical conditions, such as heart failure, using natural language processing (NLP), apply a clinical predictive model for risk stratification, allow for secure messaging to clinical and case management staff, provide a dashboard to track completion of intervention activities, and monitor patient outcomes (***Figure 2.2.2***). In this particular setting, Pieces™ facilitates identification of patients in real time, ranking patients into risk categories, notification of care team, establishing of plans, monitoring of inpatient and outpatient activity, and evaluation and coordination of tasks for improvement.

Figure 2.2.2



Preliminary Data:
Our team at Parkland Health and Hospital System developed and validated a model to predict the risk of readmissions in congestive heart failure (CHF) with Pieces™, using information available in the first 24 hours of admission in the EHR and other computerized data sets, including clinical factors (ICD-9 codes, vital signs, lab values, etc.) and electronically derived measures of social disadvantage (housing stability, census track, etc.), and adherence (pharmacy refills, outpatient appointment follow-up, etc.). This model demonstrated greater predictive probability for 30 day-readmission (C-statistic of 0.72) than prior models, including the ones used by Medicare and in multi-site heart failure trials, and has the advantage that it can be calculated in real time within 24 hours of admission.[51]

In a prospective, interrupted time-series trial with concurrent controls involving all CHF admissions to Parkland Memorial Hospital from December 2008 to November 2010, Pieces™ real-time risk stratification and a patient-tailored CHF intervention significantly reduced 30-day readmissions in patients from 26% to 21%, and the subset of Medicare patients fell from 20% to 14% ($p < .01$), putting Parkland Hospital among the top decile of hospitals nationally on this metric.[52]

Pieces™ software is flexible and can be adapted to track and coordinate a broad variety of electronically ascertainable inpatient and outpatient activities and protocols. Pieces™ has been used to develop several clinical predictive models. These include but are not limited to predicting out-of-ICU cardio-pulmonary arrest, sepsis, risk of surgical complications, 30-day readmission risk for diabetes, HIV, MI and pneumonia, risk of long-term diabetes complication and hospital risk surveillance. The automated out of ICU cardiac arrest model had excellent discrimination (c-statistic=0.85) and calibration and was more sensitive (51.6% and 42.2%) and specific (94.3% and 91.3%) than MEWS (a previously published risk score based on the

number and degree of vital sign and level of consciousness abnormalities) alone. The automated model predicted resuscitation event and death (RED) 15.9 hours before they occurred and earlier than Rapid Response Team (RRT) activation (5.7 hours prior to an event, p=0.003) and showed excellent discrimination, sensitivity and specificity.[53] Pieces has also been successfully used to electronically identify patients with diabetes to place in an e-registry within the Pieces system[54].

2.2.3 Preliminary data: CKD Collaboratory Study

Our group has conducted an NIDDK-funded study (Improving CKD Detection and Care in a High Risk Underserved Population/R34DK094115) at Parkland Health and Hospital System. This is a prospective study to *identify patients with previously undiagnosed CKD* and *implement established therapies* for these patients. The primary outcome of this study was blood pressure control for patients followed in primary care clinics with a collaborative primary care-nephrology care model enhanced by Pieces™. In this study we defined CKD by eGFR less than 60 ml/min or proteinuria/albuminuria and confirmed with repeat values more than 3 months apart. Figure 2.2.3.1 summarizes the study design using Pieces.

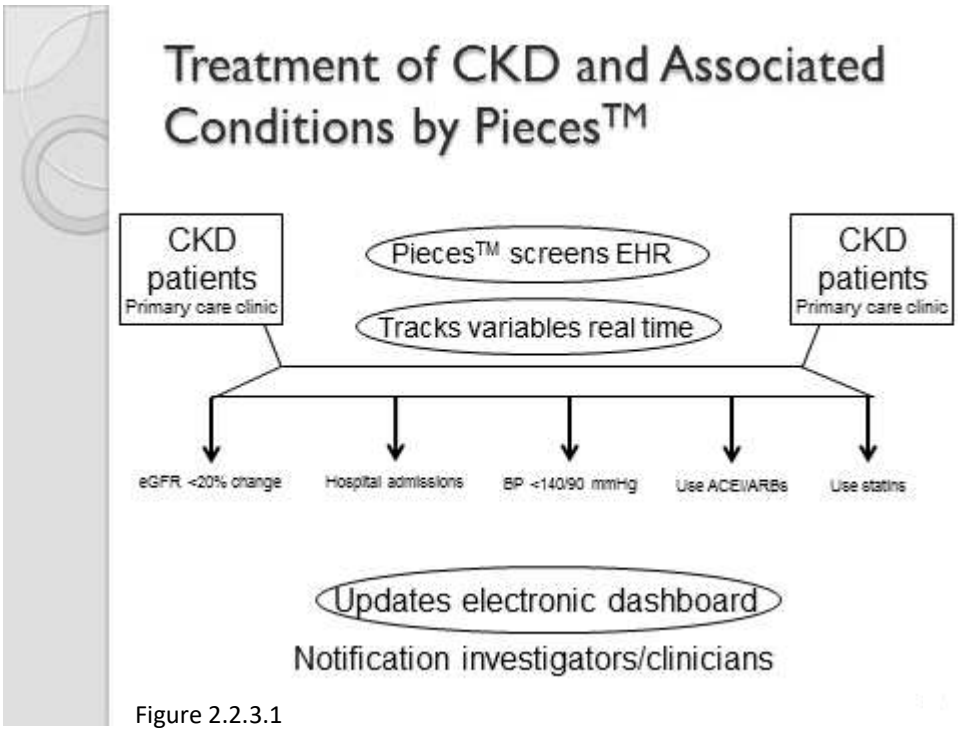


Figure 2.2.3.1

When comparing detection of CKD based on the established diagnostic criteria described above to cases previously diagnosed with CKD by ICD-9 diagnostic codes or inclusion in the problem list, we found 46-64% of patients with newly detected CKD. Treatment efforts focused on blood pressure control which was the primary outcome of the study. The results on achieving the primary outcome of blood pressure control were encouraging. BP control improved from 34.6% at baseline to 44% at most recent analysis. This accomplishment is particularly relevant given the low prevalence of blood pressure control in patients from high risk populations similar to our study group. Final collection and data analysis will be available in near future. *(see table 2.2.3.2)*

Using our collaborative model of CKD care enhanced by Pieces™ we have been able to identify a significant proportion of patients with previously undiagnosed CKD. Primary care physicians were notified of the diagnosis and eligibility of patients to participate in the study. The majority of patients approached agreed to participate in the study. This model and technology can also be applied to management of diabetes and other risk factors in CKD such as diabetes, hypertension and dyslipidemia.

	Screening	Last follow-up visit	
Clinical Measurement	% at Goal	% at Goal	
	n=107	n=107	P-value (McNemar's test)
Follow-up duration, month *median [range]*		11.2 [0.2 – 21.5]	
Systolic blood pressure	34.6%	44.0%	0.14
Diastolic blood pressure	57.9%	66.1%	0.17
ACEI/ARB	57.8%	87.2	<.0001
Statin	45.0%	79.8	<.0001

If positive test for proteinuria or albuminuria, then goal BP <130/80; Otherwise goal BP < 140/90).

Figure 2.2.3.2

Addressing the impact of multimorbidity from CKD, Diabetes and Hypertension

Given the major impact of CKD, diabetes, and hypertension, and the large gap between proven effective therapies and their application in day-to-day care, it is critical that we develop better ways to implement effective therapies in the regular care of patients with multiple chronic conditions. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines state that "people with CKD are an ideal target for interventions aimed at reduction of morbidity, hospitalizations, mortality and costs."[5]

We have recently implemented successfully a collaboratory primary care and nephrology care model for patients with CKD in a predominantly minority population using an novel technology platform that facilitates implementation of CKD care within the context of primary care practices and medical homes in the community. ICD-Pieces is a randomized, pragmatic clinical trial in four large healthcare systems in patients with coexistent CKD, diabetes and hypertension. Our hypothesis is that patients who receive care with a collaborative model of primary care-subspecialty care enhanced by novel information technology (Pieces) and practice facilitators will have fewer all-cause hospitalizations, readmissions, disease-specific hospitalizations, ER visits, cardiovascular events and deaths than patients receiving standard medical care. We will also aim to develop a better understanding of risk predictors in patients with CKD, diabetes and

hypertension to guide future recommendations of therapies that are tailored to individual patients.

2.3 Potential Risks and Benefits

Potential risks in this study could relate to the interventions to be implemented and to data security. The control group will receive usual standard of care. The intervention group will receive interventions that are already accepted as best practices. None of the proposed interventions are experimental. The study team will capture important safety data as part of the study outcomes: hospitalizations, 30-day readmissions, ER visits, cardiovascular events and death. In addition to outcome data and to maximize patient safety the study team will capture, review monthly and report quarterly to the DSMB data on the following events in the intervention group: hypotension, syncope, hyperkalemia, electrolyte disturbances, angioedema, hypoglycemia, rhabdomyolysis, myositis, drug toxicity, pregnancy while treated with ACEI of ARB, acute kidney injury, reductions in eGFR 50% or higher initiation of dialysis.

There are inherent risks associated with use of patient data the study and careful attention has been put in place to maximize data safety and protect patient privacy and confidentiality. Transmission of identifiable patient data will occur through secure FTP of HL7. Patient data will be stored in a secure database on the FISMA compliant VAZATA cloud. Access to the database will be password protected. Communication and files will be encrypted. Patient data will be de-identified prior to submitting for analysis. The approach has been already used safely at 2 of the participating healthcare systems. At this time it is anticipated that the VA North Texas Health Care System will carry out study implementation within their firewall and that patient identified data from the VA will not be transferred to the cloud at least in early stages of the study.

There are several important benefits that may result from this study. Implementation of best care practices for patients with CKD, diabetes and hypertension may improve very important clinical outcomes. Furthermore, successful implementation of this model can lead to more effective strategies to care for patients with other multiple chronic medical conditions and improve strategies for population health management. Finally, the research infrastructure developed for this study can be a model for future pragmatic trials.

3. Objectives

The overall goal of the study Improving Chronic Disease Management with Pieces (ICD-Pieces) is to improve the care of patients who have the triad of chronic kidney disease, diabetes, and hypertension. The general hypothesis is that patients who receive care with a collaborative model of primary care-subspecialty care interventions enhanced by novel information technology and practice facilitators will have fewer disease-specific hospitalizations, readmissions, all-cause hospitalizations, cardiovascular events and deaths than patients receiving standard medical care.

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to test the hypothesis that a collaborative model of primary care enhanced by novel information technology and practice facilitators to leverage data from electronic health records will allow accurate identification of patients with the triad of CKD, diabetes and hypertension using objective and reproducible criteria, and provide clinician support for implementation of best practices of care, monitoring clinical measures, adjusting treatments and reduce 12-month hospitalization rates. In this study disease-specific hospitalizations for CKD, diabetes and hypertension include hospitalizations due to cardiovascular complications, congestive heart failure, volume overload, accelerated/malignant/uncontrolled hypertension, acute coronary syndromes, myocardial infarction, stroke, coronary/peripheral revascularization, limb ischemia/amputations, diabetes complications, uncontrolled diabetes, hypoglycemia, acute kidney injury, hyperkalemia, electrolyte disturbances, medication errors, drug toxicity, and infections.

3.1.2 Secondary Objectives

3.1.2.1

The study will test if implementation of the collaborative model of primary care-subspecialty care interventions will reduce 30-day readmissions (for patients who are hospitalized), emergency room visits, cardiovascular events, deaths or disease-specific hospitalizations. In this study disease-specific hospitalizations for CKD, diabetes and hypertension include hospitalizations due to cardiovascular complications, congestive heart failure, volume overload, accelerated/malignant/uncontrolled hypertension, acute coronary syndromes, myocardial infarction, stroke, coronary/peripheral revascularization, limb ischemia/amputations, diabetes complications, uncontrolled diabetes, hypoglycemia, acute kidney injury, hyperkalemia, electrolyte disturbances, medication errors, drug toxicity, and infections.

3.1.2.2

Develop and validate predictive models for risks of hospitalizations, emergency room visits, cardio vascular events and deaths for all patients with coexistent CKD, diabetes and hypertension and predict risks of 30-day disease-specific readmissions for patients who are hospitalized.

3.1.2.3

Capture data (demographic, clinical, medications, laboratories, procedures) to phenotype patients with a triad of CKD, diabetes and hypertension.

3.1.2.4

Obtain important safety data for patients with CKD, diabetes and hypertension including adverse safety events, acute kidney injury and progression of chronic kidney disease (even for patients not hospitalized).

3.1.2.5

Obtain information on resource utilization including not only hospitalizations but also all emergency room visits, outpatient visits and diagnostic and therapeutic procedures.

3.1.2.6

Patient Reported Outcomes (PROs) are increasingly recognized as key outcomes of clinical studies challenges of obtaining direct consent from study patients and obtaining data from the control group prevent us from complete capture of PRO at this stage. We do plan to submit a proposal to capture PROs for both intervention and control groups at completion of the study. The objective will be to evaluate the impact of the collaboratory model of care on patient related outcomes (PROs) including health-related quality of life, patient satisfaction, patient perspective on quality of their care and measures of patient perception of burden related to care of their CKD, diabetes and hypertension.

3.1.2.7

Evaluate the impact of the collaborative primary care-subspecialty care model on provider satisfaction with resources and ability to manage patients with coexistent CKD, diabetes and hypertension.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

The primary outcome of this trial is all cause hospitalizations for patients with a triad of CKD, diabetes and hypertension. Specifically, the outcome will be hospitalization rates at 12 months for study participants. We will include both regular hospitalizations as defined by CMS and observation status overnight (to avoid variations related to definition of inpatient status/hospitalization using the recent implementation of the “two midnight rule” CMS-1599-F).

Hospitalizations can be ascertained objectively from the electronic healthcare record with assistance of electronic tools in each of the participating healthcare systems. If there is difficulty with adjudication of hospitalization, the steering committee will review and make a final recommendation. It is possible that some patients may be seen at a healthcare system other than one of the participating sites in this study. To maximize completeness of outcome data acquisition we will also track study patients with data from the Dallas Fort Worth Hospital Council that is a cooperative regional-sharing initiative that allows matching patients with any hospitalizations in any hospital in Dallas-Fort Worth. Patients in ProHealth in Connecticut are part of an Accountable Care Organization that receives regular and detailed reports from all hospitalizations for their members. Patients followed at the VA of North Texas may have hospitalizations outside the VA System and not tracked by the DFW Hospital Council. We will address this challenge in several ways. First, VA internal databases capture if payments have been initiated for outside hospitalizations. Second, we plan to include a standard question to the clinic workflow to ask patients about recent hospitalizations. Third, we have initiated discussions about the possibility of tracking hospitalizations of patients from the VA of North Texas via the DFW Hospital Council.

3.2.2 Secondary Outcome Measures

Secondary outcomes will include 30-day all cause readmissions (for those patients who have an index hospitalization), emergency room visits, cardiovascular events and deaths, and disease-specific hospitalizations for cardiovascular complications, congestive heart failure, volume overload, accelerated/malignant/uncontrolled hypertension, acute coronary syndromes, myocardial infarction, stroke, coronary/peripheral revascularization, limb ischemia/amputations, diabetes complications, uncontrolled diabetes, hypoglycemia, acute kidney injury, hyperkalemia, electrolyte disturbances, medication errors, drug toxicity, and infections. For those patients who are hospitalized all readmissions within 30 days of the index hospitalization will be captured from the electronic health records of the participating healthcare sites, Dallas Fort Worth Hospital Council or ACO database (for ProHealth, Connecticut) and VA of North Texas. Emergency room visits will be similarly captured from the electronic health records, DFW Hospital Council, ProHealth database and VA database.

Cardiovascular events include congestive heart failure, acute coronary syndromes, myocardial infarction, coronary and peripheral revascularization, stroke and limb ischemia/amputation. Deaths from any cause will be captured. Deaths will be classified as cardiovascular or non-cardiac related. Deaths will be captured from the electronic health records of the participating healthcare systems as well as from the Dallas Fort Worth Hospital Council and ACO database (for ProHealth, Connecticut), and VA EHR. We will also verify if enrolled patients who do not have an encounter in our systems within two year of study participation are classified as dead or alive using the Social Security Index.

Other secondary outcomes captured in the study from the electronic health records will include descriptive patient characteristics for patients with a triad of CKD, diabetes and hypertension including demographic data, information of patient comorbidities clinical data, medications, laboratories, and procedures, and changes in renal function (eGFR) and episodes of acute kidney injury as well as safety/adverse events. We will use the wealth of information available in the EHR to advance disease-specific phenotyping of our patient population.[72] Resource utilization will also be measured capturing not only hospitalization but also clinic visits and procedures (diagnostic and therapeutic).

As previously noted, Patient Reported Outcomes will not be captured initially but will be addressed as part of a future proposal in the study. Patient Reported Outcomes (PROs) are assessments directly reported by patients without interpretations by others and are increasingly recognized as key and valuable components of clinical trials[87]. A PRO survey derived for core domains and corresponding measures by the PCOR Net Reported Outcomes Common Measures Working Group (CMWG) will be used to measure health related quality of life and physical and emotional well-being of patients. Primary care practitioner reported outcomes and satisfaction with resources and ability to manage patients with coexistent CKD, diabetes and hypertension will be measured with a survey adapted from collaborative disease management initially developed for late-life depression in primary care[88].

4. Study Design

The study will employ a prospective stratified cluster randomization design. The stratum is each of the four large healthcare systems participating in the study. The unit of randomization will be primary care practices. In some healthcare systems (Parkland and North Texas VA) primary care practices are defined by an individual primary care practitioner caring for a unique group of patients with a permanently designated team of one RN and one medical assistant with no overlap with the practices of other primary care practitioners. In other healthcare systems (THR and ProHealth) clinical practices are defined as group of patients cared by practitioners sharing personnel and workflows in the same physical location and randomized as a single unit. The cluster design of the study is best suited to detect important differences in outcomes between the intervention and control groups[8,55]. The decision to use primary care practices as a unit for randomization in the study is based on the ability to implement different models of care in the active intervention sites as compared to the control sites. The collaborative model of care which includes novel information technology, subject identification, facilitation of patient care, monitoring of outcomes and participation from facilitators can be most efficiently applied to the workflow of practices when they are fully randomized to active intervention. The cluster randomization design with practices receiving collaborative primary care-subspecialty care versus standard care also limits the risk of cross-contamination between intervention and control groups in the study.

Primary care practices will be stratified by healthcare systems and randomly allocated to either intervention group or standard medical care group using a randomized permutation block within stratum. Based on the assignment of the practice where a patient receives medical care each patient will be assigned either to the intervention group or the standard medical care group.

All eligible patients of practices who are randomized to the study will be included in the comparison of the two intervention groups regardless of intervention compliance (intention-to-treat analysis) to investigate if patients in intervention group have significantly less all-cause hospitalizations than those in the standard medical care group. Evaluation will also be performed to determine treatment effects on disease-specific hospitalizations, ER visits, cardiovascular events and deaths.

There will be two study groups: active intervention group randomized to the collaborative model of care facilitated by novel information technology and practice facilitators and standard/usual care group.

The total number of patients to be studied is 10,991. *(see study table 4)*

Healthcare System	Number of Practices	Number Patients to be Enrolled
Parkland Healthcare Systems	25	3,367
Texas Health Resources	40	3,610
ProHealth Connecticut	50	3,181
North Texas VA	9	833

Table 4

Study enrollment will occur over a period of two years. The expected duration of subject participation is 12 months.

The intervention in the active group is implementation of a collaborative model of care that facilitates delivering best care practices to patients who have coexistent CKD, type 2 diabetes and hypertension. The model uses a novel information technology platform and practice facilitators with the purpose of allowing for early identification of patients with objective criteria and to implement best practices of care, monitor important clinical measures, adjust treatments and achieve improved outcomes. The intervention will be delivered in the outpatient setting.

The primary outcome measured during the trial is 12-month all-cause hospitalization rate for all the study participants. Secondary outcomes measured during the trial include 30-day disease-specific readmissions (for all patients with an index hospitalization), emergency room visits, cardiovascular event, deaths and disease-specific hospitalizations.

Other secondary outcomes measured in the study include adverse safety events, episodes of acute kidney injury and changes in estimated GFR.

Data collection for assessment of study objectives will be mainly based on information technology tools to capture data from the electronic health record. Some data fields will require collection of data from Dallas Fort Worth Regional Hospital Council, ProHealth ACO databases, VA of North Texas and Social Security Death Files Index.

There will be an interim analysis for efficacy of the intervention when 50% of the primary outcome data is available. This the consensus recommendation after review of the protocol and incorporating input from NIH, DSMB and OHRP. The study biostatisticians will review trends quarterly including patient volumes compared to goals from power calculations and inform study team and DSMB of any concerns based on trends of findings.

A DSMB (Data Safety Monitoring Board) has been assembled by the NIDDK and will oversee study planning and implementation of the study.

5. Selection and Enrollment of Participants

The total sample size of patients with the triad of CKD, type 2 diabetes and hypertension among participating sites in the four large healthcare systems in our study exceeds 28,118. The actual number of patients to be studied is 10,991.

The study will include patients 18-85 years old with CKD, diabetes and hypertension. Men, women, and minorities will participate in the study. Children will not participate as this study is focused on adults with multiple chronic conditions.

The outpatient population to be studied will be drawn from four large healthcare systems participating in the study. Parkland Health and Hospital System is the safety-net health system for Dallas County. Texas Health Resources is a large private, non-profit healthcare system network in North Texas. The North Texas Veterans Administration Healthcare System provides care for US veterans. ProHealth Physicians is Connecticut's largest network of primary care physicians.

5.1 Subject Inclusion Criteria

In order to participate in the study, patients should be 18-85 years of age and have coexistent CKD, type 2 diabetes and hypertension.

5.1.1 CKD Inclusion Criteria (present at least ≥ 3 months apart) [12,5,86]

1. There will be two or more eGFRs less than 60ml/minute or
2. Two or more positive tests for albuminuria and/or proteinuria

Albuminuria/proteinuria can be defined by quantitative criteria with albumin/creatinine ratio greater than 30, urine protein creatinine ratio greater than 200 or positive dipstick with protein detection (adjusted for urinary concentration/specific gravity) .[12,5,86]

Figure 5.1.1 summarizes identification of CKD candidate pool

5.1.2 Diabetes Inclusion Criteria [69,25]

Only patients with type 2 diabetes will be enrolled in this study.

1. Random blood glucose greater than 200mg/dL
2. Hemoglobin A1C greater than 6.5%
3. Use of hypoglycemic agents except Metformin or
4. Type 2 diabetes included in problem list

Figure 5.1.2 summarizes identification Diabetes candidate pool

5.1.3 Hypertension Inclusion Criteria [65]

1. Systolic blood pressure greater than 140mmHg on two different occasions at least one week apart
2. Diastolic blood pressure greater than 90 on two occasions at least more than one week apart
3. Use of antihypertensive agents except thiazide diuretics or
4. Hypertension included in problem list

Figure 5.1.3 summarizes identification Hypertension candidate pool

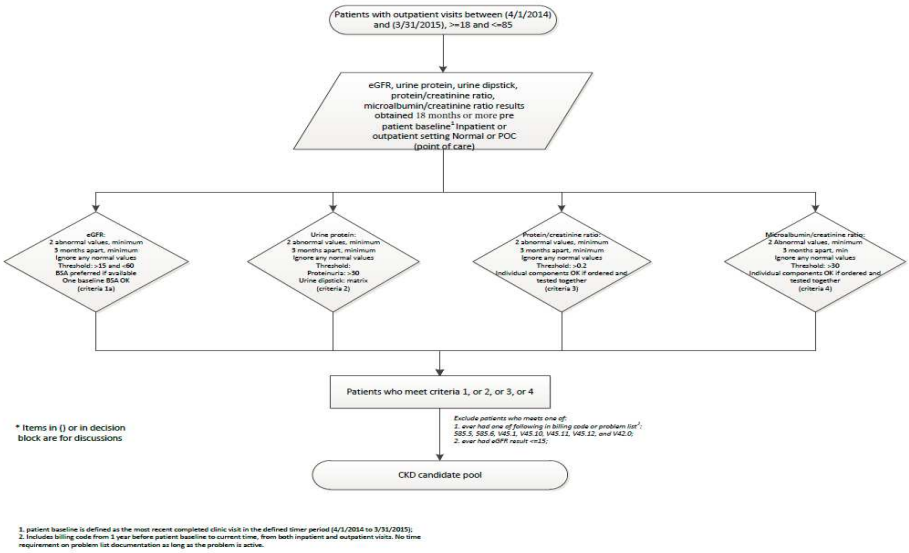


Figure 5.1.1 Identification CKD Candidate Pool

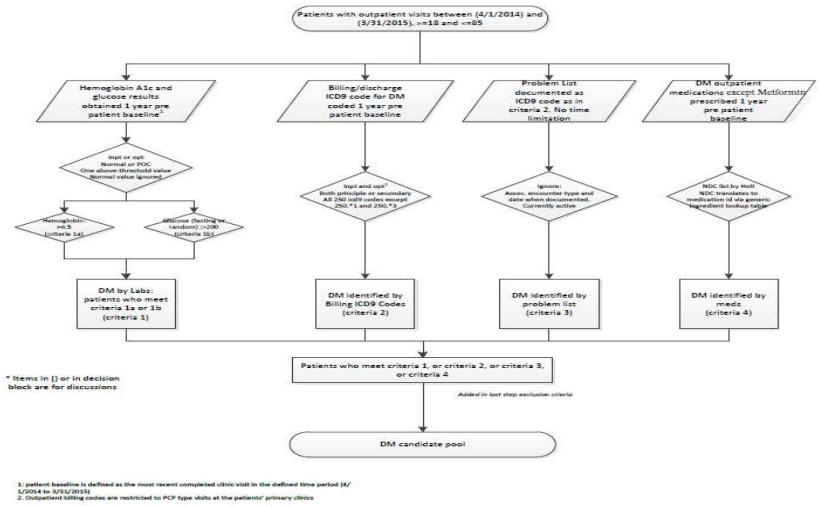


Figure 5.1.2 Identification Diabetes Candidate Pool

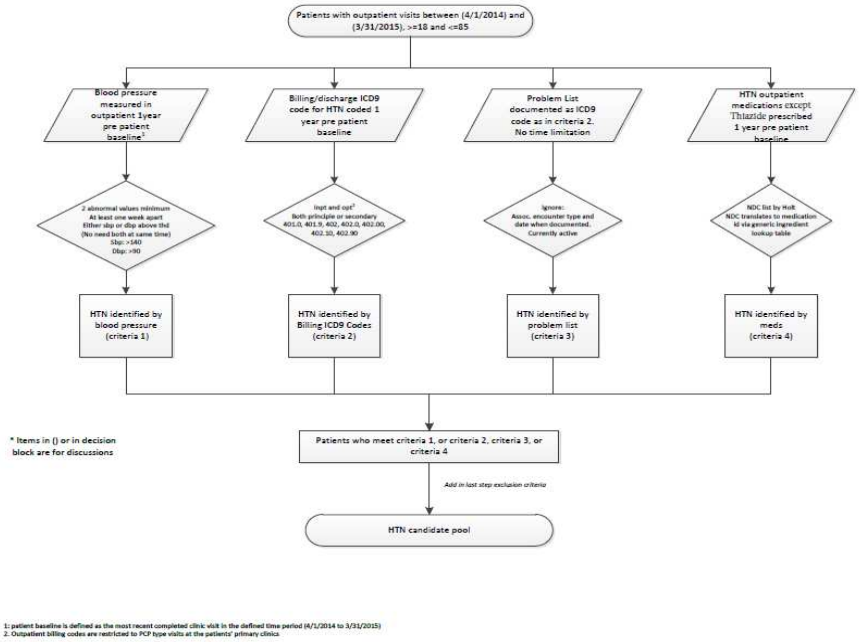


Figure 5.1.3 Identification Hypertension Candidate Pool

5.2 Subject Exclusion Criteria

All eligible patients from clinics randomized to the study will be included in the comparison of the two groups regardless of intervention compliance (intention-to-treat analysis).

Exclusion criteria will be minimal in this pragmatic trial. The collaborative model of care will not be implemented in patients younger than 18 years or older than 85 years of age or patients who have CKD stage 5/ERSD. Primary care practitioners have the option of not implementing the intervention on any of their patients if they believe benefit to be minimal or risk too high due to patient comorbidities. Patients also have the option to opt-out from the facilitated collaborative model of care.

5.3 Strategies for Recruitment and Retention

Prior to initiation of the study there will be information materials and education sessions provided to all participating sites. This will include both written material and electronic information. Resources from National Kidney Disease Education Program (NKDEP) will be provided to all practitioners.[82] There will also be special attention to selection of study champions at each participating site. In addition, there will be plans to visit most of the participating healthcare sites by members of the study team. These efforts will continue not only early in the study but throughout the study to promote study retention.

Participating healthcare systems will be provided with advance notice of possible study participants prior to upcoming appointments.

There will be review of actual enrollment of patients versus enrollment goals for every participating site. Reviews will occur monthly and reported quarterly.

5.4 Treatment Assignment Procedures

This is a prospective stratified cluster randomized trial. Primary care practices will be stratified by healthcare system and randomly allocated to active intervention or control using standard

medical care using a randomized permutation block within stratum. There will be no masking of sites randomized to active intervention.

Practitioners and/or patients can choose to withdraw for the study at any time. They can choose not to follow the intervention model (any or all of the components or tools of care). Patient can request their data be not included for analysis of outcomes.

The study can be terminated by the DSMB for various reasons including concerns about adherence to protocols, study enrollment or patient safety.

6. Study Interventions

6.1 Healthcare System Collaboratory

The pragmatic trial ICD Pieces is part of the NIH Collaboratory for Healthcare Systems Research with a special emphasis on multiple chronic conditions. The study will be conducted by a collaborative network of UT Southwestern and several other cores and four large healthcare systems that provide care to more than 2.5 million patients. *(see figure 6.1)*

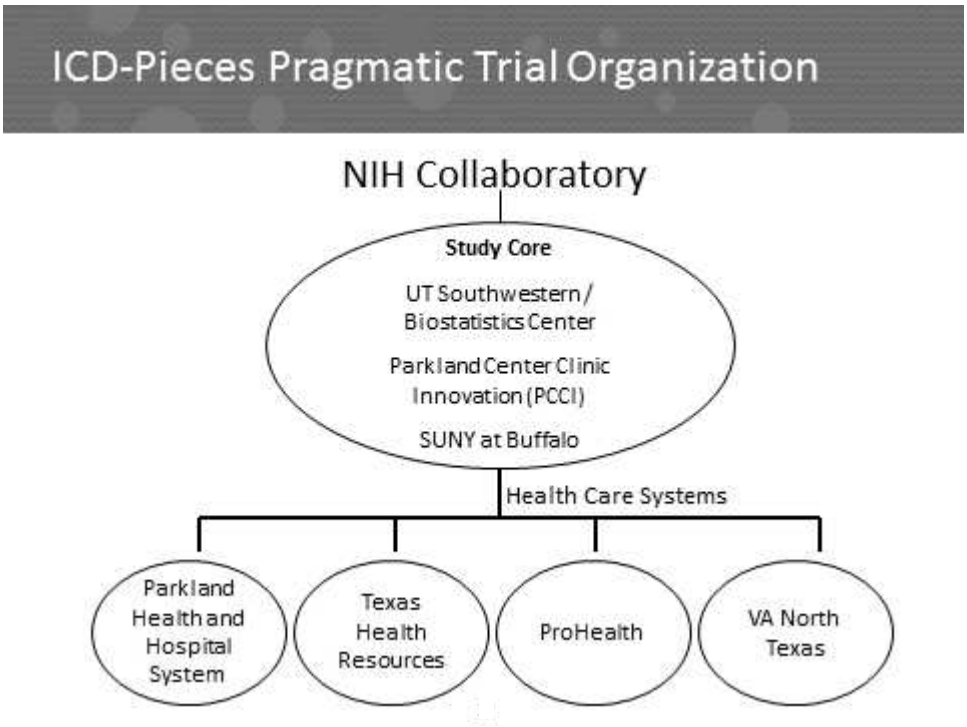


Figure 6.1

The University of Texas Southwestern Medical Center is the central academic partner for this collaboratory and has a strong commitment to both patient care and research. Parkland Health and Hospital System is an integrated healthcare system that serves as a safety net hospital for the underserved and uninsured residents of Dallas County. Texas Health Resources is one of the largest non-profit health systems in the United States serving a population close to 1 million individuals in North Central Texas. The Veterans Administration Healthcare System is the largest integrated health care system in the United States and the largest provider of care for patients with CKD in the country. The North Texas VA Healthcare System serves more than 100,000 patients in North Texas. Pro Health Physicians of Connecticut is one of the largest healthcare providers in Connecticut providing care to more than 250,000 adults every year across multiple practices.

6.2 Informatics Architecture

Pieces will be deployed through the cloud to the participating healthcare systems. *(see figure 6.2.1)* The Parkland Center for Clinical Innovation will provide specifications for data extraction using batch files and the data from each hospital will be mapped to relevant fields in the electronic health records systems. The Pieces system will access electronic health records for all patients who receive care at the participating sites for the study and to specifically detect patients with a triad of CKD, diabetes and hypertension and to detect eligible participants, facilitate management and monitor outcomes. Each healthcare system will have some differences in their electronic health records and data flow. This is being addressed with backup systems in place to access data and allow for safe and secure transmission. The North Texas VA will not be transmitting patient specific information via the cloud at least in the early stages of the trial. Data from each site will be programmed to be de-identified in the cloud and sent securely to the Biostatistics and Research Design Core at UT Southwestern. Please see *figure 6.2.2* for a model of information flow based on deployment of Pieces at participating sites of the

healthcare systems in the study. Section 15 Data Handling and Record Keeping provides additional details on data capture and transmission

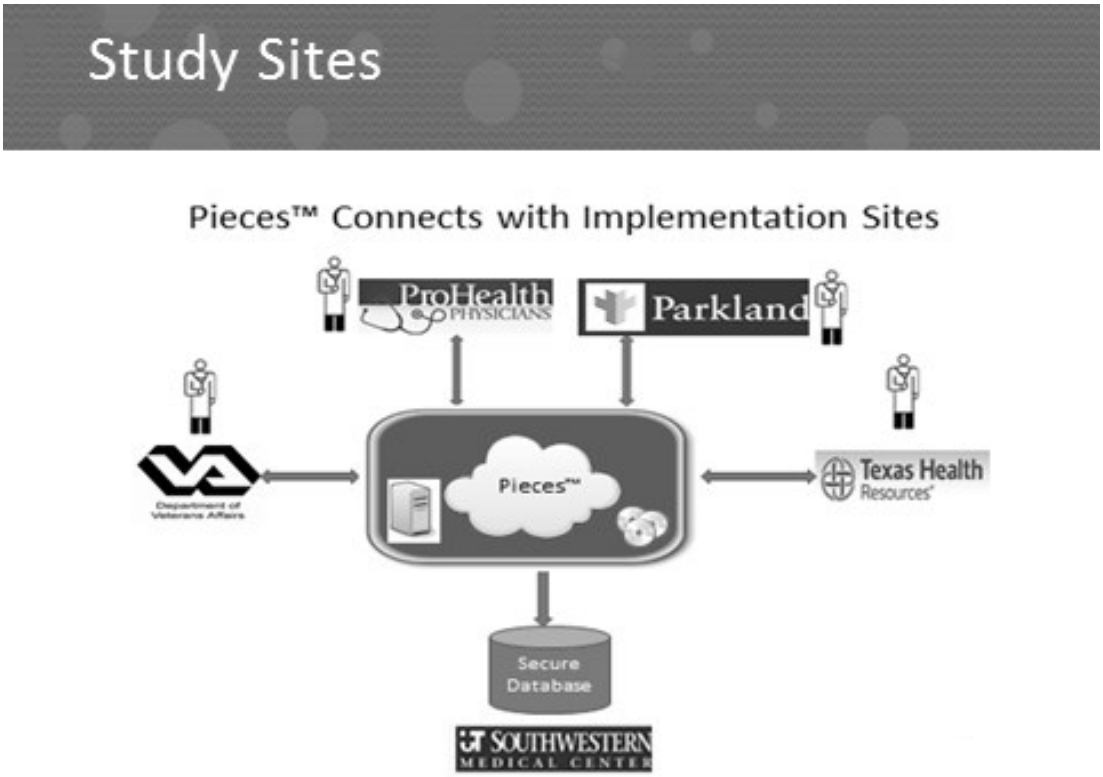


Figure 6.2.1

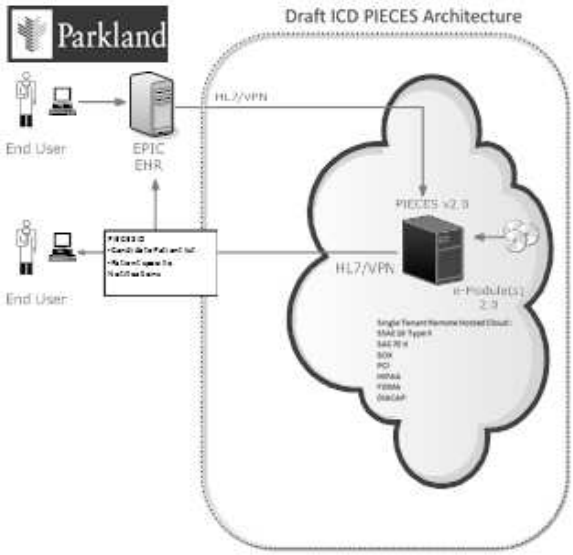


Figure 6.2.2

6.3 Practice Facilitator

A key component of the collaborative model of care for the intervention group is the introduction of practice facilitators. In order to maximize the successful implementation of care in the intervention group the role training of the practice facilitator will be standardized across sites. We will use a curriculum developed following principles detailed in the Practice Facilitation Handbook from the Agency for Healthcare Research and Quality and especially adapted for ICD-PIECES.[89] We have two content experts that will lead these efforts. Dr. Andrew Narva from NIDDK has developed educational programs which have been successfully used by NKDEP to successfully train healthcare professionals to care for thousands of patients who have CKD, diabetes and hypertension. Dr. Chet Fox from SUNY directs a training program at SUNY for practice facilitators working in primary care practices.

There will be an initial on-site course for practice facilitators led by Dr. Narva and Dr. Fox. After that initial meeting ICD-PIECES will continue to provide scheduled events by teleconference, written material and webinars to disseminate study relevant material to practice facilitators. All practice facilitators will also participate in regularly scheduled calls to review study progress. It is anticipated that these call will be at least weekly early in the study with additional calls and site visits to each site over the duration of the study.

Practice facilitators may defer in professional qualifications among the different healthcare sites. Practice facilitators will have some clearly defined responsibilities including the following:

- Receive initial and on-going training from the study team about the study, study protocol and proposed intervention
- Ensure training of designated clinic staff on clinic level activities and expectations
- Ensure necessary participation of designated clinic staff in CKD, diabetes, and hypertension care

- Coordinates with study clinic staff to ensure the following activities:
  - List of eligible patients scheduled for clinic visit weekly are received through the EHR weekly
  - Site-specific enrollment protocol are activated for eligible patients
  - Smart/Order set in the EHR are triggered for enrolled patients
  - Holds weekly conference calls with clinic representatives to answer any questions and monitor enrollment number for each clinic
- In-person visit to observe processes of enrollment and Smart/Order set trigger and other intervention activities
- Provides regular update to the site PI and monthly update to the study team on enrollment number, performance of study clinic and on-going challenges

6.4 Selection of Study Sites and Subjects

Pieces will screen electronic health records of participating healthcare systems to detect patients with a triad of CKD, diabetes and hypertension according to established inclusion criteria for the study. *(see figure 6.3.1 Detection for CKD, Diabetes and Hypertension)*

The candidate cohort of potential sites will then be randomized to active intervention (collaborative care model enhanced by Pieces) or control group (standard of care) *(see figure 6.3.2 Detection CKD, Diabetes and Hypertension).*

Within clinics randomized to intervention, Pieces will confirm patients meet inclusion criteria. *(see figure 6.3.3 Patient Identification Workflow).*

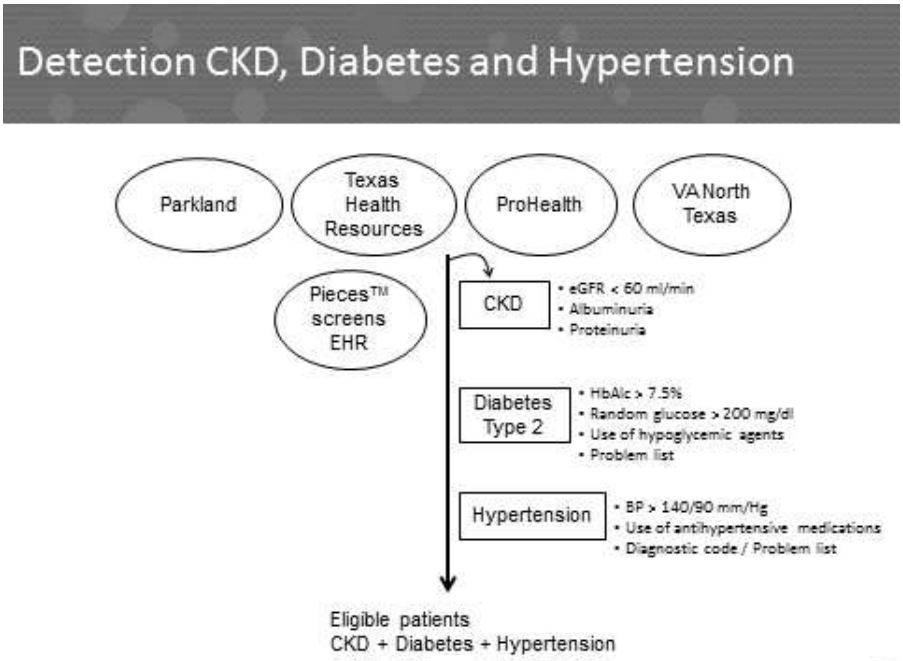


Figure 6.4.1 Detection for CKD, Diabetes and Hypertension

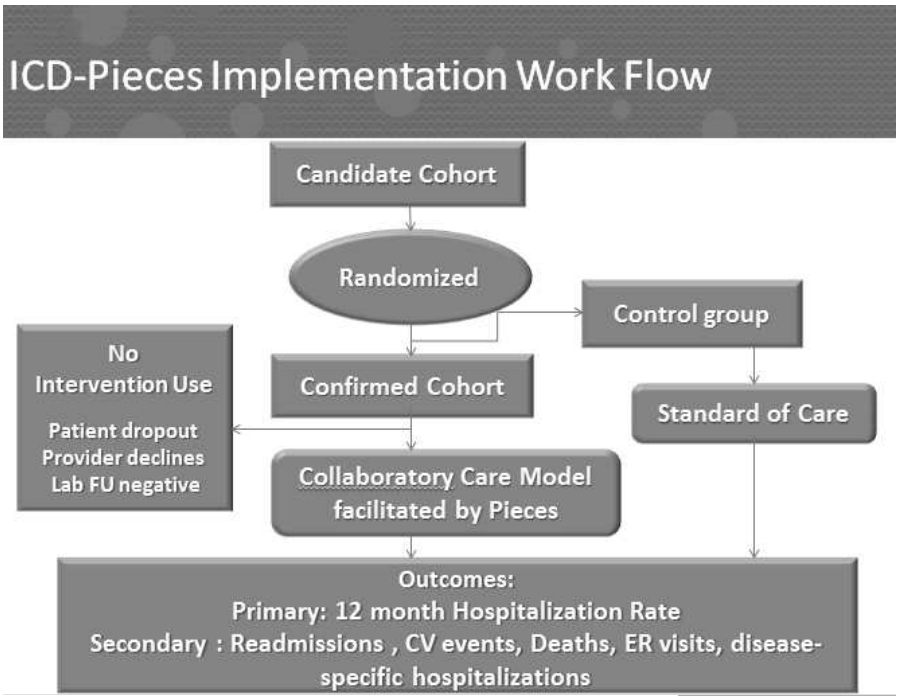


Figure 6.4.2 Detection CKD, Diabetes and Hypertension

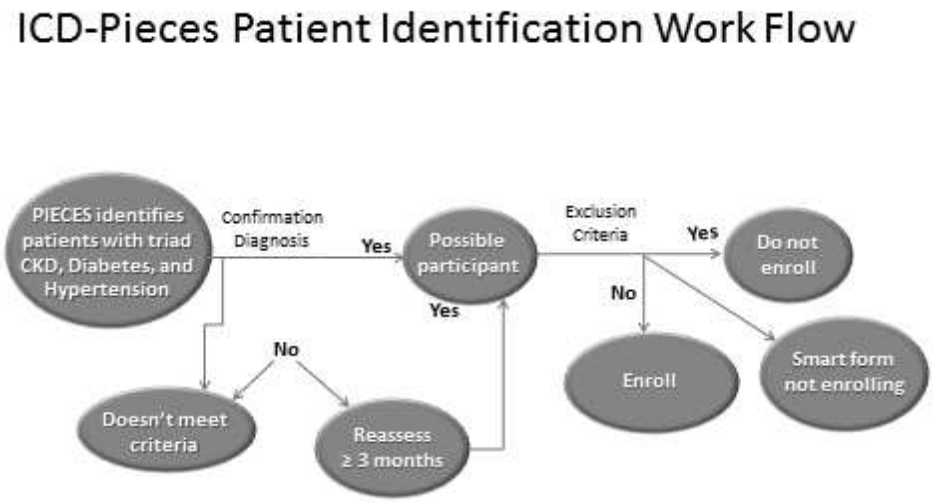


Figure 6.4.3 Patient Identification Workflow

6.5 Implementation Collaborative Model of Care

The interventions selected for this pragmatic trial are supported by prior studies, clinical evidence and/or guidelines for treatment of CKD, diabetes and hypertension.[5,25,24,65,67-71,31,34,11] Specific interventions include maintaining blood pressure less than 140/90mmHg, use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), treatment with statins, aiming for hemoglobin A1C at the recommended target for coexisting

comorbidities, and avoiding nephrotoxic medications including non-steroidal anti-inflammatory drugs (NSAIDS). Other interventions will include education on CKD for both primary care providers and for patients using material prepared by NKDEP. Material on lifestyle modification and immunizations will also be included. *(see figure 6.5.1)*

After a patient is enrolled, the primary care practitioner activates the CKD, diabetes and hypertension collaborative model of care. The primary care practitioner will also have the option to activate smart forms already constructed and available from our team *(see appendix section)* from the electronic heath record. Primary care practitioners will have the option to initiate protocols for CKD management, hypertension management, lipid and diabetes management. Protocols can be initiated via smartsets in the EHR. *(see figures 6.5.2 Initiation of Protocol from SmartSets and Links to SmartSets). The specific and detailed protocols for hypertension management and diabetes/lipid management are included in appendices.*

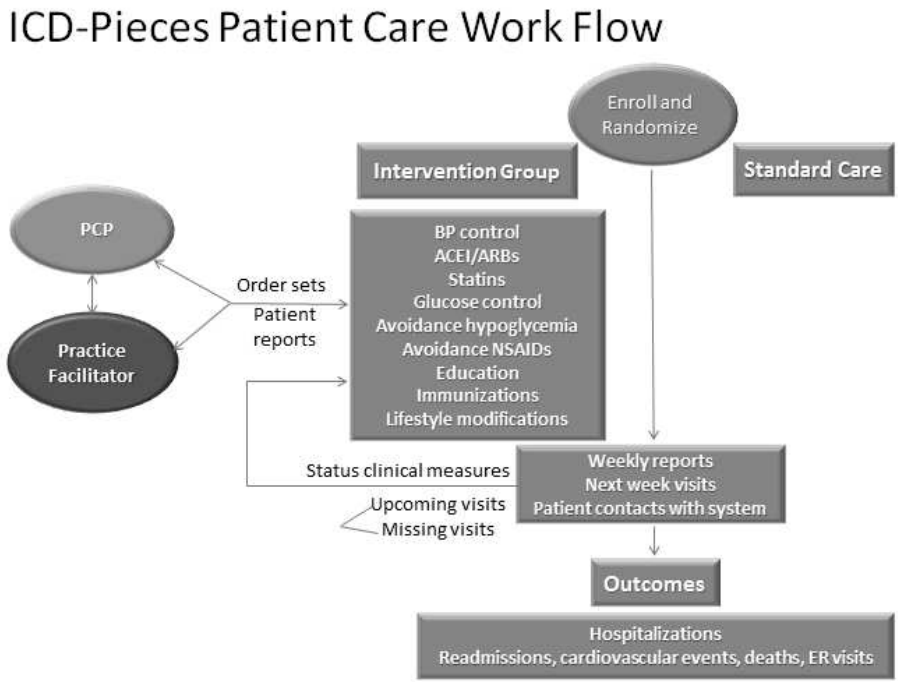


Figure 6.5.1

Figure 6.5.2 Initiation of Protocol from SmartSets

6.6 Maintenance of Provider and Facilitator Engagement

Engagement of primary care providers at the time of study initiation and throughout the entire duration will be focus of special attention by the study team. Educational materials on CKD, diabetes and hypertension will be provided to practitioners and facilitators. Materials developed by NKDEP are readily available for distribution to study sites. Primary care providers will be offered the opportunity to participate in continuing education (CME) provided as part of their participation in ICD-PIECES. In addition, efforts are underway to determine if it is possible to link active participation in the study with Quality Initiatives (QI) that could fulfill maintenance of certification (MOC) requirements.

As previously noted practice facilitators will be integrated into the study at all times including participation in the initial training curriculum, ongoing educational options and regularly scheduled study visits, conferences and reports.

6.7 Separation Control and Intervention Group

Several steps will be in place to maintain separation between groups and to assess fidelity to assigned regimen. First and foremost the selection of clinics/geographic clusters as unit of randomization for the study should reduce the risk of cross-contamination by completely separating not only providers but also facilitators, nurses, clerks and other professionals in the intervention groups from those in control groups.

We are aware that the healthcare systems in the study may at various times develop and bring for implementation competing initiatives and will review quarterly any new initiatives that the clinical leadership is planning across the healthcare systems. We will also work closely with the QI teams to be aware of any new initiatives that could overlap with ICD-PIECES. Our study team will also conduct quarterly reviews of any new national guidelines (from ASN, NKF, ADA) that could be relevant for the study population in ICD-PIECES. Any potential changes wil be discussed with Steering Committee and reported to DSMB.

We are also planning to monitor the following as indirect measures of separation between implementation and control groups:

- Activation of Smart sets
- Referrals to educators (diabetes)
- Selection of education modules (for providers and for patients)
- Linkage to pharmacy (recommended medications)
- Immunization rates

A possible consequence of the facilitated protocol is increased utilization of health services and resources. We will monitor and compare utilization rates in control and intervention groups.

7. Study Schedule

7.1 Screening

Potential study participants from each healthcare system followed in primary care clinics randomized to the study will be screened for inclusion according to the pre-established criteria for CKD, diabetes and hypertension *(see section 5.1)* and as illustrated in figure 6.3.1

There are no plans to obtain individual informed consent for patients screened or randomized in the study. *(see section 14.3)* Information about the study will be available to all patients in participating clinics and who have the triad of CKD, diabetes and hypertension. There will be an opt-out opportunity from the interventions or from use of information from any patient who requests their data not to be used for analysis.

Screening of participants will occur at an initial stage to identify a candidate cohort of patients in various eligible clinics *(see figure 6.3.2).* Patients who do not fulfill required diagnostic criteria on initial review and require a separate determination to confirm any of the three diagnosis will be rescreened at the time of a future visit *(figure 6.3.3)*

7.2 Enrollment/Baseline

Primary care practitioners will receive advanced notice (electronic and/or patient list) of eligible patients for the intervention group prior to their initial visit (visit 1). That visit will mark the first opportunity for initiation of the study by the primary care practitioner and to activate study interventions *(see figure 6.4.1).* The primary care practitioner will have the option of activating the study protocol and following recommendations using study tools/available smart forms.

7.3 Follow up Visits

Measures of blood pressure, blood glucose, kidney function (creatinine, eGFR), lipid levels, urine protein/urine albumin as well as pre-specified safety events will be captured from electronic health records at the time of patient contacts with the healthcare system for scheduled or unexpected visits for patients. Information will be then directed to primary care teams per study protocol.

Main study outcomes will be captured throughout the study for both intervention and control groups using the same tools in the electronic health record and access to DFW Regional Hospital Council, ProHealth database and VA electronic information systems.

The study does not specify the frequency of visits for study participants. It is anticipated that patients with the triad of CKD, diabetes and hypertension will usually be seen at a minimum of every 3-6months in most participating clinics.

7.4 Final Study Visit

The final study visit will be the patient visit closest to 12 months after initiation of the study for that patient. As previously stated, visits will be for ongoing care and not mandated for study/research interventions.

7.5 Unscheduled Visits

Acquisition of data/facilitation of care at the time of unscheduled visits will follow the schedule described in section 7.3. This is, however, an outpatient study. There will be capture of relevant data from hospitalizations (including major outcome measures) but study interventions and application of study tools will not be actively implemented during hospitalizations.

7.6 Early Termination Visits

Patients and/or primary care practitioners may decide at any time to discontinue participation in the facilitated collaborative model of care. Outcomes will still be captured for intention-to-treat analysis unless participants request their data/information not to be used. Table 7.1 summarizes the visits in the study.

Schedule of Events		Prior to Visit 1	Visit 1/Baseline	Visit 2 (3 months)	Visit 2 (6 months)	Visit 4 (9 months)	Visit 5 (12 months)	Study Completion
Assessment of Eligibility (Screening)		X						
Enrollment			X	X	X	X	X	
Medical History			X	X	X	X	X	
Medication Review			X	X	X	X	X	
Physical Exam (BP)			X	X	X	X	X	
Laboratories			X	X	X	X	X	
Surveys	HRQOL		X					X
	Practitioner Satisfaction		X					X
Education/Counseling			X		X			

*Most patients are usually seen every 3-6 months although more frequent visits occur in some patients based on treatments/clinical volume

Table7.1 Schedule of Visits/Events

8. Study Procedures/Evaluations

8.1 Clinical Evaluations

The study does not mandate interventions or evaluations considered experimental or outside of those recommended as part of optimal evidence-based care for patients with CKD, diabetes and hypertension.

- Medical history and emphasis on problem list and diagnostic codes.
- Medications including lists of all medications from electronic health record and medication reconciliation
- Physical examination with special emphasis to blood pressure readings.
- Education/counseling procedures. There will be emphasis on lifestyle modifications and confirmation of immunizations and interventions related to healthcare interventions. This will also be an opportunity to insure distribution of education on chronic kidney disease and diabetes. See information from NKDEP.[82]
- Criteria for dose adjustment. Recommended goals for clinical measures and suggestions for recommendations are included in the specific protocols for CKD, hypertension, dyslipidemia, lipid management and diabetes management. *(see appendix)]*

8.2 Laboratory Evaluations

- Serum chemistries including creatinine and electrolytes, GFR estimations (eGFR)
- Glucose and hemoglobin A1C
- Urine protein and urine albumin quantitative, urine creatinine and urine protein dipstick/with specific gravity
- Microalbumin/creatinine ratio and protein/creatinine ratio in urine
- Lipids.

8.3 Special Measures

- Health related quality of life and physical and emotional well-being from surveys to a small subset of participants.
- Primary care practitioner satisfaction with model of care for coexistent CKD, diabetes and hypertension

8.4 Special Measures

- All-cause hospitalizations

- Disease-specific hospitalizations for CKD, diabetes and hypertension: cardiovascular complications, heart failure, volume overload, hypertension, acute coronary syndrome, myocardial infarction, coronary/peripheral revascularization, stroke, limb ischemia/amputations, acute kidney injury, hyperkalemia, electrolyte disturbances, uncontrolled diabetes, hypoglycemia, diabetes complications, medication errors and drug toxicity, infections
- 30-day disease-specific readmissions (for patients with an index hospitalization)
- Emergency room visits
- Cardiovascular events
- Deaths

8.5 Sub-Study 1

Yield of Pharmacist Medication Reviews and Clinician Acceptance of Pharmacist Recommendations for Enrolled Patients at ProHealth

Background
ProHealth Physicians is an intervention site for a large, multisite, NIH-sponsored pragmatic clinical trial ("Improving Chronic Disease Management with PIECES") which offers virtual pharmacist support for clinicians in the care of patients with the disease triad of chronic kidney disease (CKD), type 2 diabetes mellitus (DM), and hypertension (HTN). To date, our pharmacist has conducted over 300 medication reviews for these patients. Reviews assess: a) recommended practices in CKD (e.g. use of ACEi/ARB and statins), b) glycemic and blood pressure control, and, c) medication safety, which includes avoidance of nephrotoxic agents and renal dosing. The pharmacist makes patient-centered recommendations to clinicians to optimize and improve safety of regimens. Reviews and recommendations are entered as a Clinical Pharmacist Note in the electronic health record prior to primary care appointments. The pharmacist communicates electronically with clinicians for salient issues.

Objectives
The primary objectives of the proposed sub-study are to characterize a) medication-related problems (MRPs), and b) pharmacist recommendations among outpatients over 65 years old with chronic kidney disease, diabetes, and hypertension. A secondary objective is to evaluate the acceptance of virtual clinical pharmacist support in a large Primary Care Accountable Care Organization by evaluating clinician implementation of a pharmacist's medication recommendations.

Methods
In this retrospective cohort study of 200 patients, medication-related problems and recommendations will be extracted from Clinical Pharmacist notes dated January 2017-May 2017 within the EHR.

Medication-related-problems and pharmacist recommendations will be classified as follows:

Category	**Medication-related problem**	**Pharmacist recommendation**
I. Safety	1. Contradindication 2. High dose 3. Adverse Drug Event (ADE) 4. Drug interaction 5. High risk medication (e.g. Beers List, anticholinergics)	a. Discontinue b. Decrease dose c. Renal dose adjustment d. Lab test / monitoring
II. Appropriateness	1. Needs additional medication 2. Unnecessary medication	a. Start medication b. Discontinue
III. Effectiveness	1. Ineffective 2. Low dose	a. Increase dose b. Alternative medication

This classification is based on a well-established taxonomy of MRPs. It was adapted to align with the focus of our medication reviews and patient population. Medication names and dosages will be collected to identify drug classes and specific medicines associated with MRPs.

Clinician acceptance of medication recommendations will be evaluated by review of medication profiles and Primary Care notes within one month after the timestamp of the Clinical Pharmacist Note.

Variables for the primary objective include: number of medication reviews, baseline patient characteristics (age, gender, mean eGFR and A1c, number of medications), number of medication related problems, and classification of MRPs and associated medicines. Variables for the secondary objective include number of medication recommendations accepted by primary care clinicians and acceptance rate.

Data Sources
Data will be extracted from the electronic health record; no patients will be contacted.

- *Demographics* – patient age, gender
- *Clinical Pharmacist notes* – MRPs, recommendations
- *Primary Care progress notes* –acknowledgment of pharmacist recommendations, documentation of medication changes
- *Medication profile* – medication and dose, medication changes
- *Laboratory results* – serum creatinine, eGFR, A1c, lipids, urine microalbumin, LFTs
- *Vitals* – blood pressure, heart rate

Impact
This study is important to identify common medication-related problems among these vulnerable patients with the disease triad of chronic kidney disease, diabetes, and hypertension. Results have potential to improve decision support for clinicians at the point of prescribing. This work also highlights the feasibility and value of adding virtual Clinical Pharmacist support for primary care teams in a large primary care-based Accountable Care Organization.

8.5 Substudy 2: Testing Computable Definitions of Acute Kidney Injury (AKI) in the ICD-Pieces Clinical Trial

Acute kidney injury (AKI) refers to an abrupt decrease in kidney function, resulting in the retention of waste products and in the dysregulation of electrolytes and extracellular volume[1]. In the United States, about 300,000 people die from AKI each year, and the presence of AKI increases the length of a patient's hospital stay by 3.5 days.[2] Furthermore, it is recognized that there is an association between AKI and chronic kidney disease (CKD) and end-stage renal disease (ESRD) .[3] There is evidence of marked variation in the management of AKI, which is, to a large extent, due to a lack of awareness and an absence of standards for prevention, early recognition, and intervention. Emerging data point to an urgent need to change the treatment paradigm of CKD and other AKI risk factors by educating practitioners on how to prevent AKI (including the treatment of CKD), and modify its course with modalities and treatments that can improve outcomes.

Defined criteria to document AKI for research criteria (KDIGO, RIFLE,AKIN) have been used in research studies and compared to billing diagnostic codes for identification of AKI. In two recent studies the use of billing codes to identify AKI had low sensitivity compared with current KDIGO consensus definition or modified KDIGO definition (not counting urine output decrease as a criterion). [4,5] In one study of
~34,000 hospitalized patients only 17.2% (95% CI 13.2%-21.2%) of AKI cases that were identified using serum creatinine were also identified using AKI billing codes.[4] In a more recent report using

electronic health records, the ICD-10 code corresponding to AKI (N17) was recorded in 30% of the cases documented by a laboratory based approach to find Hospital Associated-AKI identified in a reported study.[5] Furthermore, in a mini-sentinel pilot project sponsored by the US Food and Drug Administration (FDA) to improve electronic safety surveillance, the positive predictive values of ICD-9 diagnoses in identifying AKI ranged from 48%-84% at best.[6]

Improved standardized approaches to detect AKI in clinical trial adverse event reporting would improve safety monitoring and build the evidence base for defining subtypes of AKI in current studies and for future biomarker and precision medicine initiatives. We propose an additional substudy of the incidence of laboratory-defined AKI compared to administrative coding as an extension research question for the current ICD-Pieces pragmatic clinical trial. The ICD-Pieces study is focused mostly on capturing outpatient events. It is notable that 1/3 of AKI cases in a large epidemiological study were community acquired.[7]

Specific Aim 1:

Test the performance of laboratory based criteria for AKI compared to coded ICD-10 documentation of AKI in the outcomes data set of the ICD Pieces trial -UH3DK104655

As the ICD-Pieces trial will be following AKI as a subset of inpatient hospitalizations captured as part of the primary endpoint of the one-year unplanned hospitalization rate, a natural data set will be available to test for concordance of the laboratory only- based definition of AKI compared to ICD- 10 code documentation within a well- defined cohort with established baseline eGFR. AKI will be defined using KDIGO laboratory criteria. Although routine collection of information of urine output is not part of the trial, laboratory based data will be available along with the hospitalization data will be available for a section of the clinical sites including the North Texas VA hospital system, Parkland Health & Hospital System, and Texas Health Physicians Group of Texas Health Resources. This would demonstrate the feasibility of improved monitoring for adverse events, specifically AKI, in a large cluster randomized pragmatic clinical trial of patients with chronic kidney disease.

Specific Aim 2:

Document modern mappings of AKI based on the KDIGO criteria to current LOINC and SNOMED-CT Ontologies

In order to promulgate a standard modern definition of AKI based on computable laboratory values and related medical concepts and to allow exploration of concordance of alternate methods of detection of AKI based on Natural Language Processing, the investigators propose a mapping exercise to the available modern medical ontologies. This definition can be circulated at both the NKDEP Health Information Technology Working Group and through the NIH Collaboratory Living Textbook as well as other publications. To the investigators' knowledge, no such modern mapping has been published, and exhaustive mapping of the SNOMED CT ontology is unlikely to happen as part of routine clinical workflows. This resource map would allow exploration of documentation of clinical findings and concerns in routine clinical notes as an alternative method for surveillance of AKI as a clinical event.

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8.7 Substudy 3: **Understanding Decisions to Opt-Out of Pragmatic Clinical Trials**

Jeremy Sugarman, MD, MPH, MA
Kevin Weinfurt, PhD
Miguel Vazquez, MD

1. Abstract

Patients may sometimes be given the option to opt-out of pragmatic clinical research, which may mean not receiving a particular intervention based upon a study protocol or not having their data used for analyses. Yet, there is minimal information available about the reasons why patients opt-out, which may prove to very useful in assessing the ethical, scientific, and practical aspects of pragmatic clinical trials. This project involves pilot testing a short survey instrument among patients who opt-out of ICD-PIECES, a pragmatic clinical trial currently being fielded to develop a preliminary understanding of reasons for opting-out as well as assemble a cohort of patients who may be interviewed in a possible qualitative interview study in the future.

2. Objectives

a. To pilot test a short survey instrument regarding reasons for opting-out of pragmatic clinical trials.
b. To develop a preliminary understanding of reasons for opting-out of ICD-PIECES, a pragmatic clinical trial currently enrolling participants.
c. To obtain permission from patients who opt-out of ICD-PIECES for a possible in-depth interview regarding decisions related to opting-out that may be designed and conducted in the future.

3. Background

Pragmatic clinical trials and comparative effectiveness research are becoming increasing commonplace as a means of generating real-world information to guide medical decision making among patients, clinicians, payers and other stakeholders. This type of research typically poses minimal incremental risks to those involved and may be done without an explicit informed consent process. However, in such trials patients may be given the option to opt-out of the research, which may mean not receiving a particular intervention based upon a study protocol or not having their data used for analyses. Yet, there is minimal information available about the reasons why patients opt-out of pragmatic research, which may prove to very useful in assessing the ethical, scientific, and practical aspects of pragmatic clinical trials. Accordingly, the proposed research will pilot test a short survey instrument among patients who opt-out of ICD-PIECES, a pragmatic clinical trial currently being fielded. The estimated opt-out rate in ICD-PIECES is currently 1.5% of those approached.

4. Study Procedures

a. Study design. Patients who opt-out of ICD-PIECES will be approached by the ICD-PIECES study coordinator immediately following their decision to opt-out and ask them if they would be willing to answer some questions about their decision. Answering these questions will be considered to indicate consent. The information will be captured on a form that will include only basic demographic and site information unless the patient voluntarily provides permission to be contacted. Primary data will be retained by the ICD-PIECES study team. Aggregate information will be provided without any patient identifiers to the study team at the NIH Collaboratory Coordinating Center (Drs. Sugarman and Weinfurt).
b. Study duration and number of study visits. The study will take 5-15 minutes at a single encounter.

5. Inclusion/Exclusion Criteria.

a. Adult, competent patients who opt-out of ICD-PIECES
b. Willing and able to answer questions related to their decision to opt-out
c. Able to converse in English

6. Sample Size: 10-15 patients

7. Study Statistics

Data will be analyzed using standard descriptive statistics. We will endeavor to continue to enroll patients who opt-out of ICD-PIECES until enrollment for that study ceases.

8. Risks

There are no anticipated physical, financial or social risks for participating. Patients may feel uncomfortable discussing their reasons for opting-out. If this occurs, the survey can be stopped. If any unanticipated problems occur, the PI will be notified immediately and intervene as appropriate.

9. Benefits

There are no anticipated benefits to the participants. The information learned in this study should help assess and perhaps improve future pragmatic clinical trials and those who might participate in them.

10. Payment and Remuneration

None.

9 Assessment of Safety

9.1 Specification of Safety Parameters

Adverse safety events will be captured and monitored as part of the study. The primary outcome of this trial is all-cause hospitalizations for patients with a triad of CKD, diabetes and hypertension and all unplanned hospitalizations will be captured. The main secondary outcomes that will be captured in the study also include safety events including 30-day all cause readmissions (for those patients who have an index hospitalization), emergency room visits, cardiovascular events, deaths, and disease-specific hospitalizations. In this study disease-specific hospitalizations include all those hospitalizations for cardiovascular complications, congestive heart failure, volume overload, hypertension complications, acute coronary syndrome, myocardial infarction, coronary/peripheral revascularization, stroke, amputation/limb ischemia, uncontrolled diabetes, hypoglycemia, diabetes complications, acute kidney injury, hyperkalemia, electrolyte disturbances, medication errors, drug toxicity, and infections.

In this study the control group will receive standard of care. The intervention group will receive interventions that are already accepted as best practices. Primary care providers will make ultimate decisions regarding implementation of any of the interventions for both groups. In addition to the study outcome measures detailed above the following events will be captured and reported (whether they lead to hospitalizations or not) as they could be related to potential study interventions: hypotension, syncope, hyperkalemia, electrolyte disturbances, angioedema, hypoglycemia, rhabdomyolysis, myositis, drug toxicity, pregnancy while treated with ACEI or ARB, acute kidney injury, reductions in eGFR 50% or higher, or initiation of dialysis.

The study will monitor for any malfunctions on the decision support software system and SFTP used for data transmission to and from electronic health records of the study sites for Parkland, THR, ProHealth and VA of North Texas. There will also be monitoring for adherence to Manual of Procedure interventions including identification and enrollment of eligible patients, activation of study protocols and recommended follow up.

9.2 Methods and Timing for Assessing, Recording and Analyzing Safety Parameters

9.2.1 Adverse Events

The study outcomes and adverse/safety events detailed in Section 9.1 will be captured directly from the electronic health records of the participating healthcare systems, DFW Hospital Council and internal databases and event tracking forms from ProHealth and VA of North Texas as previously described. In this pragmatic trial capture of unsolicited events can occur in most instances from the electronic health records and databases. As noted above there will be confirmation for solicited adverse event including hospitalizations for patients from the VA of North Texas who may be seen in other institutions in Dallas/Fort Worth.

Adverse events will be collected throughout the entire participation of subjects in the study (12 months from enrollment to completion of the study participations for each subject). The study coordinating team will review adverse events to determine relatedness to study interventions and to grade severity as needed.

Adverse events will be classified as severe or mild/moderate. For the purposes of this study severe adverse events will include those leading to death, hospitalizations, or permanent disability/incapacity. Other safety events will be classified as mild/moderate. As the study relies heavily on event capture via the electronic health records it may not be possible in all instances to accurately differentiate between mild and/or moderate severity within the context of this pragmatic trial.

The study team will make determinations on whether serious adverse events are possibly/likely related to study interventions.

9.2.2 Expected Adverse Reactions

A list of possible safety events detailed in Section 9.1 includes most of the safety signals that could be associated with the study interventions. The study group will regularly review events capture to determine relationship to study interventions. In order to maximize patient safety we do plan to conduct a manual review of the initial 100 subjects enrolled in the study from each healthcare site. We will also review a minimum of 10 subjects from each participating healthcare system every quarter to monitor for adverse events and relatedness to study interventions.

9.2.3 Serious Adverse Events

Hospitalizations and deaths are serious events in this study. It should be noted that these adverse events classified as serious are already primary and secondary outcomes for this study (hospitalizations and deaths). Other serious events are those leading to incapacity and/or permanent disability and will also be captured as noted above.

9.2.4 Unanticipated Problems

The study team will remain vigilant for unanticipated problems. Trends of increasing frequency or rate of safety events in the intervention group will prompt review of individual cases by the study team and reporting to the oversight group (DSMB).

Other possible unanticipated problems including malfunctioning of the decision support system or non-adherence to recommended clinic protocols as well as possible mitigations are discussed in Section 13 Quality Control and Quality Assurance.

9.2.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

All participating subjects in the study including in both control group and intervention group will be under the direct care of primary care providers who will make final decisions on all interventions and direct patient care. Abnormal laboratory findings or clinical findings will be brought to the attention of the primary care provider according to the existing protocols in each healthcare system for appropriate clinical response.

9.3 Reporting Procedures

The study group will collect adverse events from all the participating healthcare systems and review at least monthly. There will be reports prepared for submission to the DSMB quarterly.

It should be noted that there will be some delay on the acquisition of data regarding some adverse events/outcomes. Hospitalizations which are not captured via the electronic health record but require reporting from the DFW Hospital Council may not be known by the study team for several months. Furthermore, information on other serious adverse events such as deaths may not be available to the study team until after review of the Social Security Death files.

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

All study subjects in the intervention and control group will be followed according to best practices by their primary care providers in following established protocols in each healthcare system. As part of participation in the study, the intervention group will continue to be monitored by PIECES and practice facilitators during the 12 months of their participation in the study.

9.5 Halting Rules

The study can be halted at any time by the DSMB recommendations if there are concerns about patient safety, lack of enrollment or poor adherence to study plans and poor adherence to protocol.

9.6 Safety Oversight (DSMB)

The study has approval from the IRB at UT Southwestern which will oversee the study for Parkland Health and Hospital Systems and ProHealth of Connecticut. There is also IRB approval from the from the Texas Health Resources IRB and the North Texas VA IRB. NIDDK has constituted a DSMB that will review and approve final study protocol, address any major changes in protocol and have ultimate authority to halt the study according to the concerns detailed in Section 9.5.

10. Clinical Monitoring

10.1 Site Monitoring Plan

There will be several levels of monitoring in the study. Members of the study team will monitor the four healthcare systems to ensure compliance with human subject protection, study procedures, and interventions. There will be an initial site visit for each healthcare system for training and assurance of compliance. Practice facilitators at each site will report patient enrollment and intervention for eligible patients every three months. Pieces will monitor interventions provided to eligible patients and progress towards achievement of enrollment targets and implementation of interventions. In addition to capture of events from the EHR, the study team will review the records involving enrollment and adherence to protocol outcomes and safety events for the first 100 patients enrolled from each healthcare system as well as a minimum of 10 patients every 3 months. There will also be similar review of the first 10 patients enrolled from every participating study site (cluster) in each healthcare system. We will also verify the functionality of the clinical decision support system by reviewing a sample of patients enrolled in the study from each site every quarter.

11. Statistical Considerations

11.1 Study Hypothesis:

It is hypothesized that the PIECES-based interventions can reduce one-year (12 months) unplanned all-cause hospitalizations for patients with a triad of CKD, diabetes and hypertension.

Study Design:

A prospective stratified cluster randomization design will be employed. Patients are clustered by clinics, which are stratified by healthcare systems, and randomly allocated to either the PIECES-based intervention or a control (standard medical care) group using a randomized permutation block within each stratum. Based on assignment of his or her clinic, each patient will be assigned either to the Pieces group or a standard medical care group. Stratified randomization log will be created using SAS PROC PLAN with variable block sizes.

11.2 Sample size consideration:

We determined sample size based on the comparison of one-year unplanned all-cause hospitalization rates between the control and PIECES-based intervention groups.

The sample size formula developed by Donner [64] for stratified randomized trials was employed. From preliminary data we observe that the rate of unplanned all-cause hospitalization during the 1-year follow-up period is 14% across all four large health care systems in standard medical care group. We expect that the hospitalization rate in PIECES group will be 3% lower than that in the standard medical care group. Electronic health records show that the number of patients with coexistent CKD, hypertension and diabetes are 4,419, 4,738, 4,175 and 1,093 in Parkland, Texas Health Resources, ProHealth, and VA North Texas, respectively. The numbers of clinics are 25, 40, 50, and 9 in Parkland, Texas Health Resources, ProHealth, and VA North Texas, respectively. From a preliminary dataset extracted from

Parkland Healthcare System and THR Healthcare System, we obtained an intracluster correlation coefficient (ICC) of 0.015.

If we assumed ICC = 0.015 to detect a 3% difference in the rate of unplanned all-cause hospitalization, a total of 10,991 patients are needed to achieve 80% power at a two-sided 5% significance level. We would need to enroll 3,367, 3,610, 3,181, and 833 patients from Parkland, THR, ProHealth, and VA North Texas, respectively. Here, 10,991 patients are 76.2% of 14,425 patients from the 4 healthcare systems participating in the study. Waiver of consent has been obtained from all IRBs overseeing the study and no informed consent will be obtained from patients. There is an opt-out option available for patients in the implementation and in the control groups and based on the nature of the interventions a small number of opt-out requests is expected. Additional practice sites/ clinics will be available at 3 of the 4 participating health care systems as enrollment sites for additional patients if required in the future.

11.3 Statistical Analysis Plan:

Standard descriptive analysis will be performed where we summarize continuous variables by mean and standard deviation, and categorical variables by count and percentage. The one-year unplanned all-cause hospitalization rates will be compared using the generalized Mantel-Haenszel procedure as presented by Donner [64], which is suitably adjusted for clustering. Furthermore, we will use generalized linear mixed model (GLMM) to examine if there is a significant difference in hospitalization rates between two intervention groups after controlling for potential confounding patient, clinician and clinic factors. The mixed model includes clinic random effects to account for within-cluster correlation. Univariate mixed models will be employed to assess the marginal association between the outcome and individual covariates. The final multivariate model will include covariates identified by the stepwise variable selection procedure as well as those considered to be clinically important a *priori*. Similar analysis will be performed to compare the rates of disease-specific hospitalization. As secondary analyses, the Kaplan-Meier plots will be generated to explore the difference in time to hospitalization between the two arms. Cox models with frailty will be implemented to evaluate the treatment effect on the event times of hospitalization, CV, and death events, controlling for confounding factors. Random effects for clinics are also included. Similar strategy of univariate and stepwise variable selection procedure in mixed model will be implemented to the Cox models with frailty. Statistical significance will be reported for p-value<0.05. All statistical analyses are performed using statistical software SAS 9.4 (SAS Institute, NC, Gary).

To construct and evaluate predictive models for unplanned all-cause hospitalizations, disease-specific hospitalizations, 30-day readmissions, cardiovascular events and deaths, the total cohort will be randomly separated into derivation and validation datasets (2/3 and 1/3 sample, respectively). Based on the derivation set, we will select independent variables with p-value<0.20 from univariate analysis as candidate variables for multivariate analysis. We will explore possible contributions to models from interactions of independent variables and from splines, transformations, and recursive partitioning for continuous variables. We will use the stepwise variable selection procedure on generalized linear mixed model (GLMM) to identify variables that are significantly associated with outcome variables such as hospitalization, 30 day readmissions, cardiovascular events and deaths. The goodness of fit criteria and the Bayes Information Criterion (BIC) will be used for model selection.

The resulting model will be externally validated based on the validation dataset. We will evaluate calibration through the Hosmer-Lemeshow test; we will measure discrimination by the

c-statistic, the area under the curve (AUC) for the receiver operating characteristic (ROC) curve and by the range of predicted risks. We will divide the patients into five groups based on the quintiles of their predicted risk by the model. We will compare the true event rate among the quintile groups to examine how well the predictive model separate patients at different levels of risk.

12. Source Documents and Access to Source Data/Documents

The main source of data will be through Pieces extraction of patient data from the EHRs of all study sites. Only the PI and study team members who are HIPAA certified will have access to this data. The data will be de-identified before transfer to the statistical team for analysis. Other sources of data is readmission data from the DFW Hospital Council, Pro Health databases and VA of North Texas databases/information.

13. Quality Control and Quality Assurance

13.1 Development of MOP and Training

The main thrust of our quality control and assurance program is to prepare a comprehensive manual of operation with sections specific to each study site and train study site staff in its operations. Study site personnel to be trained are the site PI, the Practice Facilitator and Primary Care Providers at each clinic. The site PI will provide oversight to the conduct of the study at their institution, responsible for recruitment of appropriate staff to serve as Practice Facilitator and engaging PCPs in the clinics randomized to study group. The Practice Facilitator will receive the list of eligible patients along with their PCPs to ensure that the patients are enrolled into the study and provided recommended care through triggering of the Smart Set and following protocol. The PCPs will be primarily responsible for providing recommended care to their eligible patients and determine the level of care for each patient. Training will provided to these staff by members in person meetings, web-based training and the manual of operation that outlines their expected roles, clinical workflow, opt-out consent and patient follow up. A refresher training course will be provided every three months to ensure compliance with the manual of operations.

13.2 Site Visit

We will develop a timetable to visit the clinics in the study group at least one time per year to observe the clinical workflow and adherence to the MOP. Other visits may occur if requested by clinic staff or if there are concerns with study performance

13.3 Pieces Functionality

We will assure the functionality of our decision support systems software by verifying with each site a sample of patients identified with CKD, Diabetes and Hypertension at the beginning of the implementation period and quarterly thereafter.

13.4 Monitoring Data Quality

The quality of data received from all sites will be reviewed and verified at beginning of the implementation phase and monthly thereafter to ensure problems are identified and corrected in a timely manner

13.5 Routine Progress Reports

We will prepare a monthly progress for each site to include the following:

1. Screening, Recruitment, enrollment and retention
2. Protocol compliance
3. Data quality reports - describe missing, erroneous, and inconsistent data to ensure protocol is followed and deviations are tracked
4. Site monitoring results

14. Ethics/Protection of Human Subjects

14.1 Ethical Standards

This study will follow the highest level of ethical standards. All study staff will be required to train and certify in human subject protection

14.2 Institutional Review Board

The final study protocol will be submitted to UTSW, THR and VA North Texas IRBs for review and approval. Patient recruitment will not occur until the study has been approved by the various IRB. UTSW IRB will serve as the review body for Parkland and ProHealth of Connecticut HCS. Protocol amendments and changes will be submitted to all IRBs and approval must be received prior to implementation.

14.3 Informed Consent Process

This pragmatic clinical trial will offer an opt-out option for any eligible patients in either control or intervention groups. There will be no formal informed consent obtained from each individual patient. The rationale for waiver of informed consent has been carefully reviewed and presented to the IRBs overseeing the study as well as to the federal agencies overseeing the study. The research involves minimal risk to subjects. Both groups including control (standard care group) and intervention will have access to recommended best therapies for treatment of CKD, diabetes and hypertension. In both groups the primary care provider will have the final say on what interventions are implemented for the care of CKD, diabetes and hypertension for their individual patients. The waiver of informed consent will not adversely affect the rights and welfare of participating subjects. This pragmatic trial cannot be performed at all participating

healthcare systems and practice sites without the waiver. As there will be several thousand patients enrolled it would not be logistically possible for coordinators to address the geographic and time limitations to obtain consent from such a large number of participants as to make the trial possible. The risks to patient privacy and data security will be carefully addressed with multiple safeguards as detailed in Section 15 Data Management and Responsibilities. Study subjects will be notified of findings at completion of the study.

As previously mentioned, patients who are in clinics randomized to either control group or intervention group will have an option to opt-out of the study and use of any of their health information. The goal is to give all potential patients the opportunity to know that the study will be carried in their healthcare system and to have the opportunity to decide if they want to participate and if they will allow for their data to be used in the study. Participants will be made aware of the study through various forms including posters and handouts and other media in clinics describing that the study aims to improve care of patients with CKD, diabetes and hypertension by assisting primary care providers to implement the best practices for their care. There will be reference to a phone number and a link to the collaboratory website specific to ICD-PIECES so that patients can obtain as much detail as they need to make an informed decision. If a patient does use the opt-out mechanism, the research team will document and track the instances for those patients to remain outside of the study interventions or use of any of their specific data.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

This study will be conducted in all adults 18-85 years attending the outpatient clinics of the participating Health Care Systems

14.5 Subject Confidentiality

All patient data will be maintained in a secure location. Study data to be obtained will be part of standard information available in the EHR. Access to study data in the EHR, PIECES and study databases for data collection and analysis at UTSW and PHHS will be limited to study personnel and password protected.

14.6 Study Discontinuation

Study participation can be discontinued at any time by patients or their PCPs.

14.7 Future Use of Study Specimens

There will be no study specimens collected for this study. Data will be collected and stored securely. De-identified data will be available for future use as per NIH policies.

15. Data Handling and Record Keeping
Informatics Section

15.1 Data Collection

Data capture will be aggregated on a central cloud based (Software-as-a Service) SaaS platform hosting the Pieces ™ software. Flat file transfer via SFTP will occur and HL7 based data integration will occur with a site specific selection of the best method to transmit data centrally. In the instance that external approval of data transfer cannot occur, a process of locally matching patient selection criteria on software server with a local firewall will be implemented with a process to allow deidentified data to the SaaS server will be implemented. Access to the central server will be restricted using Secure VPN tunnel with two factor authorization. The Secure Cloud Hosting Environment will be FISMA (**Federal Information Security Management Act of 2002**) compliant.

Hospitalization and Death Outcome Data:

Data requests by the National Association for Public Health Statistics and Information Systems (NAPHSIS) Death index information from the CDC will be obtained after completion of IRB submission for approval and then performed at the termination of the study a single time to obtain death outcomes after enrollment and follow up of planned time period for augmentation of EHR stored death date and death status of inpatient discharge to ascertain mortality outcomes.

Master Patient Index matching to a shared Dallas Fort Worth Hospital Council data set will occur for the THR and PHHS site using the REMPI match system to obtain inpatient hospitalization events throughout the Dallas-Fort Worth area. Patient outcomes within the outside of the Veterans Affairs System will occur with an additional research effort to assess the

feasibility of patient patching between the Veterans Affairs patient index and the DFWHC data to provide additional hospitalization events for veterans outside the VHANTX system.

15.2 Data Management and Reports

Encrypted computers stored in physical secured premise. Patient cohort selection criteria will be preserved in PheKB platform and publically available after the completion of the grant (https://phekb.org/). Snapshots of the data elements constituting candidate identification and confirmation will be stored for all patients meeting the candidate definition.

Formats RDBMS using MySQL or Sql Server environment configured to support the data model with access controls overseen by a PCCI Security officer. Deidentified final registry data sets with Safe harbor HIPAA data elements removed will be provided to the final statistics team performing predictive modeling for Aim 3 and final analysis of the planned analysis.

Data aggregation by assigned data analyst from the PCCI under terms of executed Business Associates Agreements between the parties to the grant. Analytic file extracts from the RDBMS will be exported as .csv or tab delimited txt files for additional analysis. Quality Assurance reports will evaluate the distribution and frequency of mapped data elements and validation of the final mapping of the Pieces ™ data model will be confirmed with the site coordinators. Periodic reporting on the number of candidate patients per site will be reviewed at least quarterly to monitor for target patient identification consistent with expected patient volumes from power calculations and available on request to the Data Safety Monitoring Board.

Server Data will be backed up on mirrored virtual machines within a partitioned cloud server environment with disaster recovery. RDMBS scripts, stored procedures and Pieces ™ platform executables related will be versioned control using Subversion as will data exports to the analytic teams.

DATA VALIDATION:

Annual review of value sets update form the VSAC and HEDIS will be performed to test for the impact of newly released medications or laboratory mappings. Unexpected drop offs in patient identification will also prompt analyst review of site data. Data model and queries will be stored in version control software. Data mappings for the patient selection criteria will undergo dual analyst review with an investigator and site specific revisions will undergo review with the local site investigator. Medication mappings will be explicitly reviewed for name based mappings to target list and route of administration. For example, if an NDC medication code for a blood pressure medication from the current release of RxNorm maps to an inappropriate medication (say an estrogen), inappropriate medications will be removed from final cohort selection. Laboratory values for LOINC mapped labs will be reviewed for name matching, specimen source and that diagnostic results are in expected ranges by mean, median, maximum, and minimum tables and histograms. Non-numeric text values will be reviewed to generate interpretative keys for all sites with periodic review for text values not mapping to the interpretive key table. For example, if out of range labs reporting changes for HgbA1c from '>12.1' to '>12.3', new text values not seen during the validation phase will be flagged for analyst review. ICD10 conversation dates will be tracked for all institutions and ICD10 crosswalks for inclusion.

Data transfers to federated data store in Pieces system

Data files will be transferred from participating sites via secure FTP at least once weekly to a central database using a standard data model. Local copies of the same data model will be allowed where necessary for data security approvals of participating institutions with entirely local versions of the data model within the VA Internet Firewall planned for initiation of trial activity to expedite information security and privacy concerns. Identical query logic will be used to identify patients on local copies of the Pieces data model. Federated Data Systems using the Pieces system to store research data and perform uniform selection logic. Minimal data transformation steps necessary to standardized date/time formatting and import of data with minimal transformations.

As a condition of the data use agreements signed with ProHealth Physicians, individual elements of the Safe Harbor elements of PHI are encrypted before transmission until they are needed for final data sets linkages for outcome standardization to maximize patient privacy and minimize data loss risk. As a result the data base of candidate and confirmed patients will be mirrored on the ProHealth Corporate Data ware house to allow subsequent on premises identification and generation of worklists.

Data transfers from Pieces system to participating sites

Standardized worklists that represent patients will be transmitted to the clinical sites. Patients with a candidate status and upcoming appointments in the subsequent week will be reported to the practice facilitator for additional follow up confirmatory testing to be arranged. An additional report on confirmed patients with planned visits in the coming week will also be transmitted to the sites. Additional reports on candidate or confirmed patients presenting in the prior week, not reported on the prior report due to new interval data or scheduling changes since the time of the prior report will also be transmitted. Where these data transfers can trigger additional provider notification or worklist integration with the local EHR will be permitted as a site specific IT decisions

Intellectual Property related to the Pieces ™ platform is owned by the PCCI. Data definitions and workflows of the cohort selection will be public maintained and associated predictive models for specific aim three will be public released.

Disseminations Methods

Data Sharing Plan and Public Access

We are obliged to share our data within the analytic team of the ICD-Pieces ™ trial. The authors will retain the rights to the deidentifed final data until the trial is completed. Interested parties will be able to download information about the predictive model from the PCCI website.pccipieces.org.

Short term data storage of transfer files will occurred via encrypted drives between password protected encrypted computers.

Roles and Responsibilities

PCCI data analyst

Software:

Statistical analysis planned perform in R Version, Stata MP version

MySQL Server 5.6

Pieces ™ Platform Version 2.0

Deidentification Algorithm

DeID (Nematullah et al)

16. Study Administration

16.1 Study Leadership and Governance

16.1.1 Steering Committee

The Steering Committee will include members of the executive committee, representatives from NIH, representatives from the advisory groups/ cores and the PI from each of the collaborating health care systems. The steering committee will provide direct oversight of ICD-Pieces and set policies and procedures for the study. The steering committee will be the first resource both for planning and implementing strategies and also for receiving information from the study sites. The steering committee will review all study outcomes. During the implementation phase, the steering committee will hold monthly telephone conferences and a face-to-face meeting in Dallas, TX at the beginning of the implementation period and yearly thereafter till the end of the study. PIs at each HCS are Dr. George Oliver at PHHS, Dr. Ferdinand Velasco at THR, Dr. Tom Meehan in ProHealth Physicians, and Dr. Susan Hedayati and Dr. Tyler Miller at VA North Texas Healthcare Systems.

16.1.2 Executive Committee

The Executive Committee will be responsible for all major decisions affecting the study and will provide direction, ongoing review and guide allocation of resources. Members of the Executive Committee will meet face to face or via conference call every 2 weeks or more often if there is need to address new issues before scheduled meetings. The Executive Committee members will be Dr. Vazquez, Dr. Toto and Dr. Oliver Dr. Vazquez, PI is Professor of Medicine at UT Southwestern, Nephrology Chief at Parkland Health and Hospital System and Clinical Director of the Nephrology Division at UT Southwestern. Dr. Robert Toto is Co-Principal Investigator and Professor of Medicine at UT Southwestern, Associate Dean for Translational Science, Director of the Center for Translational Medicine/Clinical Translational Award (CTSA) at UT Southwestern and Director of the Clinical and Translational Core of the George M. O'Brien Kidney Center at UT Southwestern. Dr. Oliver is Vice-President of Clinical Informatics at the

Parkland Center for Clinical Innovation. Dr. Andrew Narva, Program Director of the National Kidney Disease Education Program at NIDDK and Dr. Barbara Wells, Senior Health Services Researcher at NHLBI, provide study oversight and ongoing input on study planning and operations.

16.1.3 Conflict of Interest Policy

The UT Southwestern Office of Research Compliance conflict of interest policy is in compliance with the PHS regulation (42 C.F.R. Part 50, Subpart F).

16.2 Subcommittees

16.2.1 Technical Workgroup

The technical workgroup is led by Dr. George “Holt’ Oliver, VP of Clinical Informatics at PCCI is responsible for the technical design of the study, including mapping and deployment of the Pieces software to the study sites. Dr. Oliver is working with the IT staff from all study sites on this effort. Dr. Brett Moran, Professor of Medicine at UTSW and Chief of Health Information Management at PHHS serves as expert on use of EHR for the study.

16.2.2 Biostatistics and Research Design Core

Dr. Chul Ahn, Professor of Clinical Sciences and Director Biostatistics and Research Design Core, directs the Biostatistics and Research Design Core. Dr. Song Zhang, Associate Professor of Clinical Sciences, also works directly with ICD-Pieces. Dr. Ahn has over 380 peer-reviewed publications including new strategies for cluster randomization and has led design and analysis of multicenter clinical trials and studies on health services. Dr. Ahn and Dr. Zhang will be providing expertise with trial design, data collection/management and study analysis.

16.2.3 Diabetes Advisory Workgroup

Dr. Perry Bickel, Associate Professor of Medicine and Chief, Division of Endocrinology at UT

Southwestern, leads the Diabetes Advisory Group to provide expert input for diabetes management strategies. Dr. Bickel and his group have initiated efforts to use electronic health technology to improve inpatient and outpatient diabetes management at Parkland

16.2.4 Evaluation Workgroup

The steering committee will provide oversight on primary care practices and assessments of patient and provider satisfaction.

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Appendix I: CHRONIC KIDNEY DISEASE (CKD) HYPERTENSION MANAGEMENT PROTOCOL

This protocol will be initiated as directed by CHRONIC KIDNEY DISEASE (CKD) CHRONIC DISEASE MANAGEMENT PROTOCOL.

Protocol will be reviewed every year.

RN will perform protocol with assistance from PA or NP at same clinical site.

PA or NP may suggest deviations from protocol as deemed clinically appropriate.

Orders (except medication orders) will be placed by RN in electronic medical record using "per protocol" order mode with physician, PA or NP as authorizing provider. Medication orders may be routed to provider as suggested per protocol, but medication and dose will ultimately be selected and ordered by provider. After medication orders are finalized by provider, RN will notify patient of final decision.

Goals/Background

1. Chronic Kidney Disease (CKD) is defined as (for the purposes of this protocol):
    a. Glomerular Filtration Rate (GFR) < 60 mL/min
    b. Or presence of proteinuria, defined as any one of the following:
        i. Random Urine Protein/Creatinine Ratio > 200 mg/g
        ii. Random Urine Microalbumin/Creatinine Ratio > 30 mg/g
        iii. 24 hour Urine Protein > 150mg
        iv. Urine dipstick protein (adjusted for specific gravity)
2. Blood pressure (BP) goals
    a. For patients with CKD goal blood pressure is Systolic (SBP) < 140 mmHg AND Diastolic (DBP) < 90 mmHg

3. ACEi/ARB
    a. All patients with chronic kidney disease (with or without proteinuria) should be treated with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).
    b. Recommended ACEi: lisinopril
        i. Starting dose 5mg once daily if GFR > 10 mL/min or 2.5mg if GFR <1= 10mL/min
        ii. Maximum dose 40mg once daily
        iii. Class-specific considerations. Be aware of these potential adverse effects when conduction follow-up of initiation or titration of this medication (details on the follow-up process are below).
            1. Elevated potassium (hyperkalemia)
            2. Reduction in kidney function (increase in creatinine or decrease in GFR)
            3. Dry cough

4. Facial swelling (angioedema)

c. Recommended ARB: losartan
   i. Starting dose 25mg once daily
   ii. Maximum dose 100mg once daily
   iii. Class-specific considerations. Be aware of these potential adverse effects when conduction follow-up of initiation or titration of this medication (details on the follow-up process are below).
      1. Hyperkalemia
      2. Reduction in kidney function (increase in creatinine or decrease in glomerular filtration rate)
      3. Very rarely causes dry cough
      4. Facial swelling (angioederria)

RN BP ASSESSMENT

1. RN BP Assessment Visit
   a. Pre-Visit Planning: perform 1-2 weeks prior to appointment.
      i. Call patient
         1. Request patient bring all pill bottles to appointment.
         2. If patient has home blood pressure device, ask patient to bring home device and written home blood pressure log (after checking blood pressure twice daily for 1 week) to appointment.
      ii. GFR Assessment
         1. Review prior labs in "Results Review".
         2. Review last potassium, creatinine and glomerular filtration rate (GFR) in last 6 months.
         3. If all present within 6 months, no further action needed for GFR assessment.
         4. If no creatinine and GFR in last 6 months, order "CREATININE with-GFR.
         5. If no potassium in last 6 months, "POTASSIUM LEVEL".
         6. Compare most recent GFR with second most recent GFR. If most recent GFR is > 20% lower, discuss with provider.
         7. If GFR < 60 but >/= 30, update problem list to include "CKD Stage 3"
         8. If GFR < 30 but >15, update problem list to include "CKD Stage 4".
         9. If GFR < 15, update problem list to include "CKD Stage 5"
      iii. Proteinuria Assessment
         1. Review prior urine protein testing in "Results Review" for following results in last 1 year:
            a. Microalbumin/Creatinine Ratio, Urine, Random
            b. Protein, Urine and Creatinine, Urine (both are required as ratio must be calculated manually by dividing urine

protein by urine creatinine).

c. Protein, 24 hour, Urine
d. Urine dipstick protein (adjusted for specific gravity)

2. If labs are present in last year, no further action is needed for Proteinuria Assessment.
3. If none are available, order MICROALBUMIN/CREATININE RATIO

NOTE: "Unable to calculate" for Microalbumin/Creatinine Ratio implies zero protein present in urine.

b. Assessment of BP goal
Goal blood pressure is SBP < 140 mmHg AND DBP < 90 mmHg.

c. Provide education annually on non-pharmacologic management of hypertension.
   i. Low Sodium Diet
      1. Discuss with patient importance of low sodium diet included no added salt as well as checking labels for processed foods.
      2. Provide patient with Exit Care SmartText in Patient Instructions: DIET-2 GRAM LOW SODIUM (choose appropriate language).
      3. Refer to nutrition at same clinical site for further counseling as needed.
   ii. Avoidance of daily use of non-steroidal anti-inflammatory drugs (NSAIDs).
      1. Discuss with patient that NSAIDs (included ibuprofen and naproxen) can increase blood pressure as well as cause further kidney damage.
      2. Discuss with provider as needed to identify alternatives to daily NSAIDs.
   iii. Moderation of alcohol (less than 2 servings per day).
      1. Discuss with patient that daily alcohol consumption can raise blood pressure.
      2. If needed, provide patient with Exit Care SmartText in Patient Instructions: ALCOHOL AND DRUG ABUSE (choose appropriate language).
      3. Refer for substance abuse counseling as needed.
   iv. Importance of exercise > 3 days per week.
      1. Discuss with patient that regular exercise can lower blood pressure.
      2. Provide patient with Exit Care SmartText in Patient Instructions: PKAMB OPC EXERCISE TO LOSE WEIGHT
   v. Abstinence from nicotine products.
      1. Discuss with patient that all nicotine products can raise blood pressure.
      2. If active smoker, perform 'Ready to Quit' assessment in social history section Epic and refer to Smoking Cessation Clinic if

patient is ready to quit.

3. Provide patient with Exit Care SmartText in Patient Instructions: SMOKING CESSATION (choose appropriate language).

vi. Maintenance of optimal weight is body mass index (BMI) 20.0 to 25.0.

1. Discuss with patient that maintenance of normal BMI can improve blood pressure.
2. If BMI > 25.0
   (a) Provide patient with both of following Exit Care SmartText in Patient Instructions: DIET—CALORIE COUNTING (choose appropriate language) and DIET— LOW-FAT, LOW-SATURATEDFAT, LOW-CHOLESTEROL DIETS (choose appropriate language)
3. Refer to nutrition at same clinical site as needed for dietary counseling.

vii. Avoidance of daily use of over-the-counter decongestants (pseudoephedrine or phenylephrine).

1. Discuss with patient that prolonged use of decongestants can raise blood pressure.
2. Discuss with provider as needed for alternatives to decongestants for control of symptoms.

viii. RN Blood Pressure Assessment: Ask patient about missed doses of BP medications in last 24 hours. If any missed doses, reschedule BP measurement 1-2 weeks after improved adherence. Ask patient about use of nicotine products. Wait 30 minutes after last use before measuring blood pressure. Measure and record blood pressure according to JNC 8 standards: After patient has sat quietly for 5 minutes in chair, measure with arm supported at heart level and with legs uncrossed and feet on the floor. Obtain at least two measurements and record the average of the two —sum of systolic values divided by 2 and sum of diastolic values divided by 2. (See Page number 4 (which is page 20 of 52 including introductory section) of the following link for full details: http://www.nhibi.nih.goviguidelines/hynertension/exnress.bdf).

1. "RN BP measurement" below refers to average calculated as above per JNC 8 guidelines.
2. If patient does not have written home blood pressure log and RN BP measurement is > 140 mmHg systolic or > 90 mmHg diastolic, initiate CKDHYPERTENSION PROTOCOL and perform at this visit.
3. If patient does not have written home blood pressure log, and RN BP measurement systolic < 140 mmHg AND diastolic < 90 mmHg, no further action is necessary.
4. Home Blood Pressure Device Validation
   a If patient provides written home blood pressure log, review documentation in overview section of CKD diagnosis in problem list for date of last blood pressure device validation.

i. If validation in < 1 year, proceed to "Home Blood Pressure Log Review".
ii. If no validation in > 1 year and patient did not bring home blood pressure device, then schedule follow-up appointment in 1-2 weeks with RN. Ask patient to provide new written blood pressure log and bring home blood pressure device to appointment for comparison with RN measurement.
iii. If no validation in > 1 year and patient brings home blood pressure device, obtain measurement from home blood pressure device.
    1. Ask patient to demonstrate proper use of device and provide education as needed according to JNC 8 guidelines above.
    2. If difference > 10 mmHg (systolic or diastolic) between home device and RN measurement, disregard home blood pressure log and notify patient that device is not sufficiently accurate. a. Under CKD diagnosis in Problem List, record in Overview section: "Home BP Device Validation [DATE]: home device not consistent with RN measurement."
    3. If difference < 10 mmHg (systolic or diastolic), under CKD diagnosis in Problem List, record in Overview section: "Home BP Device Validation [DATE]: home device validated as consistent with RN measurement" and proceed to "Home Blood Pressure Log Review".

5. <u>Home Blood Pressure Log Review</u>
    a If BP cuff is validated as above and home BP log is used in clinical decision-making, log should be scanned into Epic.
    b Calculate average of seven most recent systolic and diastolic values (i.e. sum of seven most recent systolic values divided by 7; and sum of seven most recent diastolic values divided by 7).
    c If average systolic > 140 mmHg or average diastolic > 90 mmHg, initiate CKD HYPERTENSION PROTOCOL and perform at this visit.
    d If average systolic < 140 mmHg AND average diastolic < 90 mmHg, no further action is necessary.
    e Consider extenuating circumstances such as acute pain and acute psychological distress. Discuss with provider if you feel such extenuating circumstances are contributing to blood pressure elevation. Consider rescheduling RN BP Assessment Visit in 2-4 weeks to reassess.

f Assess for adverse effects every visit including class-specific considerations above as well as side effects common to many blood pressure medications which include (but are not limited to) lightheadedness and fainting.
   (i) If any new adverse effects, discuss with provider.
   (ii) If no new adverse effects, proceed to BP Medication Adherence Assessment.

g BP Medication Adherence Assessment
   (i) Ask patient about each BP medication and ask, "How many days per week do you forget your [insert BP medication]?"
   (ii) If one day or less, consider adherent by self-report.
   (iii) Review BP medication bottles if available.
   (iv) If medications are filled at Parkland pharmacy, review refill history in Cerner for last 6 months. Consider adherent if obtains within 6 days for a 30 day prescription or within 18 days for a 90 day prescription.
   (v) If not adherent by self-report or refill history, discuss with patient importance of adherence.
      (a.) Reschedule RN BP Assessment Visit in 2 weeks after improved adherence.
      (b.) If patient was deemed non-adherent on two consecutive visits, refer to clinical pharmacist for medication review and assistance with barriers to adherence (cost, complexity, etc).
   (vi) If considered adherent by self-report and refill history, proceed to "Medication Adjustment".

6. Medication Adjustment
   a If patient is already on ACEi or ARB but not at maximum tolerated dose (see above), increase dose to achieve SBP and DBP goal (as per ACEi/ARB PROTOCOL below)
   b If patient is on maximum tolerated dose of ACEi or ARB, proceed to NON ACEi/ARB PROTOCOL.
   c If patient is not on ACEi or ARB, confirm allergies with patient.
   d If no prior allergy or adverse reaction to ACEi or ARB, proceed to ACEi/ARB PROTOCOL.
   e If prior allergy to ACEi is cough, proceed to ACEi/ARB PROTOCOL.
   f If prior allergy or adverse reaction to ACEi or ARB other than cough, consult with provider safety of starting ACEi or ARB.
   g If after discussion with provider, ACEi and ARB are both considered contraindicated, update allergies as needed

and proceed to NON-ACEi/ARB PROTOCOL.

ACEI/ARB PROTOCOL

1. Consider this protocol active until completed.
2. Review "Results Review" for past potassium and creatinine (abbreviated as "Cr" and "K" respectively hereafter). If both are available, no further action is needed. If one or both is not available in last 3 months, order both CREATININE LEVEL and POTASSIUM LEVEL as appropriate (referred to as "Cr/K Check" hereafter).
    a. Lab Results Interpretation
        i. Is K > 4.9?
            1. Yes
                a Discuss with provider before starting or increasing ACEi or ARB.
            2. No
                a If not on ACEi/ARB, and no prior allergy to ACEi or ARB, route pended order to provider for lisinopril 5mg once daily and proceed to "Follow-Up" below.
                b If not on ACEi or ARB and prior cough due to ACEi but no other ACEi or ARB allergy, route pended order to provider for losartan 25mg once daily and proceed to "Follow-Up" below.
                c If already on ACEi or ARB, but not at maximum tolerated dose, increase dose and proceed to "Follow-Up" below.
                d If already on ACEi/ARB at maximum tolerated dose, consider this protocol COMPLETED and proceed to NON-ACEI/ARB PROTOCOL.
                e Follow-Up
                f Schedule RN BP Assessment Visit and Cr/K Check 1-3 weeks following initiation or dose increase. Request patient to have labs drawn prior to appointment.
    b. K Interpretation
        i. Is K > 5.4?
            1. Yes. Discuss with provider stopping ACEI/ARB
            2. No
        ii. 1. Is K > 4.9?
            3. Yes
                a Continue ACEi/ARB at current dose.
                b Provide patient with low potassium diet handout
                c Order repeat POTASSIUM LEVEL in 1 week.
                d If K is not < 5.0 on repeat evaluation, discuss with provider.
                e If K is </= 4.9, proceed to Cr Interpretation.
            4. No - proceed to Cr Interpretation.

c. Serum Creatinine (Cr) Interpretation
    ii. Is Cr >20% higher than value prior to initiation or last increase of ACEi/ARB?
        1. Yes. Discuss with provider decreasing dose by 50% (or stopping if at starting dose). Discuss follow up plan for Cr with provider as well.
        2. No
            (i) Is creatinine within 30% of baseline since initiation?
                (a) No. Discuss with provider decreasing dose by 50% (or stopping if at starting dose). Discuss follow up plan for Cr with provider as well.
                (b) Yes. Proceed to RN BP Assessment.

3. RN BP Assessment
    a. Perform RN BP Assessment as detailed above.
    b. Is BP at goal based on definitions above?
        i. Yes. Continue regimen and schedule RN BP Assessment Visit in 3 months and follow-up with PCP within 6 months.
            1. If BP continues to be at goal in 3 months, this protocol is COMPLETE and can return hypertension management to PCP.
        ii. No
            2. Is ACEi/ARB at maximum tolerated dose?
                (i) Yes. This protocol is COMPLETE. Initiate NON-ACEi/ARB PROTOCOL.
                (ii) No route pended order to provider for double prior dose of current ACE and return to "Follow-Up" above.

NON ACEi/ARB PROTOCOL

1. Discuss with provider selection of next anti-hypertensive protocol.
2. Discuss following medication suggestions with provider. These are only suggestions to guide management, but final selection is at provider's discretion.
    a. If patient has history of myocardial infarction or heart failure, recommend BETA-BLOCKER PROTOCOL.
        i. Recommend carvedilol given dual properties of heart rate reduction (beta blockade) and vasodilation (alpha blockade) and, therefore, typically greater impact on blood pressure.
        ii. Recommended starting dose: carvedilol 6.25mg twice daily.
        iii. Maximum dose: carvedilol 25mg twice daily.
        iv. Class-specific considerations
            1. Low heart rate (bradycardia)
            2. Lower extremity swelling, erectile dysfunction, fatigue.
            3. Exacerbation of asthma or chronic obstructive lung disease symptoms (shortness of breath or wheezing).
    b. If patient is on maximum tolerated beta-blocker or has no history of myocardial infarction or heart failure, recommend DIURETIC PROTOCOL.
        i. For patients with GFR > 30 mL/min, recommend chlorthalidone.
            1. Starting dose 12.5mg once daily.
            2. Maximum dose 25mg once daily. However, dose adjustment is dependent on provider assessment of volume status. All follow-up

evaluations should be discussed with provider.

ii. For patients with GFR < 30, recommend furosemide.
    1. Starting dose 20mg twice daily.
        a. Maximum dose dependent on provider assessment of volume status. All follow-up evaluations should be discussed with provider.

iii. Class-specific considerations
    1. Must counsel patients that diuretics will increase urinary frequency
    2. May worsen prostate symptoms in men.

c. If patient is already on maximum tolerated diuretic and no history of myocardial infarction or heart failure, recommend CALCIUM CHANNEL BLOCKER PROTOCOL.
    i. For patients with proteinuria, recommend non-dihyrdopyridine calcium channel blocker (CCB) verapamil SR as it may help reduce proteinuria.
        1. Recommended starting dose verapamil SR 120mg once daily.
        2. Maximum dose verapamil SR 360mg once daily.
    ii. For patients without proteinuria, dihydropyridine CCB amlodipine may be used.
        1. Recommended starting dose amlodipine 5mg once daily.
        2. Maximum dose amlodipine 10mg once daily.
    iii. Class-specific considerations
        1. Amlodipine may cause increased heart rate (reflex tachycardia).
        2. Verapamil may cause bradycardia and constipation.
           Both may cause lower extremity swelling.

d. If patient is already on maximum tolerated doses of beta-blocker, diuretic and calcium channel blocker, recommend HYDRALAZINE PROTOCOL. i. Hydralazine
    i. Recommended starting dose 10mg three times daily.
    ii. Maximum dose 100mg three times daily.
    iii. Class-specific considerations
        1. May cause reflex tachycardia.

e. If patient is already on maximum tolerated doses of beta-blocker, diuretic and calcium channel blocker and hydralazine, discuss with provider the following:
    i. Referral to Hypertension Clinic.
    ii. Referral to clinical pharmacist for full medication review and assessment of adherence.
    iii. Return management of hypertension to PCP for work-up of secondary hypertension and selection of fifth anti-hypertensive agent.

BETA-BLOCKER PROTOCOL

1. Discuss following medication suggestions with provider. These are only suggestions to guide management, but final selection is at provider's discretion.
2. Perform RN BP Assessment as detailed above.
3. Is BP at goal?
    a. Yes. Continue regimen and schedule RN BP Assessment Visit in 3 months and follow-up with PCP within 6 months.
        i. If BP continues to be at goal in 3 months, can return hypertension management to PCP.

b. No 4 is HR > 60?
    i. Yes. Route pended order to provider for carvedilol 6.25mg twice daily (or alternative beta-blocker as directed by provider) and schedule for "Follow-Up" as detailed below in 2-4 weeks.
    ii. No. Discuss with provider safety of starting beta-blocker or alternatively selection of diuretic, calcium channel blocker or hydralazine protocols.

4. Follow-Up
    a. Perform RN BP Assessment as detailed above in 2-4 weeks.
    b. Is BP at goal?
        i. Yes. Continue regimen and schedule RN **BP** Assessment Visit in 3 months and follow-up with PCP within 6 months.
            1. If BP continues to be at goal in 3 months, can return hypertension management to PCP.
        ii. No. Is HR > 60?
            1. Yes. Is beta-blocker at maximum dose?
                a. No. Route pended order to provider for double prior dose of beta-blocker and schedule for "Follow-Up" as detailed above in 2-4 weeks.
                b. Yes. Return to NON-ACEi/ARB PROTOCOL for selection of next medication.
            2. No. Discuss with provider safety of continuing beta-blocker or selection of diuretic, calcium channel blocker or hydralazine protocols.

DIURETIC PROTOCOL

1. Discuss following medication suggestions with provider. These are only suggestions to guide management, but final selection is at provider's discretion.
2. Perform RN BP Assessment as detailed above.
3. Is BP at goal?
    a. Yes. Continue regimen and schedule RN BP Assessment Visit in 3 months and follow-up with PCP within 6 months.
        i. If BP continues to be at goal in 3 months, can return hypertension management to PCP.
    b. No. Proceed with diuretic selection
4. Diuretic selection
    a. If no K or GFR in last three months then order POTASSIUM LEVEL and CREATININE WITH eGFR in EHR.
        i. Is K > 3.5?
            1. No. Discuss with provider safety of initiation or titration of diuretic or need for potassium supplementation and schedule for "Follow-Up" as detailed below in 2-4 weeks after provider has provided recommendation.
            2. Yes. Is patient already taking diuretic?
                a. Yes. Discuss with provider next choice (consider recommendations below based on GFR) and schedule for "Follow-Up" as detailed below in 2-4 weeks.

b. No. Is GFR > 30?
   (i) Yes. Recommend thiazide diuretic such as chlorthalidone 12.5mg or other diuretic selected by provider and schedule for "Follow-Up" as detailed below in 2-4 weeks.
   (ii) No. Recommend furosemide 20mg twice daily or other diuretic selected by provider and schedule for "Follow-Up" as detailed below in 2-4 weeks.

5. Follow-Up
   a. Schedule RN BP Assessment Visit in 2-4 weeks
   b. Order POTASSIUM LEVEL and CREATININE WITH E-GFR and request patient have labs drawn at least 1 business day prior to visit.
   c. Perform RN BP Assessment as detailed above in 2-4 weeks.
   d. Is K > 3.4?
      i. No. Discuss with provider change in therapy or potassium supplementation. Discuss follow up plan for K with provider as well.
      ii. Yes
         1. Is GFR > 10% lower than last value?
            a Yes. Discuss with provider decrease in diuretic dose or stopping diuretic. Discuss follow up plan for Cr with provider as well.
            b No. Is BP at goal?
               (i) If BP is still not at goal at maximum tolerated dose of diuretic, return to NON-ACEi/ARB PROTOCOL.
               (ii) If BP is still not at goal and not taking chlorthalidone 25mg or maximum tolerated dose of diuretic, then discuss with provider if dose of diuretic should be increased.
               (iii) If provider recommends to increase dose, schedule for "Follow-Up" as detailed above in 2-4 weeks.
               (iv) If provider recommends to not increase dose, return to NON-ACEi/ARB PROTOCOL.

CALCIUM CHANNEL BLOCKER PROTOCOL

1. Discuss following medication suggestions with provider. These are only suggestions to guide management, but final selection is at provider's discretion.
2. Perform RN BP Assessment as detailed above.
3. Is BP at goal?
   a. Yes. Continue regimen and schedule RN BP Assessment Visit in 3 months and follow-up with PCP within 6 months.
      i. If BP continues to be at goal in 3 months, can return hypertension management to PCP.
   b. No. Is patient already taking calcium channel blocker (CCB)?
      i. Yes - Is CCB at maximum dose?
         1 Yes. Return to NON-ACEI/ARB PROTOCOL.
         2 No. Route pended order to provider for double dose of current CCB and schedule for "Follow-Up" as detailed below in 2-4 weeks.
            a No. Does patient have proteinuria as defined above?
            b Yes. Route pended order for verapamil SR 120mg once daily and

proceed to "Follow-Up" below.

c. No. Route pended order for amlodipine 5mg once daily and schedule for "Follow-Up" as detailed below in 2-4 weeks.

4. Follow-Up
   a. Perform RN BP Assessment as detailed above in 2-4 weeks.
   b. Is HR >/= 100?
      i. Yes - discuss with provider
      ii. No. Is BP at goal?
         1 Yes. Continue regimen and schedule RN BP Assessment Visit in 3 months and follow-up with PCP within 6 months.
            a If BP continues to be at goal in 3 months, can return hypertension management to PCP.
         2 No. Is CCB at maximum dose?
            a. No. Route pended order to provider for double dose of current CCB and return to follow-up above.
            b. Yes. Return to NON-ACE i/ARB PROTOCOL.

HYDRALAZINE PROTOCOL

1. Discuss following medication suggestions with provider. These are only suggestions to guide management, but final selection is at provider's discretion.
2. Perform RN BP Assessment as detailed above.
3. Is BP at goal?
   a. Yes. Continue regimen and schedule RN BP Assessment Visit in 3 months and follow-up with PCP within 6 months.
      i. If BP continues to be at goal in 3 months, can return hypertension management to PCP.
   b. No. Route pended order to provider for hydralazine 10rng PO TID. If patient is already taking hydralazine 10mg PO TID, route pended order to provider for dose to 25mg PO TID. If patient is already taking 25mg or more TID, route pended order to provider for double current dose of hydralazine if not at maximum dose. Schedule for "Follow-Up" as detailed below in 2-4 weeks.
4. Follow-Up
   a. Perform RN BP Assessment as detailed above in 2-4 weeks.
   b. is HR >1= 100?
      i. Yes. Discuss with provider
      ii. No. Is BP at goal?
         1. Yes. Continue regimen and schedule RN BP Assessment Visit in 3 months and follow-up with PCP within 6 months.
   c. If BP continues to be at goal in 3 months, can return hypertension management to PCP.
   d. No. Is hydralazine at maximum dose?
      i. No. Route pended order to provider for double current dose of hydralazine and return to follow-up above.
      ii. Yes. Return to NON-ACEi/ARB PROTOCOL.

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Appendix II: DIABETES MANAGEMENT PROTOCOL

Goals:

The goal of this protocol is to assist primary care providers in delivering diabetes care to patients with CKD, type 2 diabetes, and hypertension. This protocol focuses on safely achieving targets for blood glucose control that are tailored to each individual based on the factors listed below and in the context of an overall care plan that promotes reduction of cardiovascular risk factors.

- Duration of diabetes
- Remaining life expectancy
- Presence and severity of microvascular complications, such as
    - Retinopathy
    - Albuminuria
    - Neuropathy
- Presence and severity of major active co-morbidities, such as
    - Coronary artery disease
    - Chronic obstructive pulmonary disease
    - Chronic kidney disease
    - Chronic liver disease
    - Recent stroke
    - Life-threatening malignancy
- Risk for severe hypoglycemia
- Financial resources
- Patient factors that affect adherence, such as motivation, family support, and insight

The short-term benefits of improving poor glucose control include the resolution of symptoms (polyuria, polydipsia, polyphagia, unintended weight loss) and the avoidance of volume depletion due to excessive glycosuria, which is especially dangerous in the elderly and those at risk for acute kidney injury, and of excessive catabolism resulting in weight loss and ketosis. Long-term benefits include reduced risk of the development or progression of the microvascular complications of diabetes, including retinopathy, nephropathy, and neuropathy.

The risks of tighter glucose control include the requirement of increased glucose self-monitoring (cost and inconvenience) and of hypoglycemia. Iatrogenic hypoglycemia is a major patient safety issue, especially in those who have blunted or absent hypoglycemia awareness and those with coronary artery disease.

Thus, for each patient, goals for glucose control must be individualized based on the degree of achievable benefit and the degree of acceptable risk. The figure below from the American Diabetes Association Position Statement on Glycemic Targets visually summarizes this risk-benefit consideration.

Protocol Figure 1

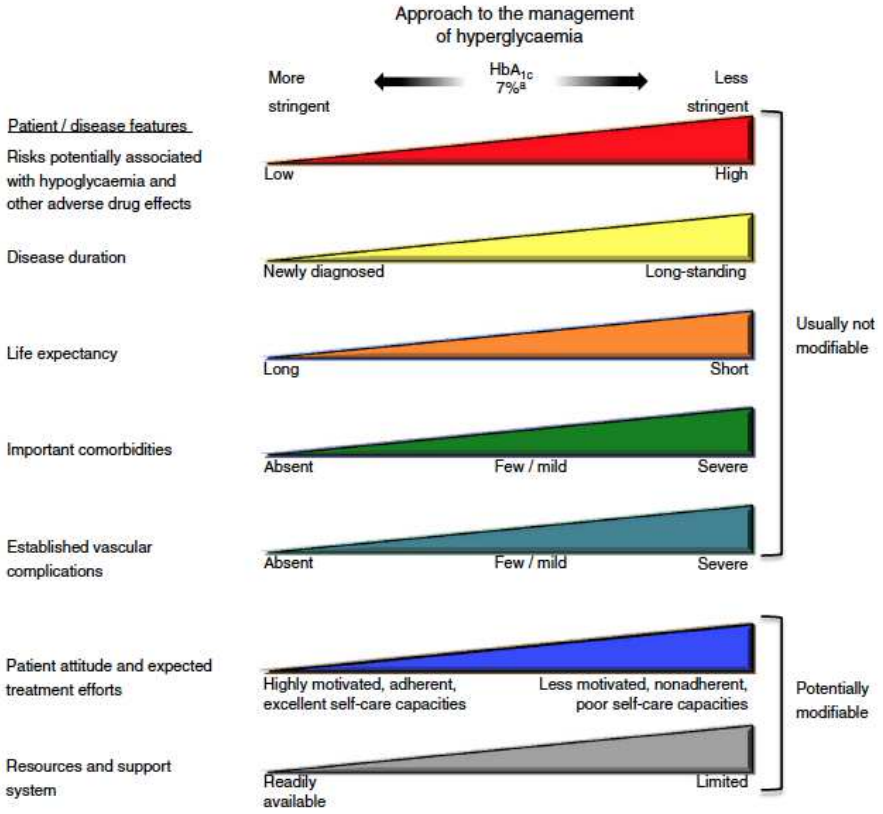

Fig. 1 Modulation of the intensiveness of glucose lowering in type 2 diabetes. Depiction of patient and disease factors that may be used by the practitioner to determine optimal HbA_{1c} targets in patients with type 2 diabetes. Greater concerns regarding a particular domain are represented by increasing height of the corresponding ramp. Thus, characteristics/predicaments toward the left justify more stringent efforts to lower HbA_{1c}, whereas those toward the right suggest (indeed, sometimes mandate) less stringent efforts. Where possible, such decisions should be made with the patient, reflecting his or her preferences, needs and values. This 'scale' is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision-making. Based on an original figure by Ismail-Beigi et al [59]. [a]HbA_{1c} 7%=53 mmol/mol

Protocol Figure 1. From Inzucchi SE et al. *Diabetologia* (2015) 58:434

The decision about what glucose control target to aim for in a given patient at a given time must take into account multiple factors that cannot be fully protocolized. *In striving to reduce the long-term risks of microvascular complications, it is important to remember that hypoglycemia, if severe and prolonged, may result in seizure, coma and death in the short-term.* Even mild hypoglycemia in someone driving a motor vehicle, for example, may result in significant harm to the patient and to others. The elderly are particularly at risk for falls resulting from hypoglycemia.

Monitoring Glucose Control: the Hemoglobin A1C (A1C)

Methods for monitoring glucose control include self-monitoring with glucose meters, continuous glucose monitors, and the hemoglobin A1C. For type 2 diabetes in non-insulin treated patients, the most pragmatic basis for making changes in therapy is the A1C, because it integrates glucose control over 2-3 months. Some caveats are necessary to recognize. First, A1C measurements may be falsely reduced in cases of shortened RBC lifespan, blood transfusions and hemolysis. Second, renal dysfunction and/or dialysis may complicate the relationship between A1C and glucose levels, so it is important to examine the patient's blood glucose logbook to assess glucose control by an independent method. In general, the A1C should be measured twice yearly in patients who are at goal and every 3 months in those who are adjusting their therapeutic regimen.

Hypoglycemia and the Rule of 15

At each visit, patients should be asked if they are experiencing symptomatic or asymptomatic hypoglycemia. Each patient should demonstrate knowledge of the symptoms of hypoglycemia and how to treat hypoglycemia. 15-20 grams of pure glucose is the preferred method of treatment for hypoglycemia (BG <70 mg/dl). The patient should repeat treatment with 15-20 grams of glucose every 15 minutes until their self-monitored blood sugar is above 70 mg/dl (Rule of 15). After the blood sugar reaches over 70 mg/dl, the patient should eat a meal within one hour or eat a snack to prevent recurrence of hypoglycemia.

Setting Glucose Control Targets Based on the A1C

Guidelines have been proposed for appropriate A1C targets based on the considerations described above.

The Kidney Disease Outcomes Quality Initiative (KDOQI) published in 2012 guidelines for the management of hyperglycemia and general diabetes care in CKD.

- KDOQI Guideline 2.1 recommends "a target HbA1c of ~7.0% to prevent or delay progression of the microvascular complications of diabetes, including DKD" (diabetic kidney disease).
- KDOQI Guideline 2.2 recommends "not treating to an HbA1c target of <7.0% in patients at risk of hypoglycemia."
- KDOQI Guideline 2.3 suggests "that target HbA1c be extended above 7.0% in individuals with co-morbidities or limited life expectancy and risk of hypoglycemia."

The VA Clinical Practice Guidelines for the Management of Diabetes Mellitus suggest glucose control target ranges based on major comorbidities, life expectancy, and the presence/severity of microvascular complications. See Protocol Table 1.

Protocol Table 1

Table G-1. Determination of Target HbA_1c Level (1) (2)

Major Comorbidity (d) or Physiologic Age	Microvascular Complications		
	Absent or Mild (a)	Moderate (b)	Advanced (c)
Absent >10 years of life expectancy	<7%	<8%	8-9% *
Present (e) 5 to 10 years of life expectancy	<8 %	<8%	8-9% *
Marked (f) <5 years of life expectancy	8-9% *	8-9% *	8-9% *

(1) Based upon the DCCT referent standard. Clinicians need to evaluate the methodology used at their site.

(2) Reflects a "goal" over time. Intensification of therapy should be undertaken based upon individual clinical circumstances and treatment option.

(a) Mild microvascular disease is defined by early background retinopathy, and/or microalbuminuria, and/or mild neuropathy.

(b) Moderate microvascular disease is defined by pre-proliferative (without severe hemorrhage, intra-retinal microvascular anomalies [IRMA], or venous bleeding) retinopathy or persistent, fixed proteinuria (macroalbuminuria) and/or demonstrable peripheral neuropathy (sensory loss).

(c) Advanced microvascular disease is defined by severe non-proliferative (with severe hemorrhage, IRMA, or venous bleeding), or proliferative retinopathy and/or renal insufficiency (serum creatinine level > 2.0 mg/dL), and/or insensate extremities or autonomic neuropathy (e.g., gastroparesis, impaired sweating, or orthostatic hypotension).

(d) Major comorbidity includes, but is not limited to, any or several of the following active conditions: significant cardiovascular disease, severe chronic kidney disease, severe chronic obstructive pulmonary disease, severe chronic liver disease, recent stroke, and life-threatening malignancy.

(e) Major co-morbidity is present, but is not end-stage and management achievable.

(f) Major co-morbidity is present and is either end-stage or management is significantly challenging.

* Further reductions may be appropriate, balancing safety and tolerability of therapy.

Protocol Table 1: From VA/DoD Clinical Practice Guideline, Management of Diabetes Mellitus, 2010, p. 49.

As eGFR declines below 60 ml/min/1.73 m^2, the risk of hypoglycemia increases. Thus, it is important to reassess glucose control targets in the setting of declining renal function. The American Diabetes Association Consensus Conference on Diabetic Kidney Disease (2014) has recommended the **A1C goal of <8% when GFR <60 ml/min/1.73 m^2** due to the increased risk of hypoglycemia.

Any target chosen for a given patient must be revised upward in the face of frequent or dangerous hypoglycemia, as well as the development of hypoglycemia unawareness. On the other hand, a more aggressive goal of <6.5%, if achieved without significant hypoglycemia, may be appropriate in "early-onset diabetes in younger patients" (Tuttle et al., 2014).

General Guidelines for Antidiabetic Medications

- Metformin, which reduces liver glucose production, is usually the first line treatment for type 2 diabetes in those for whom it is not contraindicated and who tolerate it
    - Advantages include low risk of hypoglycemia, no weight gain, and low cost
    - Long history as safe and effective
    - May reduce risk for cardiovascular events (UKPDS)
- If glycemic goals have not been reached after 3 months of therapy, adding additional oral antidiabetes medications should be guided by patient-centered considerations.
    - Refer to Protocol Figure 2 for a schematic guide to dual and triple therapy
    - In patients with type 2 diabetes who have little remaining beta cell function, insulin therapy is usually required. Refer to Protocol Figure 3 for a schematic approach to initiating insulin therapy in patients with type 2 diabetes.
    - In patients already on oral antidiabetes medications up to three oral agents, a basal insulin (glargine, detemir, or NPH) is usually added as a single daily injection. If prandial bolus insulin is later added, then sulfonylureas, DPP-4 inhibitors, and GLP-1 receptor agonists are usually discontinued. Combination of basal-bolus insulin with metformin, pioglitazone, or SGLT2 inhibitors may reduce the insulin requirement and improve control over insulin only.
- In general, one can expect a 1% decrease in the A1C after starting an oral antidiabetes medication and an additional 1% decrease after adding a second oral agent.
- If given as part of dual or triple therapy with insulin, any antidiabetes medication can be associated with hypoglycemia.

Specific Guidelines for Oral Antidiabetes Medications

- The medications listed below are the most commonly prescribed in the U.S. Other approved drugs are used less frequently due to lower efficacy or side effects.
- Recommended dose adjustments in CKD for the non-insulin diabetes medications have been published. The table below is taken from Tuttle KR et al. Diabetic Kidney Disease: A Report From an ADA Consensus Conference. *Diabetes Care* 2014,37:2864-2883.

Metformin

- Increases risk for lactic acidosis in those with significant renal dysfunction (do not use if eGFR < 30 mL/min/1.73 m^2, in those at risk for AKI, and in those with fluctuating renal function)
- **Use of Metformin in CKD**:
    - FDA label reads, "do not use if SCr ≥1.5 mg/dl in men, ≥1.4 mg/dl in women," but this restriction has been questioned due to the low incidence of metformin-induced lactic acidosis
    - Proposed recommendations from Lipska et al. Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency. *Diabetes Care*. 2011, 34:1431-1437:

▪ eGFR ≥60	No renal contraindications; monitor annually
▪ eGFR <60 and ≥45	May continue use; monitor every 3-6 months
▪ eGFR <45 and ≥30	Use caution and at lower dose (e.g. 50% maximal) Monitor every 3 months Do not start new patients on metformin
▪ **eGFR <30**	**Stop metformin**

- May cause GI side effects, including diarrhea and cramping, but these are minimized if started at low doses, taken with food, and titrated up slowly
    - Start at 500 mg once to twice daily with meals
    - Wait 1-2 weeks before increasing dose
    - If GI side effects occur, reduce dose to the dose last tolerated
    - Maximal dose is 2550 mg/day in divided doses or 2000 mg of the extended release (ER) formulation
- Prolonged use is associated with vitamin B12 deficiency

Sulfonylureas (glyburide, glipizide, glimepiride)

- Promote insulin secretion independent of ambient glucose level
    - Risk of hypoglycemia
    - Use with caution in the elderly and in CKD
    - **Avoid use in stage 3 or greater CKD**
    - Glipizide is preferred in CKD
- Efficacy is good initially but requires addition of second agent sooner than other drugs
- Risk for weight gain
- Must not skip or delay meals
- Low cost

Rapid-acting Secretagogues (repaglinide, nateglinide)

- This class, the metaglinides, are more rapid-acting than sulfonylureas and are taken before each meal
- May cause less hypoglycemia than sulfonylureas in patients who skip or delay meals
- Expensive

Pioglitazone

- Promotes insulin sensitivity in muscle and reduces hepatic glucose production
- Disadvantages include weight gain (both water and fat), edema and heart failure, and increased risk of bone fracture
- Contraindicated in NYHA Class III and IV heart failure
- Advantages include low risk of hypoglycemia and good durability of efficacy
- Generic formulation now available; low cost
- No adjustment for eGFR

DPP-4 Inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)

- Increase glucose-dependent insulin secretion and decrease glucagon secretion
- Low risk of hypoglycemia; no weight gain
- Expensive
- Possible risk of acute pancreatitis
- Possible increased risk of heart failure admissions

SGLT2 Inhibitors (canagliflozin, dapagliflozin, empagliflozin)

- Inhibit reabsorption of glucose in the kidney, thereby promoting glucosuria
- Advantages include low risk of hypoglycemia, weight loss, and blood pressure lowering
- Do not rely on intact beta cell function, so SGLT2 inhibitors are effective at all stages in the natural history of type 2 diabetes
- Do rely on renal function; as renal function falls, SGLT2 inhibitors are less effective
- When starting, consider reducing doses of diuretics or other antihypertensives to avoid hypotension
- Must use with caution or not at all in patients with eGFR <60;
- Renal dosing:
    - For canagliflozin and dapagliflozin see Table below
    - Empagliflozin: do not use for eGFR <45

GLP-1 Receptor Agonists (exenetide, liraglutide, albiglutide)

- Stimulate glucose-dependent insulin secretion, decrease glucagon secretion, delay gastric emptying, and diminish appetite
- Advantages include low risk of hypoglycemia and weight loss
- Disadvantages include requiring injection and cost
- Some experience nausea/vomiting, especially soon after starting treatment
- Rodents have developed thyroid C-cell tumors in these drugs, but the risk for humans is not known
- Contraindicated in patients with personal or family history of medullary carcinoma of the thyroid or multiple endocrine neoplasia syndrome type 2
- Some reports of exenetide drug-induced renal injury

Protocol Table 2

Table 3—Recommended dose adjustments for noninsulin antihyperglycemic agents in DKD

Medication	In patients with impaired GFR	In dialysis patients
Biguanides		
Metformin	U.S. prescribing information states "do not use if serum creatinine ≥1.5 mg/dL in men, ≥1.4 mg/dL in women" British National Formulary and the Japanese Society of Nephrology recommend cessation if eGFR <30 mL/min/1.73 m^2	Contraindicated
Second-generation sulfonylureas		
Glipizide	No dose adjustment required	No dose adjustment required
Glimepiride	Initiate conservatively at 1 mg daily	Initiate conservatively at 1 mg daily
Glyburide	Avoid use	Avoid use
Meglitinides		
Repaglinide	Initiate conservatively at 0.5 mg with meals if eGFR <30 mL/min/1.73 m^2	No clear guidelines exist
Nateglinide	Initiate conservatively at 60 mg with meals if eGFR <30 mL/min/1.73 m^2	No clear guidelines exist
TZDs		
Pioglitazone	No dose adjustment required	15–30 mg daily has been used (190)
α-Glucosidase inhibitors		
Acarbose	Avoid if eGFR <30 mL/min/1.73 m^2	Avoid use
Miglitol	Avoid if eGFR <25 mL/min/1.73 m^2	Avoid use
GLP-1 receptor agonists		
Exenatide	Not recommended with eGFR <30 mL/min/1.73 m^2	Avoid use
Liraglutide	Not recommended with eGFR <60 mL/min/1.73 m^2	Manufacturer does not recommend use (currently under study)
Albiglutide	No dose adjustment required	No clear guidelines exist—limited clinical experience in severe impairment of kidney function
DPP-4 inhibitors		
Sitagliptin	100 mg daily if eGFR >50 mL/min/1.73 m^2 50 mg daily if eGFR 30–50 mL/min/1.73 m^2 25 mg daily if eGFR <30 mL/min/1.73 m^2	25 mg daily
Saxagliptin	5 mg daily if eGFR >50 mL/min/1.73 m^2 2.5 mg daily if eGFR ≤50 mL/min/1.73 m^2	2.5 mg daily
Linagliptin	No dose adjustment required	No dose adjustment required
Alogliptin	25 mg daily if eGFR >60 mL/min/1.73 m^2 12.5 mg daily if eGFR 30–60 mL/min/1.73 m^2 6.25 mg daily if eGFR <30 mL/min/1.73 m^2	6.25 mg daily
Amylinomimetics		
Pramlintide	No dose adjustment required with eGFR >30 mL/min/1.73 m^2 Not recommended with eGFR <30 mL/min/1.73 m^2	Avoid use
SGLT2 inhibitors		
Canagliflozin	No dose adjustment required if eGFR ≥60 mL/min/1.73 m^2 100 mg daily if eGFR 45–59 mL/min/1.73 m^2 Avoid use and discontinue in patients with eGFR <45 mL/min/1.73 m^2	Avoid use
Dapagliflozin	Avoid use if eGFR <60 mL/min/1.73 m^2	Avoid use

Protocol Table 2. Tuttle KR et al. Diabetic Kidney Disease: A Report From an ADA Consensus Conference. *Diabetes Care* 2014,37:2864-2883.

Protocol Figure 2

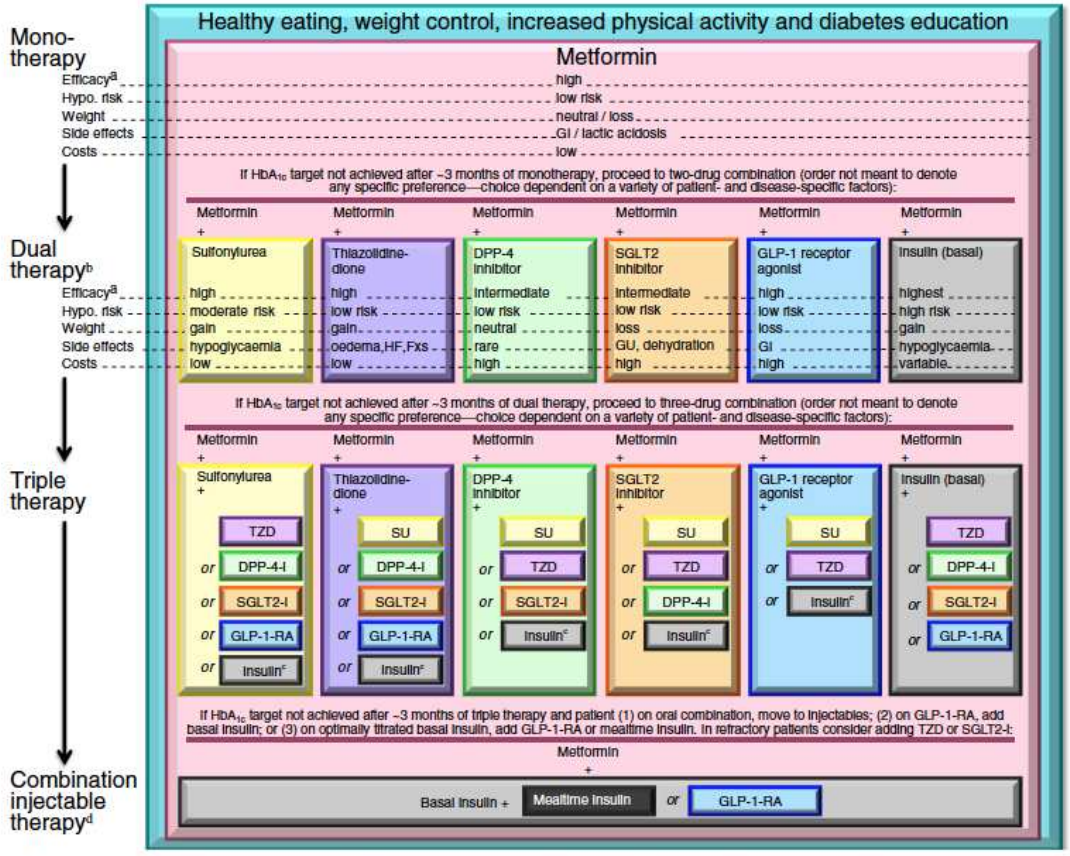

Fig. 2 Anti-hyperglycaemic therapy in type 2 diabetes: general recommendations. Potential sequences of anti-hyperglycaemic therapy for patients with type 2 diabetes are displayed, the usual transition being vertical, from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). In most patients, begin with lifestyle changes; metformin monotherapy is added at, or soon after, diagnosis, unless there are contraindications. If the HbA_{1c} target is not achieved after ~3 months, consider one of the six treatment options combined with metformin: a sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist or basal insulin. (The order in the chart, not meant to denote any specific preference, was determined by the historical availability of the class and route of administration, with injectables to the right and insulin to the far right.) Drug choice is based on patient preferences as well as various patient, disease and drug characteristics, with the goal being to reduce glucose concentrations while minimising side effects, especially hypoglycaemia. The figure emphasises drugs in common use in the USA and/or Europe. Rapid-acting secretagogues (meglitinides) may be used in place of sulfonylureas in patients with irregular meal schedules or who develop late postprandial hypoglycaemia on a sulfonylurea. Other drugs not shown (α-glucosidase inhibitors, colesevelam, bromocriptine, pramlintide) may be tried in specific situations (where available), but are generally not favoured because of their modest efficacy, the frequency of administration and/or limiting side effects. In patients intolerant of, or with contraindications for, metformin, consider initial drug from other classes depicted under 'Dual therapy' and proceed accordingly. In this circumstance, while published trials are generally lacking, it is reasonable to consider three-drug combinations that do not include metformin. Consider initiating therapy with a dual combination when HbA_{1c} is ≥9% (≥75 mmol/mol) to more expeditiously achieve target. Insulin has the advantage of being effective where other agents may not be and should be considered a part of any combination regimen when hyperglycaemia is severe, especially if the patient is symptomatic or if any catabolic features (weight loss, any ketosis) are evident. Consider initiating combination injectable therapy with insulin when blood glucose is ≥16.7–19.4 mmol/l (≥300–350 mg/dl) and/or HbA_{1c} ≥10–12% (≥86–108 mmol/mol). Potentially, as the patient's glucose toxicity resolves, the regimen can be subsequently simplified. [a]See Appendix for description of efficacy categorisation. [b]Consider initial therapy at this stage when HbA_{1c} ≥9% (≥75 mmol/mol). [c]Usually a basal insulin (e.g. NPH, glargine, [A21Gly,B31Arg,B32Arg human insulin] detemir [B29Lys(ε-tetradecanoyl),desB30 human insulin], degludec [des(B30)LysB29(γ-Glu Nε-hexadecandioyl) human insulin]). [d]Consider initial therapy at this stage when blood glucose is ≥16.7–19.4 mmol/l (≥300–350 mg/dl) and/or HbA_{1c} ≥10–12% (≥86–108 mmol/mol), especially if patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin+mealtime insulin is the preferred initial regimen. DPP-4-i, DPP-4 inhibitor; Fxs, fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; GU, genito-urinary infections; HF, heart failure; hypo., hypoglycaemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea

Protocol Figure 2. From Inzucchi SE et al. *Diabetologia* (2015) 58:436

Protocol Figure 3

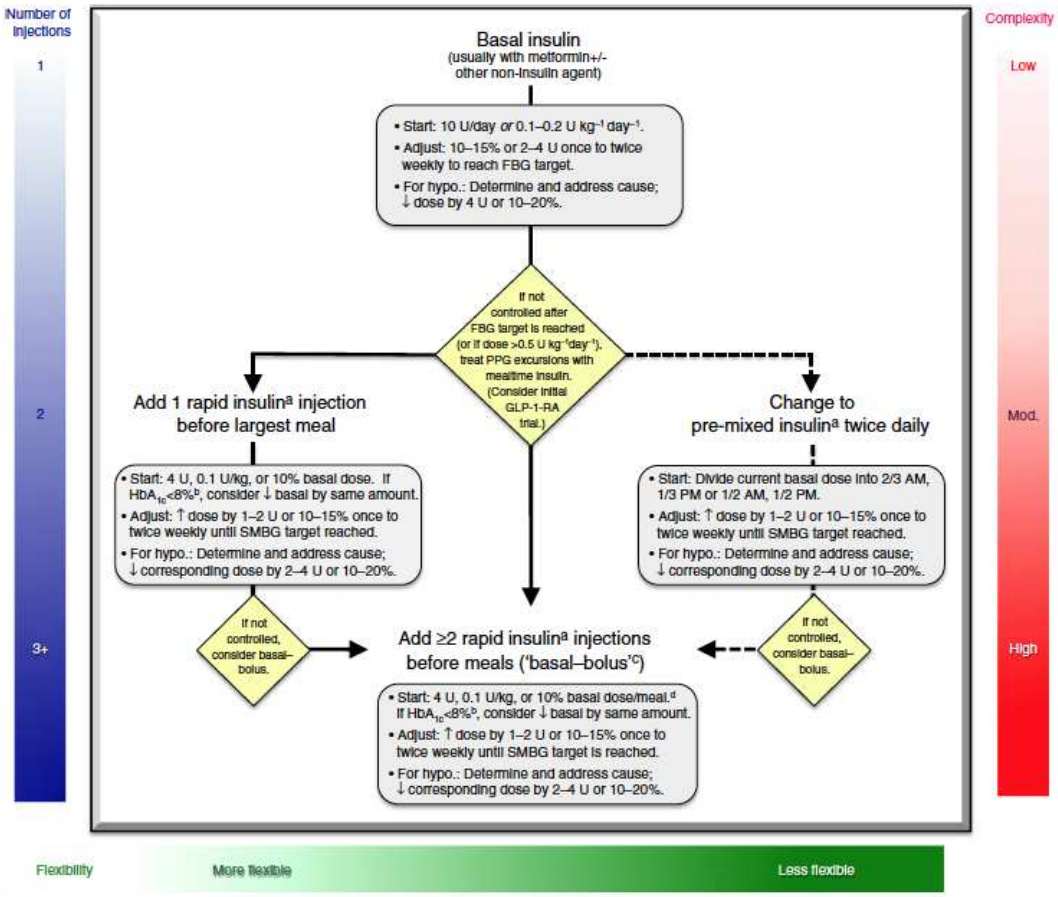

Fig. 3 Approach to starting and adjusting insulin in type 2 diabetes. This figure focuses mainly on sequential insulin strategies, describing the number of injections and the relative complexity and flexibility of each stage. Basal insulin alone is the most convenient initial regimen, beginning at 10 U or 0.1–0.2 U/kg, depending on the degree of hyperglycaemia. It is usually prescribed in conjunction with metformin and possibly one additional non-insulin agent. When basal insulin has been titrated to an acceptable fasting blood glucose but HbA_{1c} remains above target, consider proceeding to 'Combination injectable therapy' (see Fig. 2) to cover postprandial glucose excursions. Options include adding a GLP-1-RA (not shown) or a mealtime insulin, consisting of one to three injections of a rapid-acting insulin analogue[a] (lispro [B28Lys,B29Pro human insulin], aspart [B28Asp human insulin] or glulisine [B3Lys,B29Glu human insulin]) administered just before eating. A less studied alternative, transitioning from basal insulin to a twice daily pre-mixed (or biphasic) insulin analogue[a] (70/30 aspart mix, 75/25 or 50/50 lispro mix), could also be considered. Once any insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the prevailing blood glucose levels, with knowledge of the pharmacodynamic profile of each formulation used (pattern control). Non-insulin agents may be continued, although sulfonylureas, DPP-4 inhibitors and GLP-1-RAs are typically stopped once insulin regimens more complex than basal are utilised. In refractory patients, however, especially in those requiring escalating insulin doses, adjunctive therapy with metformin and a TZD (usually pioglitazone) or SGLT2 inhibitor may be helpful in improving control and reducing the amount of insulin needed. Comprehensive education regarding SMBG, diet and exercise and the avoidance of, and response to, hypoglycaemia are critically important in any insulin-treated patient. FBG, fasting blood glucose; GLP-1-RA, GLP-1 receptor agonist; hypo., hypoglycaemia; Mod., moderate; PPG, postprandial glucose; SMBG, self-monitoring of blood glucose.

[a]Regular human insulin and human NPH-Regular pre-mixed formulations (70/30) are less costly alternatives to rapid-acting insulin analogues and pre-mixed insulin analogues, but their pharmacodynamic profiles make them suboptimal for the coverage of postprandial glucose excursions. [b]HbA_{1c} 8%=64 mmol/mol. [c]A less commonly used and more costly alternative to basal–bolus therapy with multiple daily injections in type 2 diabetes is continuous subcutaneous insulin infusion (insulin pump). [d]In addition to the suggestions provided for determining the starting dose of mealtime insulin under 'basal–bolus', another method consists of adding up the total current daily insulin dose and then providing one-half of this amount as basal and one-half as mealtime insulin, the latter split evenly between three meals

Protocol Figure 3. From Inzucchi SE et al. *Diabetologia* (2015) 58:438

Another commonly used formula to design a starting multi-injection insulin regimen is to estimate the total daily dose of insulin as follows:

Total Daily Dose (TDD)= 0.5 units X body weight in kilograms

The estimated TDD for a 70 kg person would be 35 units.

Prescribe 50% of the Total Daily Dose as basal insulin and 50% as prandial insulin divided between three meals.

In the example of the same 70 kg person, prescribe 18 u basal insulin once daily and 6 u rapid-acting insulin three times daily before each meal.

For the elderly, those at risk for hypoglycemia, or significant CKD, consider a lower multiplier, e.g 0.2-0.4 units X body weight in kilograms to determine the TDD.

Recommendations for Lipid Management in Patients with Diabetes and CKD

A new KDIGO Clinical Practice Guideline for Lipid Management in CKD greatly simplifies the approach. Regardless of LDL, statins are recommended for all adult patients with both diabetes mellitus and non-dialysis-dependent CKD, unless there is a contraindication or statin-intolerance. Initial assessment of fasting lipid profile is recommended, but routine reassessment of fasting lipids on statin treatment is not currently recommended. Specific KDIGO recommendations are as follows:

Statin or statin/ezetimibe treatment is recommended for:

- Adults ≥50 years with eGFR <60 ml/min/1.73 m^2 but not treated with chronic dialysis or kidney transplant
-

Statin treatment is recommended for:

- Adults ≥50 years with eGFR ≥60 ml/min/1.73 m^2

Statin treatment is recommended for:

- Adults aged 18-49 years with CKD but not treated with chronic dialysis or kidney transplantation with one or more fo the following:
    - Known coronary artery disease (MI or coronary revascularization)
    - **Diabetes Mellitus**
    - Prior ischemic stroke
    - Estimated 10-year incidence of coronary death or non-fatal MI >10%.

Drug treatment of hypertriglyceridemia in adults with CKD is not recommended but rather therapeutic lifestyle changes are advised. Therapeutic lifestyle changes include diet changes, weight reduction, increased exercise, reduction in alcohol consumption, and improvement in glucose control if indicated. In the case of severe hypertriglyceridemia (triglycerides >1000 mg/dl), drug treatment with fibrates may be considered for patients with CK, but at doses adjusted for kidney function.

KDIGO Guidelines recommend doses for statin use in CKD that are based on regimens and doses “shown to be beneficial in randomized trials done specifically in this population” (adults with eGFR <60 ml/min/1.73 m^2 or on renal replacement therapy).

See Protocol Table 3 for recommended doses of statins in mg/day for adults with CKD.

Protocol Table 3

Table 4 | Recommended doses (mg/d) of statins in adults with CKD

Statin	eGFR G1-G2	eGFR G3a-G5, including patients on dialysis or with a kidney transplant
Lovastatin	GP	nd
Fluvastatin	GP	80[1]
Atorvastatin	GP	20[2]
Rosuvastatin	GP	10[3]
Simvastatin/Ezetmibe	GP	20/10[4]
Pravastatin	GP	40
Simvastatin	GP	40
Pitavastatin	GP	2

All statins may not be available in all countries. Lower doses than those used in major trials of statins in CKD populations may be appropriate in Asian countries. Note that rosuvastatin 40 mg daily is not recommended for use in CKD 1-2 non-transplant patients, as it may increase the risk of adverse renal events. Cyclosporin inhibits the metabolism of certain statins resulting in higher blood levels. Data based on [1]ALERT, [2]4D, [3]AURORA, [4]SHARP. Abbreviations: eGFR, estimated glomerular filtration rate; GP, general population; nd, not done or not studied.

Protocol Table 3. From *Kidney International Supplements* (2013) 3(3), p. 274

Checklist for Patient Visits

- Ask about symptomatic and asymptomatic hypoglycemia
- Review how to recognize and self-manage hypoglycemia (Rule of 15)

    - Action point: If the patient is having hypoglycemia unawareness, frequent hypoglycemia, or severe hypoglycemia, liberalize glycemic targets for at least several weeks in order to allow recovery from hypoglycemia unawareness or prevent its onset.
    - Glucagon kits are recommended for those at risk for severe hypoglycemia.

- Is the patient pregnant? Might the patient be pregnant?
- For overweight or obese patients, encourage weight loss/maintenance through sustainable lifestyle interventions. As little as 5-10% reduction in body weight may result in significant improvement in glucose control.
- Consider referral for medical nutrition therapy
- Review with the patient exercise recommendations for adults with diabetes who can safely exercise:
    - At least 150 minutes/week of moderate intensity aerobic physical activity (50-70% of maximal heart rate) over 3 days per week
    - Resistance training two days per week
- Advise smoking cessation and stopping use of all tobacco products; refer for counseling if indicated
- Confirm or administer annual influenza vaccine
- Confirm or administer pneumococcal vaccine
- Confirm yearly dilated retinal exam
- Confirm yearly diabetic neuropathy screen (vibration and 10-gram microfilament tests)
- Examine feet and instruct in foot self-exam by patients
- Consider actions to reduce the patient's cardiovascular risk profile
    - Consider statin therapy for all adults 18 or older with diabetes and CKD unless the patient is statin-intolerant or statins are contraindicated (e.g. pregnancy)
    - Follow protocols for management of hypertension to achieve ≤140/90
    - Consider whether the patient would benefit from daily aspirin (75-162 mg/day)
        - 10-year cardiovascular risk of >10% (includes most men >50 years and women >60 years who have at least one additional risk factor (family history of CVD, hypertension, smoking, dyslipidemia, albuminuria)
- Review interval medical history and instances of hypoglycemia. Adjust A1C treatment target as appropriate
- Consider screening for depression, especially if patient adherence is complicating glucose control
- Review A1C and self-monitored glucose logbook and adjust antidiabetes medications to treat-to-target.

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