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

Meeting Participants (April 20, 2015):

☒ 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*

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

Agenda Item	Discussion April 20, 2015	Current Status as of August 31, 2016
Brief review of *Improving Chronic Disease Management with Pieces* (ICD-Pieces™)	• Dr. Vazquez gave an overview of the ICD-Pieces™ project. ○ 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). ○ 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. ○ 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. ○ Participating sites will be randomized. The project team will then identify the cohort through electronic health records (EHRs)	

IRB status and approval	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. ○ The team will be enrolling candidate patients for two (2) years, and will be implementing the intervention for one (1) year thereafter. • Additional information is provided in the Summary Document attached to the original minutes. • 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. ○ According to Dr. Vazquez, the UT Southwestern IRB supports the proposed	

	approach, but a decision is pending submission of the final protocol. ○ 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. ○ 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. ○ 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	• *No changes reported*.

	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.	• The ICD-Pieces™ study has been approved with waiver of informed consent by the three IRBs with oversight across the four healthcare systems. • The ICD-Pieces™ study offers an opt-out option to all potential participants. As a result of input from one of the IRBs, similar information about the study is provided to all patients (in both the intervention and control groups) via posters, handouts, or notices (varying according to the health care system). In brief: • patients can decide to opt out for various reasons (e.g., do not want to have any of their data used in a study or do not want to be participating in any interventions); and

	▪ 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	• all patients have access to the same general information about the study (avoiding having some patients with access to more detailed information than others before deciding to opt-out).

	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.	• The ICD-Pieces™ project obtained a HIPAA Waiver and Research & Development Committee approval.

	○ 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*. ○ 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. ○ 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.	• The general plans for monitoring and oversight are similar, but at the request of the NIH, the ICD-Pieces™ team has added plans to capture event rates for the primary outcome (all-cause unplanned hospitalizations) across participating healthcare sites. As discussed during the April 2015 meeting, there is no mechanism for real-time capture of primary outcome data and no plans for a formal interim analysis. Still, the ICD-Pieces™ team has agreed to keep track of the primary outcome rates by healthcare system. The team will capture event rates for the primary outcome as available from the healthcare systems and will report these quarterly to NIH and the DSMB. The study team and NIH will review the intraclass correlation coefficient and recruitment goals based on the most updated data.

	• 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.	• *No additional information reported.*
Other	*No other issues or concerns raised*	• *No additional information reported.*
Additional regulatory or ethics issue(s) that arose after the meeting		• The clusters in ProHealth were adjusted from geographic areas to practices sharing personnel and workflows for the care of a defined panel of patients. This also facilitated compliance with regulations in the state of Connecticut requiring a Practice Agreement between primary care practitioners and PharmDs acting as practice facilitators in this study.
Additional follow-up information		• According to Dr. Vazquez, the April 2015 meeting was extremely valuable to advance the ICD-Pieces™ study. Participation of the

		key stakeholders during that discussion provided clear direction, focus, and momentum to their planning and related processes.