NIH Collaboratory *Rethinking Clinical Trials®*
Health Care Systems Research Collaboratory

Ethics and Regulatory Core

UH2 Project: Improving Chronic Disease Management with Pieces (*ICD-Pieces*™)
Miguel Vazquez, MD

April 20, 2015
4:45pm – 5:45pm EST

Attendees:

☒ Monique Anderson, MD *Duke Clinical Research Institute*	☒ David Karp, MD *UT Southwestern Medical Center IRB*	☐ Marcel Salive, MD, MPH *NIH / NIA*
☐ Spencer Ballard, BA Parkland Health and Hospital Systems	☒ Jonathan McCall, MS *Duke Clinical Research Institute*	☒ Robert Starr *NIH / NIDDK*
☒ Josie Briggs, MD *NIH / NCCIH*	☒ Jerry Menikoff, MD, JD *OHRP*	☐ Irene Stith-Coleman, PhD *OHRP*
☒ Elaine Collier, MD *NIH / NCATS*	☒ Cathy Meyers, MD *NIH / NCCIH*	☒ Jeremy Sugarman, MD, MPH, MA *Johns Hopkins University*
☐ Brett Hagman, PhD *NIH / NIAAA*	☐ Jeri Miller, PhD *NIH / NINR*	☒ Robert Toto, MD *UT Southwestern Medical Center*
☒ Catherine Hammack, JD, MA *Duke Clinical Research Institute*	☒ Eric Mortensen, MD *VA North Texas Health Care System IRB*	☒ Teresa Turbeville *Texas Health Resources IRB*
☐ Susan Hedayati, MD *Dallas VA Medical Center*	☒ Andrew Narva, MD *NIH / NIDDK*	☒ Miguel Vazquez, MD *UT Southwestern Medical Center*
☒ Adrian Hernandez, MD, MHS *Duke Clinical Research Institute*	☒ George (Holt) Oliver, MD, PhD *Parkland Health and Hospital Systems*	☒ Wendy Weber, MD, PhD, MPH *NIH / NCCIH*
☒ Adeola Jaiyeola, MD, MHSc *Parkland Health and Hospital System*	☐ Jane Pearson, PhD *NIH / NIMH*	☒ Kevin Weinfurt, PhD *Duke Clinical Research Institute*
☐ Cheri Janning, BSN, RN, MS *Duke Translational Medicine Institute*	☒ Ivor Pritchard, PhD *OHRP*	☒ Barbara Wells, PhD *NIH / NHLBI*
☒ Julie Kaneshiro, MA *OHRP*	☒ Tammy Reece, MS, PMP, CCRA *Duke Clinical Research Institute*	☐ James (Gregg) Wright *UT Southwestern Medical Center IRB*

These minutes were circulated to all attendees for two rounds of review and they reflect all corrections that were received.

Agenda Item	Discussion	Action Item
Brief review of *Improving Chronic Disease Management with Pieces* (ICD-Pieces™)	• Dr. Vazquez gave an overview of the ICD-Pieces™ project. o The study's overarching goal is to improve chronic disease management for a triad of conditions—chronic kidney disease, diabetes mellitus, and hypertension—by using a collaborative model of primary care with nephrology-based specialty interventions to reduce adverse events associated with those conditions (particularly hospitalization). o The intervention is the implementation of best practices by using medical informatics to identify patients and a practice facilitator who facilitates the interventions (all of which are accepted best practices), continuously monitor clinical outcomes, and adjust interventions. The control group will receive the current standard of care. o The primary outcome is hospitalization. Secondary outcomes include thirty (30)-day readmissions, cardiovascular events, emergency department visits, and death. Additionally, the team will analyze outcomes that are possibly related to the intervention, such as hypotension and hyperkalemia. o Participating sites will be randomized. The project team will then identify the cohort through electronic health records (EHRs) before approaching potential subjects who are offered the opportunity to "opt-out" of participation. The "opt-out" mechanism will be provided to all potential subjects in control *and* intervention groups; Dr. Vazquez and his team would like for people to be given the opportunity to decide and control whether they want to participate *and* their data can be used in the study at all. o The team will be enrolling candidate patients for two (2) years, and will be implementing the intervention for one (1) year thereafter.	

IRB status and approval	• Additional information is provided in the Summary Document attached hereto. • Official IRB submissions and approvals are pending approval of the final project protocol, the most current version of which will be finalized after final recommendations from the Data and Safety Monitoring Board (DSMB) are received. Upon receipt and integration of the DSMB's revisions, the ICD-Pieces™ project team will submit the final protocol to the participating IRBs for their approval. • Dr. Vazquez explained that he and his team have discussed the proposed interventions and the opt-out method mechanism with the IRBs involved—those under UT Southwestern, the VA North Texas Health Care System, and Texas Health Resources. o According to Dr. Vazquez, the UT Southwestern IRB supports the proposed approach, but a decision is pending submission of the final protocol. o The Texas Health Resources IRB has received and reviewed the protocol and expressed initial concerns regarding the opt-out mechanism as opposed to an opt-in method with express informed consent; these discussions are ongoing. o The VA North Texas Health Care System IRB has not yet reviewed the protocol.	
Risk *Does the project meet regulatory criteria for being considered minimal risk?*	• Dr. Vazquez explained that the control group will receive the usual standard care; in other words, patients in the control group will have access to all the same interventions to which they would otherwise have access. The intervention group will receive interventions which are already accepted as best practices; *none* of the proposed interventions are experimental, and they *do not* carry any risks beyond what is expected in standard medical care. • The IRBs indicated that ICD-Pieces™ likely constitutes minimal risk, but are withholding their official decisions pending submission of the final protocol, as explained above in *Brief Review of Improving Chronic Disease Management with Pieces*. Each of the IRBs further agree that the determination of minimal risk depends more on the risks of *data security* than the risks of the intervention itself. o The IRBs believe that the minimal risk determination should focus on risks to confidentiality and privacy insofar as the ICD-Pieces™ team will be sending	

	identifiable patient data to a "cloud," or a group of remote computer servers and software networks, as explained below in *Monitoring and Oversight*. ○ Nonetheless, the Southwestern IRB is fairly certain that the project's data management plan and procedures will be robust enough to ensure that the risk to privacy and confidentiality posed by data security would *not* exceed minimal risk. • OHRP did not express any concern regarding the proposed minimal risk determination.	
Consent *Planned processes for relevant subjects*	• The ICD-Pieces™ team proposes an opt-out mechanism in lieu of consent. ○ Dr. Vazquez explained that if a patient does opt out, the practical consequence is that that patient's data will not be used, and their care will *not* be altered in any way other than that they would not receive the intervention. In other words, even if that patient were in one of the clinics randomized to an intervention, that patient would be managed like every other patient in one of the standard (or control) groups. ○ Dr. Vazquez explained that he believes that the project constitutes minimal risk (as explained above in *Risk*). ○ Dr. Vazquez further explained that considering the number of the facilities involved, their sizes, and the rates of events expected to occur in each, it is not practicable to conduct this study if individual consent is required. ▪ All resources—finances, time, personnel, and others—would be consumed by the process of obtaining informed consent from the expected fifteen thousand (15,000) patients involved. ▪ In addition to resource issues, the geographical spread of the participating clinics presents a pragmatic barrier. ○ Dr. Vazquez explained that his team will make participants aware of the study through various forms of public media. Patients will be informed via posters, handouts, and other media that a study about improving the care of patients with the aforementioned triad of conditions is being conducting in their healthcare system, and that the goal of the study if for their providers to be able to provide them (the patients) with the best practices of care. These posters, handouts, and other media will include a phone number and a link to a website whereby	

	patients can reach the ICD-Pieces™ team, who will provide as much detail as the patients need to make an informed decision. ○ In response to questions about the particular information about potential risk and benefit included in the aforementioned media, Dr. Vazquez explained that at this point in the project's development, they have not delineated these details. However, after extensive discussion about which *exact* risks would need to be communicated, the attendees acknowledged that it is only the foreseeable risks of the *research* (rather than the risks of standard care) that must be described in the notice to participants. In other words, patients must be informed of the risks of the research from which they may opt out; the research team is not required to inform them of the risks of the standard care which they may otherwise receive. Participants on the call expressed the view that the exact risks that need to be communicated should satisfy the requirements of what might be disclosed during informed consent. ○ Concerns of the opt-out mechanism continued with a discussion of documentation. In other words, assuming that the project does use the opt-out mechanism, the research team must document and track the instances in which a patient opts out of the study. This process raises issues similar to those of obtaining and documenting individual consent, such as burdening the IT infrastructure and imposing overhead that may affect (or even change) the study. Dr. Vazquez and his team acknowledged that documenting opt-out decisions will create more work, but it is doable from an IT perspective. The again emphasized that they value patients' opportunity to be aware of the study and to opt-out. ○ Dr. Vazquez explained that the clinicians should not be considered subjects because his team will not be looking at data evaluating them. They will analyze data by stratum (or healthcare system) and will analyze individual clinics with respect to enrollment, but will not look at individual practitioners. However, because some of the sites will be solo-practitioner sites, the concern that analyzing such sites is effectively analyzing physicians was raised. Dr. Vazquez emphasized that practitioners' agreeing to be involved in the study should *not* put them at risk and the team will take efforts to ensure this is the case.	

	• Dr. Vazquez emphasized that the proposed approach should not adversely affect patients' rights and welfare. • The ICD-Pieces™ team plans to inform all patient-participants of the study and explain and/or make available its findings upon its completion.	
Privacy *Including HIPAA*	• As previously mentioned in *Risk*, there is some concern regarding the team's use of identifiable patient data. Although it will later be de-identified for analysis, these identifiable data will be used within systems and will be transferred to a cloud. Such use, transfer, and storage poses some risk to patients' privacy and confidentiality. However, Dr. Vazquez explained that this process is already in use in other models of care in two of the health systems. Further, as previously explained, the Southwestern IRB is fairly certain that the project's data management plan and procedures will be robust enough to ensure that the risk to privacy and confidentiality posed by data security would *not* exceed minimal risk. o It should be noted that at this time the VA North Texas Health Care System will *not* participate in the cloud transfer, at least in the early stages of this study.	
Monitoring and Oversight	• Dr. Vazquez explained that he has met with the DSMB, and that although they are interested in the efficacy of the intervention, their primary interest is *safety*. o Accordingly, the project team will track safety events, such as the primary outcome (unplanned hospitalization) and secondary outcomes (cardiovascular events, emergency department visits, and death). They will also track safety events that are possible outcomes of the interventions (such as hypotension and hyperkalemia) or that could be related thereto. The team will regularly inform the DSMB of any such events. o Further, they plan to do an informal interim analysis of safety events, but *not* of outcomes due to incomplete data. ▪ The team explained that some information will not be available to them in real time, as patients may visit other healthcare systems for care at any time throughout the study; these data will eventually be made available to them, but there will be some delay. Thus, the team plans to do an	

	informal interim analyses to monitor safety and ensure that they are meeting recruitment goals. • It was suggested that the team could structure their plan to defer to the DSMB at a specified point for a decision regarding interim analyses; for example, at the end of year two, or when the team has collected fifty percent of the data, the DSMB decides whether or not an interim analysis should be conducted.	
Issues beyond this project *Regulatory and ethics concerns raised by the project, if any*	• The attendees identified the broad concepts of gatekeepers and the opt-out mechanisms as important issues.	
Other	*No other issues or concerns raised*	

ICD – Pieces

Improving Chronic Kidney Disease Management with Pieces

Ethics and Regulatory Group Discussion, April 7, 2015

1. Participating Institutions

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2. Specific Aims

Specific Aims Improving Chronic Disease Management with Pieces: Planning Phase

Chronic kidney disease (CKD), diabetes and hypertension are three chronic medical conditions that increase morbidity, mortality, resource utilization and costs. Among adults in the United States the prevalence of CKD has increased to more than 14% and diabetes and hypertension are now the two leading causes of end-stage renal disease. Among patients with CKD, more than 40% also have diabetes and more than 50% also have hypertension. It is known that CKD, independent of diabetes and hypertension, is associated not only with progression of kidney disease but also with excessive cardiovascular morbidity and mortality. The triad of CKD, diabetes and hypertension is even more devastating. Specifically, the cardiovascular morbidity and mortality burden among those with this triad is excessive. Important progress in identification of effective treatments for the triad has been made; however, CKD progression to ESRD and CV morbidity and mortality remain at unacceptably high levels. For this reason the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines published in 2013 stated "people with CKD are an ideal target for interventions aimed at reduction of morbidity, hospitalizations, mortality and costs". Unfortunately, there is a significant gap in translating these treatments into clinical practice. In addition, many minorities, including African-Americans and Hispanics, suffer from a disproportionate burden of CKD, diabetes and hypertension and do not receive these treatments.

We recently implemented a collaboratory primary and nephrology care model at Parkland Health and Hospital System for patients with CKD in a predominantly minority population using a novel technology platform (**Pieces** - *Parkland intelligent e-coordination and evaluation system*) that facilitates implementation of CKD care within the context of primary care practices and *medical homes* in the community. *Pieces*™ leverages information from the electronic health record to identify people with diagnosed and previously unrecognized CKD and provides clinician support for implementation of recommended practices, monitoring outcomes and guiding therapies. Preliminary data indicate that this model results in improved BP control in this real world setting: Within six months the fraction of people with BP at goal improved from 34.8% to 41.6%%. We also have successfully used Pieces™ to develop risk prediction models for heart failure readmissions and deaths and for out of the intensive care unit cardiac arrests and deaths. This model has tremendous potential to fill the unmet need of implementation and adoption of treatments that can improve patient outcomes.

We now propose a randomized pragmatic trial in four large health care systems to test our model of care in patients who have CKD, diabetes and hypertension. **Our hypothesis is that patients who receive care with our collaborative model of primary care-subspecialty care enhanced by novel information technology (Pieces™) will have fewer hospitalizations, readmissions, CV events and deaths**

than patients receiving standard medical care. *To test our hypothesis we propose the following Specific Aims for the Planning Phase (UH2) of this Demonstration Project:*

Specific Aim 1. Establish a Health Care Systems Collaboratory to conduct a pragmatic trial to improve care of patients with three chronic coexistent medical conditions: CKD, diabetes and hypertension. We will form a collaborative network among four large health care systems that provide care to more than 1.5 million patients-including more than 20,000 patients with a triad of CKD, diabetes and hypertension. The participating health care systems include Parkland Health and Hospital System, Texas Health Resources, ProHealth Physicians of Connecticut, and the North Texas Veterans Healthcare System. Each has a fully functional electronic health record (EHR) needed to carry out this project.

Specific Aim 2. Establish functionality across the 4 participating health care systems of a technology- enhanced model of collaborative care by primary care practitioners for patients with CKD, diabetes and hypertension. In collaboration with the NIH and the Clinical Coordinating Center, we will finalize detailed plans for trial design and implementation at study sites, deployment and testing of Pieces technology platform in the different EHRs of the participating sites, complete processes for data extraction, and address regulatory oversight and human subject research protection. The collaboratory will be directed by an executive committee. Four advisory groups will provide input to a steering committee to direct all aspects of the project. A PI from each of the 4 participating health care systems will lead all the members of the team at that site in the preparations for and conduct of the study.

We have assembled a strong group of large healthcare systems that serve a large ethnically and socioeconomically diverse population in two locations in the United States. We have published experience with our novel software, Pieces^{TM} for predicting outcomes in heart failure and have successfully deployed this model for managing patients with CKD and diabetes at Parkland, and at Texas Health Resources for heart failure readmissions. These collaborations demonstrate the feasibility of using this system in diverse EHR systems that will ensure our success in forming a functioning collaboratory. Our collaborative model approach to care for patients with multiple chronic conditions using the unique and novel technology platform provided by Pieces^{TM} makes this proposal highly innovative.

Specific Aims Improving Chronic Disease Management with Pieces: Implementation Phase

Patients with diabetes and hypertension have a high prevalence of CKD. Patients with coexistence of CKD, diabetes and hypertension have a high risk for hospitalizations, readmissions, CV events and premature death. Many patients with CKD, diabetes and hypertension do not receive therapies proven to be effective. There is a clear need to improve the care of these patients and address the major disease burden and public health implications of the coexistence of CKD, diabetes and hypertension in the US. In response to the NIH Health Care Systems Research Collaboratory RFA-RM-13-012 we

propose a pragmatic trial to test a model of implementation of care to improve major outcomes (hospitalizations, readmissions, CV events and deaths) for patients who have CKD, diabetes and hypertension. We have experience with implementation of a collaborative, technology-enhanced, community-based model as part of a CKD implementation project sponsored by NIDDK. We have experience working with large Health Care System (HCS) partners key to this proposal not only implementing CKD care models but also with development of risk models for other chronic medical conditions and successful reductions in hospital readmissions. Moreover, we will use data management resources with solid record of success in other large studies involving multiple sites.

We now propose a randomized pragmatic trial in four large health care systems to test our unique model of care in patients who have CKD, diabetes and hypertension. **Our hypothesis is that patients who receive care with our collaborative model of primary care-subspecialty care enhanced by novel information technology (Pieces) will have fewer hospitalizations, readmissions, CV events and deaths than patients receiving standard medical care.** To test our hypothesis we propose the following Specific Aims for the Implementation Phase (UH3) of this Demonstration Project:

Specific Aim 1. Conduct a randomized pragmatic clinical trial of management of patients with CKD, diabetes and hypertension with a clinician support model enhanced by technology support (Pieces) compared with standard of care. We will enroll patients from primary care practices in 4 health care systems and randomize 15,737 patients to standard of care management or to management with a clinician support model enhanced by Pieces and practice facilitators. The primary outcome of this trial will be hospitalizations for any cause. Secondary outcomes will include: a) 30-day readmissions, b) disease-specific hospitalizations, c) cardiovascular events, d) ER visits, and e) deaths from any cause. The study will be monitored by a data safety and monitoring committee composed of experts in clinical trials of people with multiple chronic conditions

Specific Aim 2. Develop and validate predictive models for risks of hospitalizations, cardiovascular events and deaths for all patients with coexistent CKD, diabetes and hypertension and to predict risk of 30 day readmissions for patients who are hospitalized. Accomplishing this aim will allow us to take full advantage of the IT framework established for the conduct of this pragmatic trial. We will also prepare to use findings from this trial to improve management of chronic medical conditions and plan future studies. The predictive models for risks of a) hospitalizations, cardiovascular events and deaths for all patients with coexistent CKD, diabetes and hypertension and b) 30 day readmissions for patients who are hospitalized will be derived and validated using data extracted from the electronic health records of more than 20,000 adult patients CKD, diabetes and hypertension. The participants will be recruited from Parkland Hospital, Texas Health Resources, ProHealth Physicians, VA of North Texas Healthcare System between September 1, 2015 and August 31, 2017. We

will also evaluate the model and patient satisfaction and patient preferences, as well as practitioner satisfaction with implementation, acceptance and treatment recommendations.

Our proposal addresses a particularly challenging combination of 3 chronic medical conditions (CKD, diabetes and hypertension) that frequently coexist and have major public health implications. *Our trial is pragmatic and randomized with rigorous controls and tests the implementation of several accepted and well-characterized interventions which will be coordinated and applied broadly to patients with CKD, diabetes and hypertension to evaluate very important outcomes: hospitalizations, readmissions, cardiovascular events and deaths.* Our interventions will be simple and directly implemented by the primary team caring for patients in the community within the context of the medical home model. Our participating health care systems serve very different patient populations, have very different structures and use different electronic health records all of which will make our findings applicable not only to diverse patient populations but also many practices and health care systems.

We anticipate that the findings from this pragmatic clinical trial will allow us to improve the care of patients with chronic kidney disease, diabetes and hypertension. Strategies learned from this trial should establish a foundation for future studies that test approaches to care for other chronic medical conditions. Furthermore, findings from this trial should also inform future strategies for implementation of accepted care models and interventions to improve the care of patients with multiple chronic medical conditions.

3. Study Leadership and Governance

A. 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. Ruben Amarasingham at PHHS, Dr. Ferdinand Velasco at THR, Mr. John Lynch in ProHealth Physicians, and Sr. Susan Hedayati and Dr. Tyler Miller at VA North Texas Healthcare Systems.

B. 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. Amarasingham. 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. Amarasingham is Associate Professor of Medicine at UT Southwestern, President of the Parkland Center for Clinical Innovation and Director of the Bioinformatics Core of the CTSA at UT Southwestern. 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.

4. Study Summary

A. Protocol Summary

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 a collaborative model of primary care and subspecialty care interventions enhanced by novel information technology and practice facilitators will allow to leverage data from the electronic health records to identify 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 reducing 12-month hospitalization rates for CKD, diabetes and hypertension.

Secondary objectives are to test if implementation of the collaborative model of primary care-subspecialty care interventions will reduce disease-specific hospitalizations, 30-day readmissions (for patients who have an index hospitalization), emergency room visits, cardiovascular events or deaths from any cause. Disease-specific hospitalizations in this study have been pre-specified in this study to include 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.

Other secondary objectives are 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. Another secondary objective is to evaluate the impact of the collaborative primary care-subspecialty care model on patient related outcomes (PROs) including health related quality of life, patient satisfaction and patient perspectives on quality of care. Other secondary objective is to 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. Objectives also include collection of demographic data and clinical descriptive data to assist phenotyping patients with a triad of CKD, diabetes and hypertension. Additional secondary objectives include obtaining 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). There will also be collection of 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 unplanned hospitalizations for patients with CKD, diabetes and hypertension. Specifically, the outcome will be hospitalization rates at 12 months for all study participants. We will capture all-cause 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.

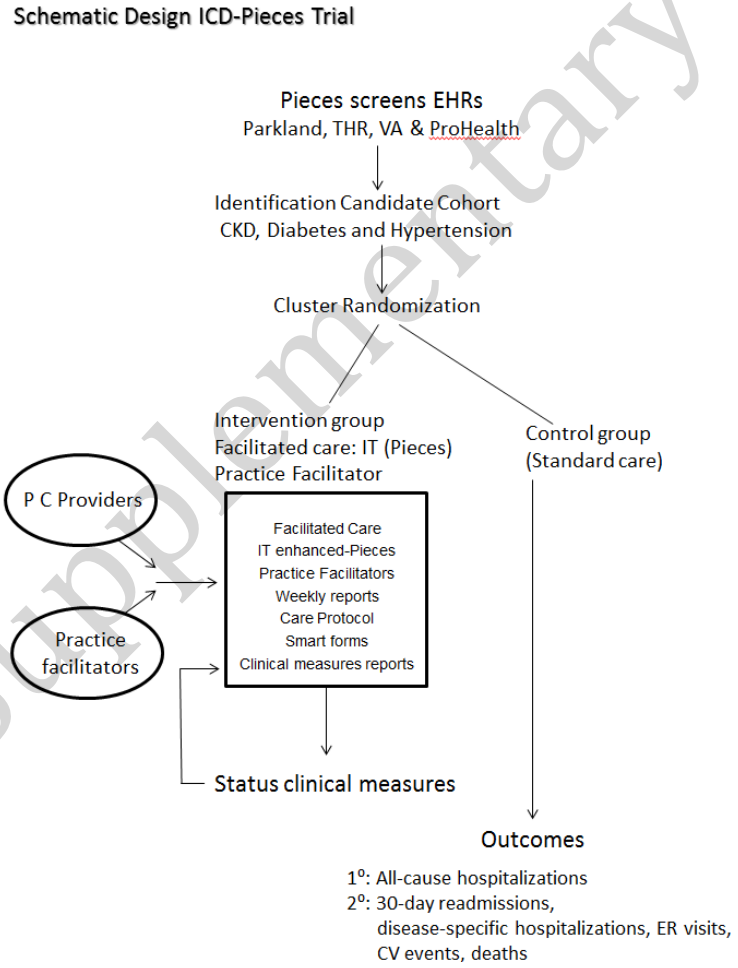
Secondary outcomes captured in the study will include 30-day readmissions (for those patients who have an index hospitalization), disease-specific hospitalizations, emergency room visits, cardiovascular events and deaths. Disease-specific hospitalizations for CKD, diabetes and hypertension will include 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.

Patient reported outcomes (PROs) will be captured with a PRO survey derived from core domains and corresponding measures by the PCOR Net Patient Reported Outcomes (PRO), Common Measures Working Group (CMWG). Primary care practitioner reported outcomes and satisfaction with resources and ability to manage patients with CKD, diabetes and hypertension will be measured with a survey adapted from collaborative disease management.

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 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



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 15,737 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.

B. 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.

C. Data Analysis

Study Hypothesis:

It is hypothesized that the PIECES-based interventions can reduce one-year (12 months) hospitalizations for patients with 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.

Sample size consideration:

We have determined sample size based on the comparison of one-year disease-specific hospitalization rates between the control and PIECES-based intervention groups.

The sample size formula developed by Donner [64] for stratified randomized trials will be employed. From preliminary data we observe that the rate of disease-specific hospitalization during the 1-year follow-up period to be 13.8% 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 15,103, 6,931, 6,813, and 6,382 in Parkland, Texas Health Resources, ProHealth, and VA North Texas, respectively. The numbers of clinics are 11, 82, 67, and 89 in Parkland, Texas Health Resources, ProHealth, and VA North Texas, respectively. The average numbers of patients per clinic are 1,373, 84.5, 101.7, and 71.7 in the four healthcare systems. From a preliminary dataset extracted from the Parkland healthcare system, we obtained an intracluster correlation coefficient (ICC) of 0.0028. To be conservative, we assume an ICC of 0.005 for sample size calculation.

If we assumed ICC = 0.01 to detect a 3% difference in the rate of disease-specific hospitalization, a total of 27,712 patients are needed to achieve 80% power at a two-sided 5% significance level. We would need to enroll 11,881, 5,452, 5,359, and 5,020 patients from Parkland, THR, ProHealth, and VA North Texas. If the assumed ICC is 0.005 a total of 15,737 patients are needed to achieve 80% power at a two sided 5% significance level. We will enroll 6,747, 3,096, 3,043 and 2,851 patients from Parkland, THR, ProHealth, and VA of North Texas.

5. Risk Determination

Participation in ICD-Pieces involves minimal risk for study participants. The interventions in both control group and intervention group carry very low risk for study participants. There is no infringement of patient welfare or inherent rights of patients. The study cannot be performed with traditional processes for obtaining informed consent from all participants. We plan to provide information to all the study participants in both control and intervention group of findings from the trial when the study has been completed.

5.1 Risks for Participants in the Control Group

Participants in the control group with a triad of CKD, diabetes and hypertension will receive usual care. Patients will have access to all accepted interventions that are considered standard of care for this patient population. The primary care practitioner can decide what are the best interventions to treat CKD, diabetes and hypertension for all patients in the control group.

There is a risk of loss of confidentiality for patients in the control group when their data is accessed by the study team. Based on the safeguards in place, this risk should be minimal. The information in the electronic health records on participating patients will only be accessed for patient care purposes by personnel within the healthcare system. Data from the electronic health records used by the research personnel in the study will be password protected and deidentified once forwarded for data analysis.

5.2 Risks for Participants in the Active Intervention Group

Patients in the clinics randomized to active intervention have a similar risk of loss of confidentiality to that of patients in the control standard of care group. This is a minimal risk as described in the prior section.

The interventions to be implemented in the active group of care facilitated by Pieces and the practice facilitator are all accepted as best care practices and based on established medical evidence. All interventions are sound and accepted as optimal care for patients with a triad of CKD, diabetes and hypertension. The specific interventions including blood pressure control, administration of angiotensin converting enzyme inhibitors/angiotensin receptor blockers, use of statins, glucose control, avoidance of hypoglycemia, avoidance of nephrotoxic drugs, education of patients and providers, immunizations and referrals for diabetic eye exams and diabetic foot care should all improve care of participating patients if implemented according to recommendations and facilitated by the interventions proposed in the study.

As previously noted, the primary care physicians have the final say on what specific recommendations facilitated by Pieces and the practice facilitators will be implemented in any individual patient. Primary care physicians have the option of implementing all, some or none of the recommendations. This should add extra

protection to all participating patients as the primary care physicians are always expected to be looking for the best interests of their patients and to avoid any intervention that could be expected to carry a higher than minimal risk.

There are some unavoidable risks related to the use of standard and accepted therapy including some of the medications and interventions in the study period. Participants will be carefully monitored for serious events including hospitalizations, disability, incapacitation or death. Other safety events will also be captured including syncope, hyperkalemia, hypotension, angioedema, hypoglycemia, rhabdomyolysis, myositis, use of ACEI/ARBs during pregnancy, acute kidney injury, reductions exceeding 50% in eGFR and/or dialysis initiation.

In addition to the risk of loss of confidentiality of protected health information, there may be a perception of increased burden from institution of therapies that may require monitoring and coming for laboratories or visits more often. Again, the study does not mandate additional visits and any additional laboratories or visits required as part of the implementation of some interventions will be consistent with best care practices and accepted for patients with a triad of CKD, diabetes and hypertension whether they would be enrolled in the study or not if such an intervention had been instituted.

6. Consent Process

6.1 Information provided to all patients in the control group and the intervention group

There will be information provided to all patients throughout the participating clinical sites about the conduct of the pragmatic clinical trial to improve the care of patients with CKD, diabetes and hypertension. The information will be available in writing via posters and information sheets in all participating sites. There will be information with telephone numbers and links to the study website for additional information and options for opt-out. Specific information included will be the title of the study, sponsor of the trial, the goal of the trial and how to access the study team via telephone or electronic means for additional information or opt-out options. The printed information and website will clearly specify in culturally sensitive and appropriate language that the main purpose of the study is to put in place interventions to assist primary care physicians to provide the best possible care to their patients with CKD, diabetes and hypertension across different clinics in different healthcare systems.

6.2 Rationale for waiver of informed consent

We are requesting waiver of requirement for informed consent for this pragmatic clinical trial based on the following criteria.

1. The research involves no more than minimal risk to subjects.

   Noted above both groups including intervention and control (standard care group) will have access to recommended best therapies for the treatment of CKD, diabetes and hypertension. Participation in the study does not involve risks higher in magnitude than those organ early encountered in their daily life and regular examinations or testing.

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.

   Patients who are receiving treatment for CKD, diabetes and hypertension at any of the participating clinics in the healthcare systems in the study will be provided information about the study trial and option to opt-out. In addition, there will be information provided to patients in both intervention and control groups about study findings at the completion of the study. Patients will have the option to contact the study personnel via telephone or electronic/website at any time during the study. Primary care physicians always have the option of deciding which interventions to institute for their patients. Patients have the option of electing

not to participate or allow their data to be used for the study at any time they request.

3. This research cannot be performed at all participating healthcare systems and practice sites without the waiver.

   The interventions in this study include accepted treatments based on best medical evidence for treating patients with CKD, diabetes and hypertension. Given the large number of patients participating in the study, it is not possible to obtain individual informed consent from each participating patient. The cluster randomization design by using this study based on primary care practices is key to avoid cross-contamination of the usual care group by the interventions facilitated in the implementation group facilitated by information technology in practice facilitator.

7. Waiver of HIPAA Authorization

The ICD-Pieces trial will be conducted with a waiver of HIPAA authorization. Justification for waiving HIPAA authorization is based on the following criteria provided in the HHS Regulation 45 CFR 164.512:

1. The use or disclosure of protected health information (PHI) involves no more than a minimal risk to the privacy of individuals because a) processes will be in place to protect PHI from improper use or disclosure; b) PHI will be destroyed at the earliest possible time; and c) there will be no improper use or disclosure of PHI.

Processes to protect PHI from improper use or disclosure include i) limiting access to patient data to trained research personnel who have knowledge about protecting patient confidentiality, ii) transmitting data from EHRs of collaborating sites to PCCI database through secure FTP or HL7 iii) Storage of data in secure database on the FISMA compliant VAZATA Cloud, and iv) De-identifying patient data by removing the 18 PHIs as defined in 45 CFR 160.103 before transmission to the UTSW database for final analysis. PCCI has executed Business Associate Agreements (BAA) with all participating sites.

2. The research could not practicably be conducted without the waiver.

The aim of the trial is to evaluate effectiveness of a collaborative model of primary care-subspecialty care interventions enhanced by novel information technology and practice facilitators to improve the care of a broad population of patients who have the triad of chronic kidney disease, diabetes, and hypertension rather than to assess efficacy of an intervention for a selected subset of patients. The trial is being conducted in four large healthcare systems with up to 249 clinics/practices located in broad geographic areas of Texas and Connecticut and requires enrolling up to 15,737 patients. The practice facilitator will be overseeing several clinics and cannot be physically present in any one clinic to administer consent. The health care providers at each clinic who will be generating trial data through routine clinical care are not research personnel and thus are not able to administer research documents such as a HIPAA waiver of authorization. Under this implementation model, obtaining authorization from participants for use and disclosure of PHI is not practicable.

3. The research could not practicably be conducted without access to and use of the PHI.

The researchers at PCCI require access to PHI in order for Pieces to identify candidate patient for enrollment in the trial, confirm enrollment, monitor intervention received, and monitor progress towards intervention goals and study outcomes. In order to enumerate study outcomes, PHIs will be required for data linkage to the DFW Hospital Council REMPI database for complete hospitalization data and the CDC death database for complete death data. For patient identification and monitoring, we need the first and last

name, Zip code, address, date of service, and date of birth (DOB), Medical Record Number (MRN) and encounter numbers. For data linkage to the DFWHC database, we need the REMPI number which is generated from the hospital MRNs. For data linkage to CDC database, the SSN and DOB are needed. No PHIs will be transmitted to UTSW research database for final analysis because patient data will be de-identified.

8. Monitoring and oversight

The trial is being conducted under a cooperative agreement between the National Institutes of Health and the University of Texas, Southwestern (UTSW) with subcontracts from the UTSW to PCCI/ Parkland Health and Hospital system and University of Buffalo, NY. Subcontracts were executed between PCCI/Parkland and the three other participating HCS—Texas Health Resources, ProHealth of Connecticut and VA of North Texas—because PCCI will be working with them directly to deploy Pieces. The Institutional Review Board of the UT Southwestern is serving as the IRB of record for both Parkland and ProHealth, while THR and VA IRBs will serve both institutions individually.

An independent Data and Safety Monitoring Board (DSMB) has been appointed by the National Institutes of Health. The DSMB has reviewed the protocol and will monitor trial progress, data quality, intervention and clinical/laboratory data, outcome event rates, and interim analyses during the conduct of the study in accordance with a Data and Safety Monitoring Plan. The DSMB will have the authority to make formal recommendations to the NIH about early termination of the trial for futility, efficacy, or safety.

Additionally, the study has appointed an external advisory council of seasoned researchers from within UTSW that will monitor study activities and outcome data and provide advice when necessary.

9. Issues beyond this project (Regulatory and ethics concerns raised by the project, if any)

Is the notification signed by patients about using their data for research and opt out option at clinic enrollment sufficient to support the use of patient's data in ICD-Pieces trial?

How much information do we need to provide patients in the trial to serve as adequate notification and what is the best way of providing this information? Is it better not to inform patients about the research at al than to provide minimal information?

What is the best Opt-out method?