Official Title: Reducing CV Risk in Prediabetes Patients Using EHR-Based Decision Support

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PROTOCOL

To improve implementation of evidence-based prediabetes care, a randomized study of the implementation and impact of a prediabetes Clinical Decision Support (CDS) intervention on cardiovascular (CV) risk in prediabetes patients (18-75 years old, body mass index (BMI) ≥25 kg/m^2, current smoker, uncontrolled blood pressure [BP] or lipids) is justified based on these considerations: (a) over 75% of rural primary care providers (PCP) now use EHR systems[22]; (b) in a previous randomized trial, we showed that CDS in primary care clinics significantly improved BP and glucose control in adults with diabetes; (c) this CDS system elicits evidence-informed patient treatment preferences using human-computer interfaces; (d) the CDS system is minimally disruptive of clinic workflow with 80% use rates in targeted diabetes patients and 95% provider satisfaction; and (e) treatment and prioritization algorithms are Web- based and therefore easily updated and highly scalable to any medical group that uses EHRs.

The objective of this project is to systematically and pragmatically improve care and CV risk factors in a population of predominantly rural adult prediabetes patients at high risk for developing diabetes and CV events by implementing aWeb-based CDS system that integrates with local EMR systems and presents the patient and PCP with personalized, evidence-based drug and lifestyle treatment recommendations. To accomplish this objective, we addressed the following specific aims and hypotheses:

Specific Aim 1: Cluster-randomize 34 primary care clinics with 450 PCPs and over 11,000 high-risk adult prediabetes patients to one of two study arms: (a) Usual care (UC) clinics or (b) Intervention (CDS) clinics,which use an EHR-linked, Web-based Prediabetes CDS system designed to improve prediabetes care.

Hypothesis 1 (H1): Relative to those treated at UC clinics, eligible 18 to 75-year-old prediabetes patients at high CV risk treated at CDS clinics will have significantly more favorable trajectories in CV risk estimates over a median 24-month follow up.

Hypothesis 2 (H2): Relative to those treated at UC clinics, eligible 18-75 year-old prediabetes patients with uncontrolled CV risk factors at CDS clinics will have significantly more favorable trajectories in specific CV risk factors, including BP, lipids, smoking, HbA1c, and weight over a median 24-month follow up.

Hypothesis 3 (H3): Relative to those treated at UC clinics, eligible 18 to 75 year-old prediabetes patients at high CV risk treated at CDS clinics will have significantly more favorable patterns of metformin and statinuse over a median 24-month follow up.

Specific Aim 2. Assess the cost of the CDS intervention from the health system (payer) perspective through utilization analyses.

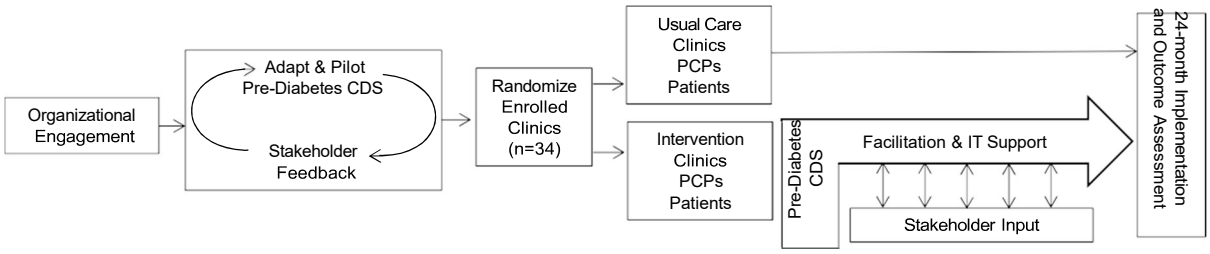
Hypothesis 4 (H4): After controlling for demographics and baseline clinical status, eligible patients with prediabetes treated in UC clinics versus CDS clinics will have significantly lower annual healthcare costs from the index date over a median follow up of 24 months.

Specific Aim 3: Describe critical facilitators and barriers for the prediabetes CDS implementation process, outcomes, and future dissemination using a mixed-methods approach.

Note that a previously included cost-effectiveness hypothesis (Hypothesis 5) was not tested due to lack of efficacy of the study intervention. Project results will provide a template for implementation of personalized CDS tools in rural and urban health settings, resulting in more efficient, effective rural healthcare that can be applied across many clinical domains,incorporates patient treatment preferences, and could substantially and sustainably improve the quality of CV care and clinical outcomes of millions of Americans with prediabetes in medically underserved areas.

Overview of Study Implementation Process and Design: The implementation process has four primary components (Figure 1): a) initial organizational engagement; b) adapting and piloting the Prediabetes CDS with Essentia primary care providers and patients; c) a group-randomized controlled study of the adapted CDSin 34 primary care clinics blocked on size and Essentia geographic service area; and d) evaluation of the implementation process and outcomes. It is critical to note that implementation is an iterative process, both in the adaptation phase and during the randomized controlled trial of implementation and outcomes. Continuous feedback is provided to and from organizational leaders, providers, and patients to better understand the facilitators and barriers to implementation and to guide refinements of the CDS.

Figure 1. Study Implementation Process and Design



Group-Randomized Study Eligibility Criteria

Study Sites: The group-randomized controlled study will be implemented in 34 Essentia Health primary care clinics in Minnesota, North Dakota, and Wisconsin. Essentia clinics have used the Epic® EHR since 2004 and have, on average, 14 PCPs (range: 1-56) and 377 prediabetes patients at high CV risk per clinic. Eighty-four percent of the Essentia geographic service area is rural, with 56% of the patient population and 66% of clinics located in this rural area. Average household incomes are less than $35,000 for 42% of patients, and 45% live in health professional shortage areas.

Study Participants: PCPs and Patients: To participate, **PCPs** must practice at one of the 34 Essentiaclinics and meet these eligibility criteria: (a) be an adult-care general internist, family physician, non-obstetric nurse practitioner, or physician assistant, and (b) provide ongoing primary care for 15 or more prediabetes adults ages 18-75 with high CV risk. There are currently 441 eligible PCPs which should ensure a more robust understanding of implementation barriers and facilitators in a large PCP community.

To be considered for inclusion in primary or secondary analyses, **patients** must meet all the following eligibility criteria at the time of their indexvisit: (a) be 18-75 years old, (b) have no evidence of diabetes in the previous 12 months (based on lab values, diagnosis codes, use of medications, or on problem list), (c) not be pregnant (d) have the most recent fasting plasma glucose of 100–125 mg/dL or HbA1c 5.7-6.4% within the prior 24 months, (e) have the most recent BMI ≥25 kg/m^2, (f) have at least one of the following uncontrolled CV risk factors: current smoking, a diagnosis

of hypertension with index visit BP ≥140/90 mm Hg or no diagnosis of hypertension but two consecutive BP ≥140/90 mm Hg, or ACC/AHA 10-year CV risk ≥7.5% and LDL either untested or ≥70 mg/dL and not on a statin, (g) no hospice care or chemotherapy for cancer within previous 12 months, and (h) have at least one subsequent primary care visit after the index visit. The patient accrual period (for first index visits) will be 12 months, followed by a 26-month observation period. Thus, patients will have 26 to 38 monthsof follow up, with an expected median of 32 months follow up after the index visit. Pilot data indicate that non- pregnant eligible adults have a median of 6 primary care visits over a 24-month period, ensuring broad inclusion in the analysis. We conservatively estimate an average of 25 eligible patients per consented study PCP with few losses due to death (<1%) in the study period. Few patients switch primary care clinics in Essentia and we accurately match over 98% of patients to a regular PCP. Ultimately, after accounting for all eligibility criteria, we anticipate over 6,600 eligible patients for Aim 1 and Aim 2 analyses. For Aim 1 and Aim 2 analyses we will retrospectively collect CV clinical information and will ask for a waiver of patient consent. The IRB has waived consent in prior and existing evidence-based CDS studies. Patients specifically recruited for focus groups and surveys will be consented and receive
modest compensation for those activities.

Description of Usual Care (UC) and PrediabetesCDS Intervention Conditions.

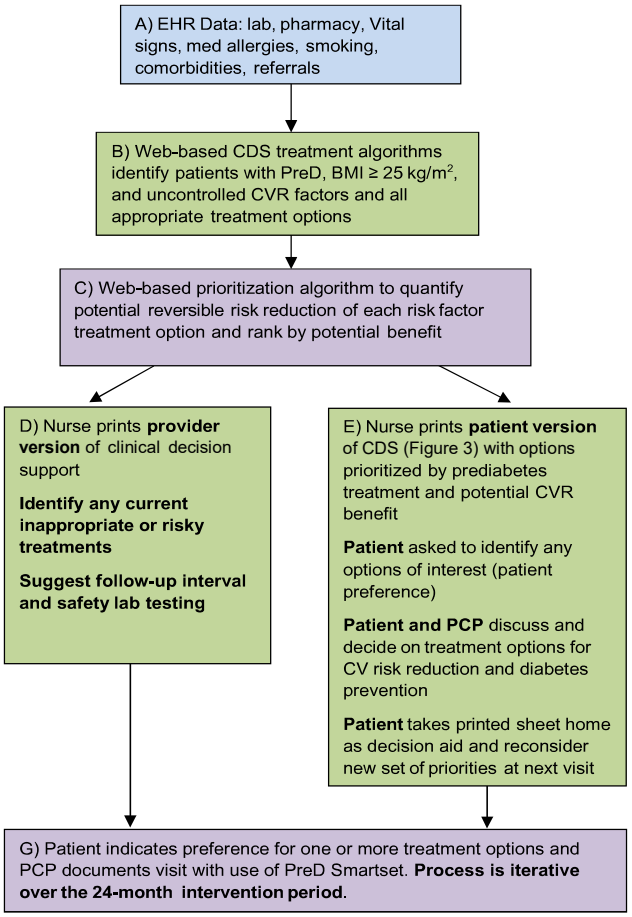
UC Condition. UC clinics and their consented PCPs will have no access to the CDS intervention.

Prediabetes CDS System: The Prediabetes CDS intervention is rooted in a series of antecedent studies that have developed successful forms of CDS for diabetes. The process flow of the intervention is shown in Figure 2.Specific steps in implementation of the Prediabetes CDS intervention are described below.

Step A. Extract Clinical Data from EHR and Send to Web site. In HL102144, we created the programming to securely extract pharmacy, laboratory, vital signs, demographic, comorbidity, smoking, and drug allergy data from the EHR and export it to a Web server within the HealthPartners Medical Group (HPMG) firewall. These data pathways are debugged and function seamlessly. We will modify the programming to identify prediabetes patients 18-75 years at high CV risk and adapt the CDS to evidence-based prediabetes care recommendations in the ADA Standards of Diabetes Care, published every January in *Diabetes Care.*

Step B. Treatment Algorithms. Web-based **treatment algorithms** that identify evidence-based treatment options appropriate for BP, lipids, tobacco, and BMI are developed for 40- to 75-year-old high-CV risk patients. They will be adapted for evidence-based prediabetes treatment, including use of metformin. **Treatment**

Figure. 2 Schematic representation of Prediabetes CDS showing how treatment options are identified, prioritized, and presented to patients and primary care providers at the point of care.



recommendations provided through the CDS intervention are based on: (a) all current medication prescriptions for glucose (including metformin), BP,lipids, and smoking cessation; (b) current renal function, liver function, creatinine kinase level, and comorbid conditions such as coronary heart disease, congestive heart failure, chronic kidney disease, dementia, and depression, which affect the appropriate use of these classes of medications; (c) personalized evidence-based glucose, BP, lipid, and weight management goals; and (d) medication allergies listed in the EHR. Medication recommendations are specific (what drug, what dose) based on clinical care guidelines for prediabetes and CV risk factors. The CDS identifies risky prescribing events and suggests alternative clinical actions. A diabetes glucose-management algorithm also exists and will deploy upon conversion from prediabetes to diabetes. These treatment algorithms have been effective with adult diabetes patients (R01DK068314) and will be updated every 6-12 months or when major changes occur to reflect new care guidelines and U.S. Food and Drug Administration medication actions.

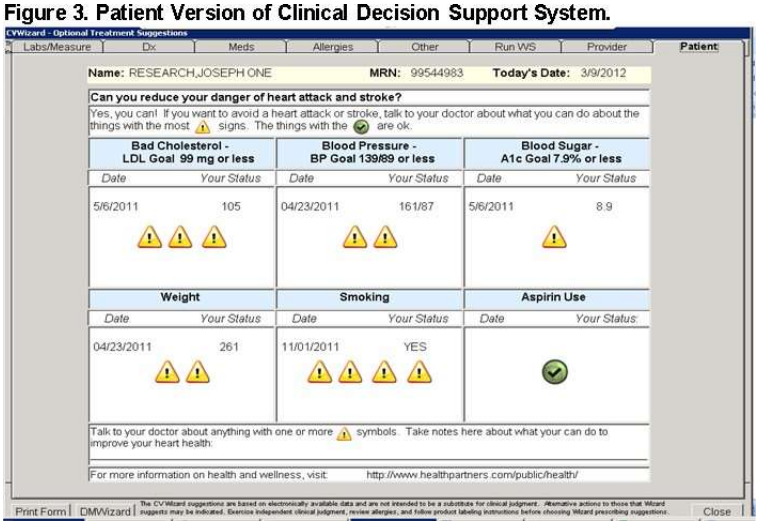
In this study, prediabetes clinical goals will emphasize appropriate management of BP, lipids, smoking

cessation, weight, and glucose using metformin or other pharmacologic agents, and referral to nutrition, physical activity, or weight-loss therapy. For lifestyle strategies, providers can refer willing patients directly to appropriate evidence-based clinical therapy or community resources.

Step C. Prioritization Algorithms. The CDS will provide diabetes prevention recommendations to all patients. CV risk reduction will be prioritized. Web-based prioritization algorithms use a patient's data to estimate the potential achievable reduction in CV risk with management of each out-of-control CV risk factor (BP, lipids, BMI, and tobacco). In previous work, we developed a 4-step approach to estimate the CV risk reduction that can be achieved for each CV risk factor: (a) Run the CV risk equation with real values of systolicBP, HDL, total cholesterol, BMI, and smoking status, and save this first score. (b) Re-run the same CV risk equation but replace one observed elevated risk factor value (eg, observed systolic BP ≥140 mm Hg) with the evidence-based optimal value (systolic BP=140 mm Hg) and save this second score; (c) subtract the two scores to estimate CV risk reduction that could theoretically be achieved by control of the selected out-of- control CV risk factor (SBP in this example); (d) Repeat this process for each out-of-range CV risk factor, one at a time, thus estimating CV risk reduction that may be achieved for each individual risk factor that is out of control. The estimates are then ranked based on the potential CV benefit of treating each individual risk factor. We will use this approach with prediabetes patients' at high CV risk. We acknowledge that this approach is imperfect. It assumes additivity and extrapolates risk equation estimates to individuals; however, prioritization is based on *relative risk reduction* within a patient using the same CV risk equation. Furthermore the ACC/AHA10-year pooled ASCVD risk engine must be used for 40-75 years olds while the Framingham 30-year CV risk score is used for 18-39 year olds. In previous projects, these estimates were found clinically credible with PCPs, who view them as superior to intuitive judgments of CV risk reduction. Drug effects on BP and lipids arebased on published reports and are adjusted downward for patients already on multidrug regimens. A similar evidence-based approach will be used to incorporate the effect of metformin use on CV risk.

Step D: Presentation of Prioritized CV Treatment Options to PCPs and Patients. The CDS clinic workflow is illustrated in Figure 2. At a clinic visit, the following protocol is automatically implemented:
(1) When the rooming nurse enters the patient BP in the EHR, biometric data is automatically transferred to a secure Web server. If the patient has prediabetes, is overweight or obese, and has atleast one other elevated CV risk factor, a "Best Practice Alert" (BPA) automatically displays; (2) based on the BPA, the nurse deploys the CDS witha single click on the visit navigator and, with an additional click, prints the patient and PCP interfaces; (3) if a patient's mental and physical status appears stable, the nurse hands the patient interface sheet(Figure 3) to the patient, saying, "The yellow marks show how you can reduce your danger of diabetes, stroke, or heart attack later in life. If you are ready to work on any of these things, please talk with your doctor during your visit today."

Figure 3. Patient Version of Clinical Decision Support System.



(4) If the PCP prefers, the printed PCP interface is placed in the basket outside the exam room for visit planning before entering the exam room. Otherwise, the PCP interface is displayed when the PCP opens the EHR during the visit. The printed PCP interface is a powerful visit-planning tool that most PCPs prefer to view before entering the exam room; (5) the PCP discusses patient questions or treatment preferences related to the prioritized CV risk reduction or diabetes prevention CDS recommendations; and (6)based on patient preferences, the PCP completes the Prediabetes Smartset (see below) or books a follow-upvisit.

The prediabetes CDS PCP interface is patient-specific. If medications are indicated, the CDS will specify either initiation or titration of drugs based on current medications, distance from goal, and other clinicaland comorbidity considerations. Options for local clinic- or community-based lifestyle interventions are provided to facilitate lifestyle management referrals. On the Patient Interface, the estimated CV risk reduction of each treatment is a simple visual display (Figure 3). This approach is preferred because many patientshave low numeracy, and time-dependent risk information is difficult to interpret. This visual display has been well-received in earlier studies and shown to be a strong motivational strategy. However, for

patients with strong numeracy and health literacy, the PCP interface may be given. The presentation of CV risk factor domains with treatment options facilitates patient and provider decision-making based on patientreadiness to change. Patient readiness is a key predictor of subsequent adherence and success of treatment, as we and others have shown.

Step E: Prediabetes CDS Smartset: The Prediabetes CDS will also include a personalized 'virtual' checklist,or Smartset, to streamline prediabetes patient management by grouping diagnoses, medications, tests and procedures, and patient follow-up. The Smartset serves multiple purposes, it: (a) invites PCPs and patients to select evidence-based prediabetes and CV care-management options that best fit their current needs and readiness, including metformin use and lifestyle change referrals, (b) incentivizes the PCP and patient to takean action, (c) quantifies the percentage of visits at which each intervention PCP is using the CDS, and (d) enables us to give feedback to PCPs and clinic leaders on comparative use of the CDS.

Step F: Iterative Use of the Prediabetes CDS over a Series of Visits. A key design feature of this intervention is its repeated use at all office visits of eligible patients during the intervention period. The CDS is automatically activated at any visit during the study period for eligible patients and provides updated treatment priorities and recommendations at each visit. Pilot data indicate that eligible patients average 4-6 primary care visits during a 24 month period, assuring that nearly all intervention patients have at least 3 exposures to the CDS. The CDS can also be manually activated by the PCP. In our previous study, almost 70% of eligible PCPs maintained use of the CDS system. With strong support from Essentia leaders and PCP leaders, we expect similar use rates.

Prediabetes patients converting to diabetes will continue to receive appropriate CV risk reduction prioritization and evidence-based glucose and aspirin treatment recommendations, thus facilitating timely treatment transition for newly diagnosed diabetes and reducing the lag time often reported between conversion to diabetes and being clinically diagnosed and treated.

Implementation of the Prediabetes CDS Intervention: Key implementation stages include: organizational engagement; adapting, piloting, and refining the Prediabetes CDS; and implementing the Prediabetes CDS group-randomized study. Key informant interviews, focus groups, surveys,usability testing, EMR data, and continuous quantitative and qualitative feedback between researchers and stakeholders will be used to monitor the implementation process and outcomes.

Organizational Engagement: As part of the initial engagement process, Essentia leaders and PCP leaders have already provided letters of support for the prediabetes CDS. Further engagement with Essentia leadership, informatics personnel, and key providers will occur through in-person meetings, conference calls, informational meetings, and identification of critical personnel to participate in the development, adaptation, and piloting processes of this study.

Adapt and Pilot Test the Prediabetes CDS: All CDS algorithms and interfaces will be extensively tested to confirm clinical validity and acceptability to providers and patients. Special attention will be given to the prioritization and treatment algorithms related to metformin use, to usability testing of the PCP and patient interface screens and the Prediabetes Smartset, and to the lifestyle intervention referral resource tool. The resource tool, updated semi-annually, will include a map and list of evidence-based programs and descriptions of location, delivery mode, program type, program intensity, potential benefits, costs, and contact information. Essentia leaders, providers, Patient Council, patients, informatics personnel, and local community organizations will be engaged in the development and adaptation process through meetings, in-person usability testing, and key informant interviews.

After initial programming, the research team will pilot the treatment and prioritization algorithms, the patient and PCP interfaces, and the Prediabetes Smartset on a series of eligible prediabetes patients. After several rounds of iterative testing, feedback, and modifications, we will recruit five PCP-nurse teams from Essentia clinics not included in the randomized implementation study and pilot the Prediabetes CDS and Care Coordination Team (CCT) protocols in eligible patients for 4 weeks. PCPs and nurses will provide written consent and offered compensation to complete online surveys and provide within-CDS and CCT protocol feedback on their experience with the CDS system, including the clinical utility of prompts and their impact on clinic workflow.

Implementation of the Randomized Control Study: We will train intervention clinics to use the CDSusing group and individual meetings with all intervention clinic PCPs, rooming nurses, and clinic staff, plus

webinars and email reminders with links to a short instructional video demonstrating rooming nurse and PCP roles in prediabetes CDS use. Training will be completed and the CDS fully implemented at all intervention clinics within 30 working days of clinic randomization. To ensure high intervention implementation fidelity, all intervention clinic staff will receive weekly email reports showing CDS rates of use among all eligible patients. The project manager will communicate (in-person, by e-mail, or by telephone) with each Intervention clinic's nurse managers each month throughout the full implementation period to assess continued use of the CDS and to gather feedback. Furthermore, the CDS provides an open-ended feedback mechanism for providersto give implementation researchers and staff timely feedback on issues, concerns, and proposed refinements about the CDS so it can be more effectively and efficiently implemented and used at the intervention clinic sites.

Ongoing communication and feedback with stakeholders throughout the engagement, adaptation, pilot testing, and implementation phases will allow us to assess various components of the RE-AIM and CFIR frameworks to best determine mediators of CDS implementation, use, clinical outcomes, and future implementation and dissemination throughout Essentia primary care clinics and other health systems.

Definition and Measurement of Variables: We will use a mixed-methods approach to examine the facilitators and barriers for (a) successfully achieving and maintaining CV risk factor control among prediabetespatients at high CV risk (Specific Aim 1) and for (b) sustainable implementation in Essentia primary care clinics(Specific Aims 2 & 3). Appendix A contains the protocol for measuring the study variables.

Aim #1- (a) Cardiovascular Risk Trajectories (H1): There is no validated CV risk engine developed with a prediabetes population. Therefore, we propose to use the ACC/AHA 10-year pooled CV risk engine to estimate annual rate of change in CV risk as our primary outcome. We will use the lipid equation for patients with lipid data available to calculate CV risk at the index and all post-index visits and, to minimize missing CV risk values, the BMI equation at the index and all post-index visits for the remaining patients. The BMI equation estimates higher CV risk relative to the lipid equation. Because the calculation method will be consistent across all visits within each patient this difference will not bias the estimated rate of change in CV risk. CV risk scores for each patient will be calculated at each primary care visit from the index through the entire follow-up period using available EHR data elements. As depicted in Figure 2 Step A, at each visit we will search for the most recent data elements, looking back over a period appropriate for each risk component (i.e., 12 months for BP values or medications, DM diagnosis, smoking, BMI; 48 months for lipids). H1 will be supported if the annual rate of change in CV risk scores from the index visit through the end of the follow-up period is lower (ie, less increase) among patients in the CDS relative to UC clinics**; (b) Modifiable diabetes and CV risk factors (H2):** Risk factors needed to calculate the CV risk scores (weight, systolic blood pressure, HDL-c, LDL-c, totalcholesterol, smoking), are extracted from EHR files as in Figure 2 Step A. H2 will be supported if annual rate of change in CV risk component trajectories are lower among patients in the CDS relative to UC clinics**; (c) Metformin and statin use (H3):** Data to assess drug treatment are from EHR files such as prescribed medications. The presence or absence of appropriate drug use will be assessed at each visit. H3 will be supported if appropriate drug use improves over the follow-up period among patients in the CDS clinics relative to UC patients.

Aim #2 – Health Care Costs (H4): Costs for this analysis include intervention costs and incrementalmedical care costs, defined from the health system perspective. Intervention costs include implementation and maintenance and training but exclude research and development costs. Standard accounting methods will be used to measure the cost of the CDS intervention. Medical care costs will include the cost of all prescribed medications and clinic services—including laboratory, lifestyle counseling, and physician services—incurred prior to and up to a 24-month post-index date period by participants in each study group, as indicated by Essentiabilling and clinical encounter data. Reliance on Essentia billing records for measuring medical care utilization may miss costs incurred in other health systems; however, this opportunity is expected to be equal across randomized study arms, and cross-system medical utilization at the clinic level is expected to be limited in this study population. For this reason, though, emergency visits and hospitalizations will be excluded from the analysis—and generally, these events are too infrequent in a sample of this size to accurately predict impact of the study intervention on hospital costs.

While market prices generally are a good estimate of the costs for medical services, the paid amount in this claims system is specific to Essentia at a particular time and may provide a biased view of costs between pre- and post-intervention periods. To address this, we will use Total Care Relative Resource Values™ (TCRRVs), which are a nationally standardized set of measures that have been endorsed by the National Quality Forum and are derived from Centers for Medicare and Medicaid Services (CMS) relative value units

(RVUs). TCRRVs extend CMS RVU measures to include utilization categories, such as laboratory services and medications, which do not have CMS RVU weights. Specifically, TCCRVs defined during the midpoint of patient accrual and follow-up (e.g., 2019) will be used to convert claims to represent U.S. dollars.

Aim #3 Facilitators and Barriers of Implementation: For this analysis, we use the personalized medicine RE-AIM framework described by Gaglio and Glasgow and selected components of the CFIR model. Key RE-AIM metrics are: a) the percent and type of patients ***reached***, b) for whom is the intervention ***effective*** in improving outcomes, c) what percent of clinics and providers have ***adopted*** the intervention, d) how consistently is the intervention ***implemented***, and e) how well are the intervention components and their effects ***maintained*** and spread. Key components of the CFIR conceptual model that will be examined include but are not limited to stakeholder perceptions on: intervention source; strength and quality of the evidence-base; iterative adaptability and testing of the CDS, including usability testing; complexity and packaging of the CDS; whether the CDS meets provider and patient needs; external policies and incentives affecting implementation; informal and formal communication processes, including CDS feedback loops; implementation climate and readiness; engagement of stakeholders; fidelity of implementation; and provider knowledge, attitudes, beliefs, and self- efficacy about the CDS.

We will examine facilitators, barriers, and solutions to the implementation process using the following **mixed methods approach**: (a) meeting minutes; (b) semi-structured interviews conducted with 8-10 key stakeholders among Essentia leaders conducted during Year 1 to understand organizational support and guide CDS adaptation and implementation and Year 4 to better understand future dissemination the CDS system; (c) CDSpatient focus groups conducted in Year 4, with discussion focused on perceived barriers and facilitators to achieving CV risk factor control, use of the CDS, and interactions with providers; (d) CDS provider focus groups conducted in Year 4 among four rural and two urban CDS intervention clinic teams and conducted during routine morning clinic meetings with discussions on patient-provider decision making, how to improve CDS use and effectiveness, and the potential for future CDS adoption by other primary care clinics; (e) cross- sectional provider surveys conducted in Year 2, (prior to implementation) and Year 4 (post-implementation) among 50 UC and 50 CDS providers to assess perceptions of primary practice systems using the 20-item Physician Practice Connection Research Survey, the 10-item System (i.e., CDS) User Scale, and other measures; and, (f) patient surveys conducted during the implementation study on a cohort of 250 CDS patients and 250 UC patients. Patient survey eligibility criteria include at least two PCP visits within 12 months before their index date, and the index visit will automatically trigger delivery of the first of two patient surveys. Surveys will be available in Spanish. Our analysis will be on participants with an index visit and at least one more visit during the study. Patient experience will be assessedusing the Clinic and Group Consumer Assessment of Healthcare Providers and Systems (CG-CAHPS). Patient perceptions of prediabetes care management will be assessed using the Patient Assessment of Care for Chronic Conditions (PACIC-plus). We will also assess patient-reported depression (PHQ-9), physical activity (BRFSS), select dietary behaviors (5-A-Day Fruit and Vegetable screener and BRFSS), and participation in clinic- and/or community-based lifestyle education, counseling, and programs.

Measures of Covariates for Primary and Secondary Analyses: One predictor of CV risk, risk factor, and drug use outcomes is the binary indicator for study condition (CDS or UC). The second key predictor is time elapsed in years between the patient's index visit to each subsequent measurement. Several other measures merit consideration as dependent outcomes, moderators or mediators in primary analyses. These include (a) number of PCP patient encounters, (b) patient characteristics including demographics and pre-intervention clinical values and comorbidities (EHR ICD-10 diagnosis codes and problem lists), and (c) provider characteristics such as age, gender, type of provider, full-time or part-time work status,, specialty board certification status, and proportion of eligible study patients. Patient or provider characteristics may also be used to adjust for covariate imbalance introduced by clinic randomization.

Analysis Plan.

Aim 1 Analytic Approach. Aim 1 pertains to the effectiveness of the Prediabetes CDS intervention, predicting that it will improve the annual rate of change in CV risk (CVR) and individual risk factors relative to UC. Patients age 40-75 at index are included in the Aim 1 analyses because the CDS was programmed to deliver the intervention via treatment recommendations (Figure 2, Step B) to this age group. Rate of change outcomes (e.g., H1, H2) will be tested using random coefficients models in which all available index and post-index outcomes (H1 CV risk, H2 CV risk factors) will be predictedfrom fixed effects for clinic-randomized treatment group, years elapsed since index CVR, the treatment by years elapsed interaction and the index outcome value. Outcomes measured only once per person will follow the same approach, omitting predictors that incorporate years elapsed since index and where warranted including an offset for follow-up time.

Random clinic and patient intercepts will account for clustered observations as appropriate. The link function and error distribution for each model will be determined by the distribution of each outcome. The relationships between years elapsed and CV risk and risk factor outcomes are expected to be linear. The tenability of this assumption will be checked for each outcome and more complex relationships (e.g., non-linear, spline) modeled if warranted.

The years elapsed parameter will estimate the annual rate of change in CV risk and risk factors among patients in UC clinics in the absence of intervention, while the treatment by years elapsed parameter estimates the difference in the annual rate of change among patients in the CDS relative to UC clinics. It is expected that CV risk will decrease, or increase at a slower rate, among patients in CDS relative to UC clinics. Similar patterns of improvement, or slower worsening, are expected for CV risk factors. Finally, the treatment group parameter is expected to estimate more appropriate pharmacologic use among patients in CDS compared to UC clinics.

2.2.6.1 H1 Sample size justification. We conducted a power analysis to estimate theminimum detectable slope of the treatment by time parameter (power=.80, α_2=.05) given the anticipated sample size (15 CDS clinics, 7-11 providers per clinic * 25 patients per provider = 2625-4125 CDS patients, 3 CVR per patient).. The patient sample size was divided by the design effect, Neff = N / [1 + (n_{clus} – 1)ρ], to approximate the effective independent patient sample size (Neff) implied by clinic intraclass correlations (ICC) of ρ = .001-.02. The CVR sample sizes (Neff patient * 3 CVR/pt) were divided by the design effect implied by a patient ICC=0.80. The resulting effective CVR sample sizes were used to estimate the minimum detectable standardized linear regression coefficient (β_{CDS}) relative to β_{UC}=0. When ICC_{clin}=0.001, the minimum detectable β_{CDS} =0.044-0.055; when ICC_{clin} =0.005 β_{CDS} =0.061-0.070; and when ICC_{clin} =0.02 β_{CDS} =0.103-0.108.

Aim 2 Analytic Approach : Incremental medical costs will be estimated using standard health econometric methods. A generalized estimating equation (typically assuming a gammadistribution and log link function) will be used to estimate annualized costs by study arm while allowing clustering by clinicand controlling for demographics, time, and baseline clinical risk factors. The marginal effect of being assignedto an intervention clinic will provide an estimate of the incremental medical cost associated with the CDS intervention. The estimates assume that the CDS is implemented in a large health system with an EHR capable of exporting data to Web-based clinical algorithms. **Aim 3 Analytic Approach:** For measures not addressed in Specific Aim #1 and #2, measures of centrality will be computed for each of the RE-AIM measures. As an example, 24-month CDS use rates will be determined to assess the completeness of implementation. Mixed models will assess changes in patient- and provider-reported outcomes using the Aim 1 analytic approach, with distributional and model modifications made as appropriate to each outcome**.** For patient and provider experience survey metrics we will describe theproportion of respondents indicating highest satisfaction for specific items at each time point and change over time for these items and for composite scales. Spearman correlations will be used to examine relationships between items, scales, and other study outcomes. Information first will be extracted and orchestrated into categories, themes, and patterns that emerge from and are grounded in data. Coding schemes will be developed and tested using the system recommended by Strauss and Corbin. Classification schemes and typologies will be used to identify and develop themes and concepts emerging from the data. Once coding has been completed and thematic and conceptualmaterial developed, we will also use descriptive data analysis to examine the importance and intensity of categories by their repetition within and across interviews, using counts and frequencies.

Missing data. Because all data elements required for calculating the Aim 1 primary outcome measures(eg, HbA1c, weight, systolic BP, LDL-c, smoking) are drawn from EHR, they will be high quality and available for virtually all tests performed for patients in the analytic dataset. The absence of a measured CV risk factor will result from lack of a factor having been assessed rather than its failure to be documented. As such,missing values will be rare and can be assumed to be missing at random.

Secondary analyses. The primary analytic model is sufficiently flexible to accommodate non-Gaussiandata by specifying alternate error distributions and link functions. As such, secondary efficacy outcomes (eg, treatment mediators and modifiers) and treatment-effect patterns (heterogeneity across demographic and clinical subgroups, persistence of effects) will be analyzed using the Aim 1 approach, with distributional accommodations and model modifications made as needed.