Improving diabetes outcomes and health disparities through a patient activation intervention addressing unmet resource needs

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all the stipulations of the protocol, including all statements regarding confidentiality, according to local legal and regulatory requirements and applicable US federal regulations.

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LIST OF ABBREVIATIONS

ACA	Affordable Care Act
CRN	Cost Related Non-Adherence
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
ED	Emergency Department
EHR	Electronic Health Record
FMBS	Financial Management Behavior Scale
GAP	Guest Assistance Program
Health-ITUEM	Health IT Usability Evaluation Model
HLC	Honey Locust Communications
IVR	Interactive Voice Response
MCDTR	Michigan Center for Diabetes and Translational Research
RCTs	Randomized Control Trials
SDH	Social Determinants of Health
UMHS	University of Michigan Health Services

1 BACKGROUND AND SCIENTIFIC RATIONALE

1.1 Project Background

High rates of health-related financial burden and unaddressed social determinants of health (SDHs) are key drivers of adverse health outcomes for people with diabetes. Increases in patient cost-sharing across all insurance types, coupled with unaddressed SDHs affecting patients' health (e.g. food insecurity, unstable housing) have created significant stressors for individuals with complex and expensive conditions like diabetes.[8-11] In 2014, 1 in 4 families reported financial burdens from managing their out-of-pocket healthcare expenses[8], and 1 in 5 reported trouble meeting basic needs.[9,12] Financial stressors (actual and perceived) are major barriers to treatment adherence.[2] Nearly one-third of chronically ill adults report cost-related non-adherence (CRN)- taking a smaller dose of medication, taking medications less frequently, delaying or not fulfilling prescriptions, and borrowing medicines from someone else to avoid additional expenses.[1] Eleven percent of people with chronic illnesses (17.5 million Americans) report both CRN and food insecurity.[9] Failure to identify and address unmet medical resource needs and SDHs leads to uncontrolled disease, high rates of avoidable healthcare use (emergency department (ED) visits, hospitalizations), high healthcare costs, and premature morbidity and mortality.[2-3,13]

Value-based reimbursement models create greater need for interventions that improve outcomes. Delivery systems increasingly operate in a value-based reimbursement structure where they are rewarded for improving patient outcomes. In every type of care setting, providers who disproportionately serve patients with social risk factors tend to have worse performance on quality measures.[7] High patient volume as a result of the Affordable Care Act (ACA) provides little time to adequately meet the needs of complex patients. Given that social factors are key determinants of health, providers serving patients with multifaceted needs require efficient and effective approaches to ensure that their patients can access affordable, necessary services and resources to effectively manage their health. Failing to do so can compromise access to care and further widen population-level health disparities.

There is increased recognition to screen for and address health-related financial burden and unmet SDHs. Most interventions seeking to address cost-related barriers to adherence have narrowly focused on price transparency and lowering insurance costs related to prescription medications.[13-14] Community and health system partnerships to address broader and health-related financial burden, have become more common with ACA initiatives.[15] The typology of different approaches include integrated efforts between different entities (e.g. state, health plan, health system) and social service and community resource organizations. Randomized controlled trials of screening tools for unmet SDHs have shown increased uptake of social resources and fewer unmet needs among patients.[16-18] Pre-post evaluations and retrospective analyses of coordinated health-system community organization programs have shown reduced urgent care use and lower expenditures for high utilizers of care.[19-21] However, few rigorous evaluations are available on the most effective approaches that improve care outcomes, especially disease control. Proven approaches for screening and addressing health-related financial burden and unmet SDHs are heavily reliant on deployment of personnel to conduct screening. These programs are not scalable and very few employ universal screening of their patients or provide adequate follow-up. Further, we would not locate any interventions that address these needs alongside proven approaches to addressing broader determinants of adherence.

Need for effective, scalable interventions to address SDHs that do not overburden delivery systems. Evidence-based, scalable interventions are needed to address health-

related financial burdens and unmet SDHs that impair the ability of adults to effectively manage their chronic conditions. Delivery systems are increasingly pressured to simultaneously implement guideline-recommend care, quality and prevention efforts and behavioral counseling on a growing population of complex patients. New approaches and tools are needed to support complex patients that does not compromise time and resources needed to provide optimal care. Screening for and addressing SDHs must be comprehensive, feasible, evidence-based, and efficient. Activating patients to address health-related financial burden and unmet SDHs is an investment that would maximize the time of both patients and providers, and become generalizable to diverse practice settings. Technology-based approaches represent a promising, scalable approach to screen for SDHs, provide information on locally available resources to meet identified needs, and prompt patients to seek out resources, share information efficiently with their providers, and make behavior changes that can improve health status.[22] Communication technologies such as smartphones and tablets that provide internet access are increasingly available to patients across the spectrum of socioeconomic status.[23-24] Text-messaging and interactive voice response (IVR) methods are effective in improving patient monitoring, self-care behaviors, adherence, and in turn disease control.[25-30] They can also be integrated into health systems given the universal adoption of electronic health records. We reviewed >100 chronic disease and financial management/literacy mobile apps available on the market. We found that none link individuals to low-cost resources that comprehensively address health-related financial burden and SDHs, while also providing skills training and feedback in navigating complex healthcare and community resource infrastructures, and attending to other determinants of meeting disease management goals.

Activating patients to address health-related financial burden and SDHs could have broad translational impact and improve diabetes outcomes. The high prevalence of patients' health-related financial burdens and unmet SDHs, the lack of attention these burdens receive in clinical settings, and the serious consequences of CRN on health all underscore the need to test and evaluate practical, scalable, and effective solutions to the spectrum of burdens impacting health. Through the proposed study, we will provide a more in-depth understanding of the extent to which automating screening to identify health-related financial burdens and unmet SDHs before clinic visits, and activating patients to take steps to access suggested resources and engage in self-care, improves disease control. We will also identify the mechanisms through which this occurs. This contribution could have broad translational importance to improving clinical outcomes of complex patients and reducing health disparities in an era where delivery systems strapped for time and resources must re-orient to value-based reimbursement models.

Unaddressed SDHs and socioeconomic vulnerabilities will be critical issues for our country into the foreseeable future. Although the ACA increased access to care, gaps in health insurance eligibility and benefits persist, and costs to consumers are rising annually and creating significant national concern. Diabetes and many other chronic conditions have high out-of-pocket costs for testing supplies and special foods that will likely never be fully covered, even with a single payer system. Automated resource delivery through our intervention is expected to benefit a wide range of people, especially the under-insured, who comprise about 25% of the population (31 million people), primarily low and middle-income families.[33]

Current approaches to screen for and address health-related financial burden and unmet SDHs are fragmented, and not offered to all patients with or at risk for poor health outcomes. Accessing resources is heavily reliant on time-limited providers. We do not know whether and how addressing health-related financial burden and unmet SDH's in clinical settings actually

improves health outcomes. Such evidence is necessary to reduce disparities and support wider adoption of effective strategies in an era of value-based reimbursement.

The proposed research is innovative because it represents a substantive departure from the status quo by providing a comprehensive, low-literacy e-health tool to guide patients through identification of health-related financial burdens and unmet SDHs that impact disease management, support to link them to resources, and effectively communicate with providers around these needs, while simultaneously addressing broader determinants of adherence. The proposed work will evaluate the effectiveness of this approach in a high risk, uncontrolled diabetes population. It will also provide rich information on how the impact of our intervention on health status and disease control is different across groups defined by patient characteristics. Aim 2 will also provide evidence regarding behavioral mechanisms through which improved outcomes are achieved in Aim 1. The e-health intervention 1) includes generalizable resources, 2) generates a summary of identified needs and resources for the patient to give their providers in an easily digestible format, and 3) can be easily integrated into comprehensive chronic disease self-management programs and delivery systems that do not have consistent processes for addressing economic issues or unmet social needs. Given the increasing penetration of health IT in low-resource populations, our approach of using a web-based intervention optimized to tablets and smartphones will be increasingly generalizable, and thus have the capacity to enhance health in high-risk groups. Our preliminary data (see Approach subsection) suggests that activating patients, automating the process to link them to resources, and providing automated follow-up to support self-care is highly acceptable and changes behavior. Our intervention will address a significant gap in care by addressing modifiable social and behavioral determinants of health outcomes by providing a practical, accessible, and scalable way of delivering options to meet diverse patient needs.

1.2 Preliminary work

1.2.1 Expertise: This proposal is informed by a pilot study from the PI and co-investigators' expertise and prior work. Our multidisciplinary team is ideally suited to conduct this research. **The PI, Dr. Minal Patel, is a new/early stage investigator.** She has published 10 first-authored peer-review studies examining health-related financial burden, CRN, and unmet SDHs in the management of chronic illnesses, which inform this proposal and the completed pilot work described below. Dr. Patel designed CareAvenue and led the pilot study. She is currently the PI on funded studies aiming to develop and evaluate e-health interventions, including a multi-site trial to increase capacity for health insurance navigation in economically disadvantaged communities. **Dr. Michele Heisler** is a primary care physician who has led multiple randomized control trials (RCT) of health system-based approaches to improve outreach and support for patients with complex needs, especially in primary care. She is also the director of the Michigan Center for Diabetes and Translational Research Center's (MCDTR) Peer Support Core. The proposed study will draw on her expertise in the clinical management of diabetes, CRN, addressing SDHs in clinical settings, prior federally funded RCTs of health system-based diabetes programs, and the development and evaluation of successful e-health tools to help prepare diabetes patients before care visits to prioritize their needs. **Dr. Kenneth Resnicow** is an internationally recognized expert in design and evaluation of health promotion and e-health interventions in community and primary care settings. The proposed study will draw on his expertise in conceptualizing and designing theory-based tailoring, and autonomy-supportive interventions that train diverse patients in action-oriented communication techniques. **Dr. John Piette** is the Associate Director of the MCDTR and the head of MCDTR's Intervention and Technology Core. Dr. Piette has more than 15 years of experience developing effective IVR systems and text messaging protocols to enhance chronic illness care domestically and in low-

resource settings. The proposed study will draw on this expertise in CRN, and prior RCTs using e-health interventions to improve self-management and outcomes among vulnerable populations with diabetes and other chronic illnesses. **Dr. Hae Mi Choe** is a clinical pharmacist member of the leadership team overseeing diabetes innovation within the University of Michigan Health system. She has expertise in the expansion of the pharmacist role in ambulatory care clinics and the integration of new technologies in primary care. The proposed study will draw on her expertise to develop content that improves patient awareness of the ability of health professionals, such as pharmacists, to address economic burden and unmet social needs. **Dr. Peter Song** is a statistician with extensive experience in developing analytic methods for correlated data from longitudinal surveys with applications in chronic disease studies. His extensive published work in biostatistics aligns with the proposed research, such as longitudinal data design and analysis, methods of handling missing data and confounders, and mediation analysis. **Dr. Xu Shi** is an Assistant Professor of Biostatistics. Her research focuses on developing novel statistical methods for high volume and high variability administrative healthcare data such as the electronic health records (EHR) data. She has extensive experience in longitudinal data analysis, causal influence, data linkage and interoperability, natural language processing, and semiparametric efficiency theory. Drs. Patel, Heisler, Resnicow, Choe, and Piette are all affiliated with the MCDTR (NIDDK-P30DK092926).

1.2.2 Pilot study of CareAvenue (HUM00097785): CRN and unmet SDH screening and feedback

The PI (with mentorship from co-investigators Heisler and Resnicow) recently completed a pilot study of CareAvenue- an automated, pre-visit, e-health intervention designed to identify perceived financial burdens and unmet SDHs, and provide solutions.[6] (This initial pilot study (HUM00097785) informed both the pilot and intervention components of the study described in this protocol (HUM00149794)) Through the pilot, we 1) successfully identified diabetes patients experiencing CRN or financial burden, 2) identified both health-related and broader unmet needs impacting patients' self-management, and 3) prompted patients to address these risk factors; all without relying on clinical staff and personnel to deploy the intervention. We recruited 101 individuals with diabetes reporting CRN or perceived financial burden at the time of clinic visits at the University of Michigan Health System Metabolism, Endocrinology & Diabetes Clinic. Eligible participants were asked to use CareAvenue on a tablet (it took 5 minutes to complete the process). CareAvenue first asked participants to identify their sources of financial burden related to their diabetes management and rate each burden on a 5-point Likert scale. It then asked them to identify diabetes-specific and broader basic needs (e.g. food assistance, housing, employment) that they would like more information on. Based on their insurance and information preferences, CareAvenue then generated a list of both local and national resources. A trained research assistant then printed and gave the tailored resource list to the participant before the participant saw his/her provider. All resources underwent critical review by four clinic social workers.

In this feasibility pilot, outcomes of interest included CRN behaviors, uptake of resources, diabetes distress, and communication. Each domain was measured using items adapted from previous studies[33-35] at baseline and 2-months following participants' use of CareAvenue. The Health IT Usability Evaluation Model (Health-ITUEM) framework[36] informed the assessment of perceived ease of use and perceived usefulness of CareAvenue via validated instruments.[37-38]

The mean age of participants was 50 years (SD=15.3), 47% reported a household income <$40,000/year, and 37% were unemployed, thus increasing generalizability to socioeconomically vulnerable patients. Participants found the intervention to be relevant and useful. Acceptability of CareAvenue across 14 indicators was >90%, and we had a 94% retention rate at the 2-month follow-up.

Because this was a feasibility study including a sample of only 101 participants and short follow-up, we were limited in statistical power. However, our outcomes demonstrated improvement in the hypothesized direction 2-months after using CareAvenue (see Table 1). We saw changes in uptake of cost-reducing resources 2-months post intervention, including purchasing food at farmers' markets and food assistance programs (32% to 36%), and use of online diabetes educational resources (29% to 40%), medications savings clubs through local retailers (9% to 15%), and support groups (9% to 16%).[6] More individuals reported that they discussed their concerns with health professionals (13% to 25%). We saw significant increases in household financial management measured through the Financial Management Behavior Scale ($p<0.01$).[39] Our findings were similar when comparing subsets of participants with high versus low literacy levels. The positive impact of the intervention was seen among the most vulnerable participants: lowest income, low education, unemployed, taking 7 or more medications, high out-of-pocket diabetes-related expenses, moderate to high diabetes-related distress (see Table 1). Overall, our study found that regardless of patient health literacy, automated pre-visit screening and feedback for health-related financial burden was both feasible and acceptable and significantly improved uptake of resources, communication with health professionals, and fewer individuals were skipping doses of medicine due to cost over a 2-month period.

Factors	Baseline	2-month follow-up
Patient-provider discussion of out-of-pocket costs	33%	36%
Talking to the pharmacist about out-of-pocket costs	13%	25%
Patient perception of importance of out-of-pocket cost discussion	84%	88%
High level of diabetes-related distress	43%	38%
CRN behaviors		
Taking small doses to save money	9%	6%
Missed doses due to cost	11%	4%
Deciding not to fill or refill a prescription	13%	10%
Spending less money on food or basic needs to pay for medicine	15%	9%

Table 1: CareAvenue Pilot Test Outcomes

2 OBJECTIVES

The overall objective is to determine the extent to which activating patients to address health-related financial burdens that impact treatment adherence and unmet SDHs improves disease control, and the mechanisms through which primary and secondary outcomes are achieved. The specific aims of the study are listed below.

Aim 1: Determine the effectiveness of CareAvenue relative to usual care in improving glycemic control and patient-centered outcomes such as CRN behaviors and perceived financial burdens. We hypothesize that participants randomized to CareAvenue will have a change inHbA1c (**primary outcome**) compared to usual care. We will measure the change in HbA1c at baseline, 6 months (-2 weeks/+4 weeks), and 12 months (-2 weeks/+4 weeks) using an HbA1c machine. Additionally, we hypothesize that other patient-centered outcomes (**secondary outcomes**) will change compared to usual care. Secondary outcomes will be measured at baseline, 6 months (-2 weeks/+4 weeks), and 12 months (-2 weeks/+4 weeks). They include blood pressure (measured with an automated blood pressure cuff), Cost-related non-adherence behaviors with prescribed treatment regimens related to diabetes, Cost-related non-adherence behaviors with prescribed treatment regimens related to other conditions being managed, Perceived financial burden, and unmet social risk factors.

Aim 2: Examine mediators and moderators of the effectiveness of CareAvenue on primary and secondary outcomes. We hypothesize that the intervention will significantly improve skills and self-efficacy in uptake and use of resources leading to decreased financial burdens, perceived stress of unmet SDHs, and improved adherence to treatment regimens, with these changes being the primary mechanism through which improvements in glycemic control are achieved. We also hypothesize that CareAvenue will be most effective among patients with high need for resources and low self-efficacy in navigating resources at baseline.

3 EXPECTED RISKS AND BENEFITS

3.1 Expected Risks

3.1.1 Confidentiality

Risk: Breech of confidentiality of information and identification.
Likelihood of risk: Rare
Seriousness to the subject: Information about the participants health, financial situation, and demographic information connected to their identify (age, marital status, etc.) may be obtained by someone outside of research staff
Measures taken to minimize risk: All recruitment and data collection activities will take place in private rooms. All data collected will be coded so that no direct participant identifiers are linked with data. Access to the code that links data with identifiable information will be held only by the Data Manager and Project Manager. All other research staff, including the data collection staff, and the investigators will only have access to specific and select information on an 'as needed' basis. The coded database will be password protected and stored on a secured, encrypted University of Michigan drive.

When data must be shared for study purposes it will be shared through the University of Michigan School of Public Health secure, HIPAA-compliant fax line or stored virtually via a secure, HIPAA-compliant web application hosted by the University of Michigan, DropBox at U-M, or through MiShare, a secure virtual file transfer system hosted by Michigan Medicine Health Information Technology & Services (HITS).

Participant data for IVR calls will be maintained by a HIPAA-compliant platform within the University of Michigan Health System. All participant data collected and transmitted through the intervention website will be sent encrypted via TLS/SSL secure transfer.

SMS participant data will be stored on HIPAA-compliant University of Michigan servers. In order to send and receive SMS messages, the SMS platform will transmit and receive messages through Twilio. Messages will be automatically redacted from Twilio's servers, to ensure that participants' messages and identifiable data such as phone numbers are not stored in Twilio's logs.

To the extent that logbooks or paper records need to be maintained for purposes of the study, they will be kept locked in file cabinets in a locked room accessible to research staff only. All consent forms will be stored in the same manner. All data with identifiable

information be destroyed as soon as it is no longer needed for completion of study related activities.

3.1.2 Risks Related to HbA1C Fingerstick

Risk: Discomfort at the site of the blood draw from the HbA1c rapid test.
Likelihood of risk: Likely
Seriousness: Bruising, bleeding, or slight swelling at the site of the stick

Risk: Fainting from the blood draw from the HbA1C rapid test
Likelihood: Rare
Seriousness: Participant will need professional medical assessment

Risk: Local infection from the blood draw from the HbA1C rapid test
Likelihood: Rare
Seriousness: Ranging from need for over the counter antibiotics to the need for professional medical treatment

Measures taken to minimize the risk: The first procedure of protecting participants from risks associated with the HbA1c test using a rapid fingerstick is proper training of all research staff taking these assessments in line with university of federal guidelines. Staff of the University of Michigan Department of Pathology will thoroughly train research staff on taking HbA1c assessment using established protocols (see letter of support). Procedures include those that emphasize sanitation, cleaning the site of the prick with alcohol before and after, and properly disposing of gloves and fingersticks after each assessment. Once trained, research staff can train additional staff on use of the HbA1c machine. A second protection for participants from risks associated with the HbA1c test using a rapid fingerstick is providing first aid and standard procedures in line with university and federal guidelines in the event of an adverse health event. All research staff will undergo Biosafety Training for Laboratory Personnel offered by the University of Michigan Institutional Biosafety Committee. For participants in the virtual appointments, trained staff will provide additional support and instructions during the at-home testing of HbA1c.

3.2 Expected Benefits

The proposed work has potential to streamline how non-medical issues are addressed in clinical settings. This work has significant potential to promote adherence with diabetes treatment regimens and has the potential for significant impact in improving the management of chronic conditions and their associated complications.

The potential benefits for participants in this study include direct assistance with addressing CRN issues related to uncontrolled diabetes, less perceived financial burden with diabetes care, and fewer unmet needs.

4 ELIGIBILITY

The study population will be adults (over 18) with poorly-controlled diabetes treated in a large healthcare system who engage in CRN or perceive health-related financial burdens.

4.1 Inclusion and Exclusion Criteria

Study participants will meet the following criteria:

- 18-75 years of age
- Have access to a telephone that can receive and send text messages
- diagnosis of diabetes with prescribed anti-hyperglycemic medication
- most recent (within the past 6 months) recorded hemoglobin A1c (HbA1c) level of ≥7.5% for individuals ≤70 years and >8.0% for individuals between 70-75 years in age
- positive report of financial burden or CRN using screening questions developed and validated from prior work[33-37]

Exclusion criteria include significant cognitive impairment precluding individuals from completing the study as evidenced by ability to complete study intake procedures and current participation in another diabetes study.

4.2 Source of Participants

We will recruit potential participants from the University of Michigan's Diabetes Research Registry and the University of Michigan Medical School Office of Research DataDirect. The Diabetes Research Registry and DataDirect meet HIPAA security and privacy requirements and provide streamlined access to potential participants' electronic health records (EHR). The study team will be accessing participants' electronic health records (EHR) via the Diabetes Research Registry and the University of Michigan Medical School Office of Research DataDirect. Over 6,000 (18–75 years) diabetes patients are included in the registry and receive care at the University of Michigan's ambulatory care clinics. Thirty percent of registrants have type 1 diabetes, and 70% have type 2 diabetes, with equal proportions of men (49.6%) and women (50.4%). Mean age is 54.3 ± 15.9 years, mean duration of diabetes is 15.8 ± 11.2 years, and 30% of registrants are racial/ethnic minorities.[46] Registrants tend to have many complications and comorbidities, thus an ideal population for the proposed study. As of January 2017, the proportion of adult patients in the Diabetes Research Registry with an HbA1c test ≤ 7 was only 24%, and the proportion with HbA1c ≥9 was 24%. From our pilot study in the same health system, 77% of individuals approached and interested in participating reported either financial burden with their diabetes treatments or engaging in a CRN behavior, 47% reported a household income <$40,000/year, and 37% were unemployed. Based on these data and the high retention in our pilot study at follow-up (94%), the Diabetes Research Registry will provide an adequate recruitment pool of at least 1,500 eligible participants to achieve our recruitment and retention goals.

4.3 Vulnerable Populations

4.3.1 Inclusion of Women and Minorities: We will enroll eligible patients who give informed consent, regardless of their gender, race, or ethnicity. We expect the study to roughly reflect the racial, ethnic, and gender distribution of the University of Michigan Diabetes Research Registry (DRR)'s patients with diagnosed diabetes. The DRR has over 5,000 registrants, 30% with type 1 diabetes and 70% with type 2 diabetes. There are almost equal proportions of men (49.6%) and women (50.4%), average age is 54.3 ± 15.9 years, and average duration of diabetes is 15.8 ± 11.2 (Mean ± SD) years. Thirty percent of DRR patients are racial/ethnic minorities. We are oversampling African American and Latino/Hispanic participants by 50%. Every effort will be made to recruit racial and ethnic minority patients and

various genders. We will also recruit participants accessed through the University of Michigan Medical School Office of Research's DataDirect.

4.3.2 Inclusion of Children: This study will focus on adults with a diagnosis of diabetes over the age of 18. Individuals under the age of 18 will be excluded from this study given their financial dependence on an adult. The intervention is designed at the cognitive and developmental and decision-making ability of adults over the age of 18. Children may directly benefit from the intervention through the inclusion of adults, given that the intervention may benefit the household financial situation, therefore an additional intervention exclusive to children may be needlessly redundant.

4.3.3 Economically or Educationally Deprived: As this study population has inclusion criteria of positive report of financial burden or CRN, people with low-income are a key audience for this intervention.

5 PARTICIPANT ENROLLMENT AND RETENTION

5.1 Participant Enrollment

Trained recruitment staff will make initial contact with potential participants via phone or email. Email, address, and telephone lists will be obtained from the University of Michigan Diabetes Research Registry and DataDirect. A study flyer containing study information will also be posted in University of Michigan locations and clinics. Potential participants will be provided with general information about the study and what would be required in order to participate. Participants will be contacted during normal business and early evening hours.

Potential participants who indicate interest in the study will be screened for inclusion/exclusion criteria over the phone. Those participants who are interested in being part of the study and are eligible to participate will be read pertinent parts of the consent form in order to provide them with a thorough understanding of the potential risks and benefits (participants will also go through a full consent process prior to initial data collection). If a potential participant indicates they are interested and are screened eligible but are then difficult to reach, the study team will mail them the study flyer previously mentioned that was posted in UM locations and clinics.

All recruitment and screening will take place in private rooms to ensure participant privacy. Messages left for the participant will not disclose any information about the potential participant. No information about the participant or study will be given to anyone who answers the phone other than the participant. All information with personal identifiers will be stored in either a locked cabinet in a locked office (when paper log books are needed) or on a secured drive on password protected computers.

For patients who are not able to be reached, decline participation, or are ineligible, patient subject identifiers will be destroyed as soon as possible once one of these terminating events occurs. Data will be collected from people who indicate they are not interested in participating in the study (i.e., reason for non-interest, socio-demographics for participants who are eligible and still not interested). We will also collect ineligibility reason for people who are determined to be ineligible to participate in the study. This data will be anonymized with all personal identifiers attached to the information destroyed. The aggregate, anonymized data will be kept for analysis.

5.2 Participant Retention

To further support participant retention the study team will mail participants a series of postcards throughout study participation: thank you postcard, scheduling reminder postcard, happy birthday postcard.

6 STUDY DESIGN AND PROCEDURES

6.1 Experimental Design and Randomization

We will test our hypotheses using a two arm-randomized control trial. In exploratory analyses, we will examine individual differences in response to treatment. We will collect outcome data at 3 time points: baseline, and 6 (-2 weeks/+4 weeks) and 12 months (-2 weeks/+4 weeks) after initial engagement with CareAvenue**.** Data collectors and analysts will be blind to the study hypotheses, and analysts will be further blinded by which group participants are allocated to.

Participants will be randomized to either usual care or the intervention group receiving CareAvenue. Usual care is defined as existing practices for addressing patients' financial burden and non-medical issues in the clinic flow. We will provide all control group participants with contact information for the Guest Assistance Program (GAP) at the University of Michigan Health System (UMHS). GAP provides assistance with medical and non-medical needs and resources to patients receiving medical care at UMHS. It consists of social workers who work with clients to help them access a variety of resources. Providing contact information for GAP to the control arm will ensure another layer of blinding of the intervention, and provides an opportunity to assess the benefits of an autonomy supportive, multi-component skills-training intervention on outcomes.

6.2 Study Participation

The study duration is five years. The recruitment phase of the study begins in year one and final data collection concludes in year 5. A study timeline can be found in Appendix 1. Individual participant participation will last approximately 1 year from time of enrollment to completion of data collection. See Appendix 2 for a flowchart outlining participant participation requirements throughout the study.

6.3 Overview of the CareAvenue Intervention

CareAvenue, is an interactive website optimized for use on a smartphone or tablet interface. CareAvenue can be completed independently by participants with a variety of computer literacy levels. Our initial pilot work (HUM00097785) demonstrated that no participants, even those with low health literacy, required technical assistance to complete CareAvenue. The PI's current work in low-income, ethnically diverse populations with a low-literacy website intervention embedded with videos also demonstrates that participants require little assistance in navigating website content. Figure 2 shows a flow diagram of CareAvenue. Following an introduction video for CareAvenue, participants will be asked to select aspects of their health and unmet basic needs they find financially burdensome. Additionally, participants will be asked to select resources for which they would like more information on low-cost options. Participants will then watch a video to learn about different care team members and their roles. Then participants will be routed through 5 different categories of resource domains focusing on health and unmet social risk factors in sequential order: 1) medications/supplies, 2) nutrition and food access, 3) diabetes education, 4) health insurance issues, 5) other unmet needs. Figure 2 details the resources. For all resources, we will use an existing, comprehensive resource available

nationwide that connects people to local resources. For each resource, participants will be given instructions on how to navigate the resource on their own. Users will also view videos (in each resource domain) to learn about the different resources and how to communicate with their provider and other health care team members to obtain assistance. After participants review the five domains, they will view a video on practical tips for financial management (see description below). Finally, for each participant, the website will generate an action plan listing the participants' responses, a list of the care team members, a list of the resources for the domains shown in the website, and the financial management topics. Participants will be encouraged to give their provider a copy of the action plan, which will be generated in an easily digestible format to facilitate efficiency in patient-provider communication. CareAvenue will provide options to either print out the action plan to bring to a clinic visit, or request the study team to mail it to the participant or have the study team facilitate the plan being incorporated into their medical health record with HITS support; members of the study team will not access the health record.

6.3.1 Videos: In Year 1, we are developing a series of 8, 1-5 minute videos to embed into CareAvenue. An introduction video will be created to explain what CareAvenue can offer and how to use it. A video will be developed to introduce participants to different care team members. Five videos will be developed to correspond to each of the available solutions guiding participants through the process of navigating communication with their doctor and care team about obtaining resources for selected burdens and learning about the possible benefits of each recommendation. See Appendix 3 for a full breakdown of intervention topics.

A series of focus groups with physicians by the PI[40] revealed that physicians would like to be able to better utilize the care team to address patient's financial burden and unmet needs. Video modeling can facilitate the learning of new behaviors.[41] The videos will help model for participants how to ask their doctor to obtain a referral or facilitate connection to available professionals within the care team with expertise on addressing specific sources of burden. It will also explain the roles of different health professionals and who is best equipped to assist with specific sources of burden. The last video will describe best practices for household financial management. Best practices will be derived from the Financial Management Behavior Scale (FMBS), a highly reliable measure of financial management, savings and consumer debt (Cronbach alpha=0.81).[39] The FMBS was reviewed by financial planners and counselors during development, who verified it has high content and face validity in measuring important financial management behaviors such as staying within a budget or spending plan and saving money from each paycheck.[39] The video we develop will illustrate broad tips from the four domains of the FMBS: 1) cash management, 2) savings and investment, 3) credit management/use, and 4) insurance.

The videos will be developed using storytelling methods to communicate key learning points. Storytelling is an effective patient education method for inspiring behavior change and increasing health literacy by simplifying complex ideas while making them actionable in a short period of time.[42-43] We will use realistic scenarios, case studies, and characters in an active learning, entertaining format to present content. Honey Locust Communications (HLC) (see Support Letter) is developing the videos and making adjustments to the CareAvenue website in partnership with QUICCC NextGen led by Dr. Piette (see Resources). HLC will use user-centered design principles.[44] They will use words, phrases and concepts familiar to the user, rather than system-oriented terms. Only relevant information will appear in a natural and logical order designed in a manner that minimizes the user's memory load.

6.3.2 Follow-up via IVR and text-messaging: Automated IVR and text-message follow-up will be incorporated into the intervention for 1) inquiry around needs being met and appropriate

follow-up (IVR), 2) self-management support (IVR), 3) behavioral reinforcement (text-message), 4) motivation (text-message). These methods have a proven track record for fostering adherence behavior in chronic disease management broadly.[29-30] We will develop a bank of text messages tailored to intervention content and oriented towards behavioral activation to follow up with resources. Text messages will be sent to participants 3-5 times per week (4-5 times per week for intervention participants and 3-4 times a week for control participants) for 52 weeks. The intervention text messages include content about CareAvenue, whereas the control messages do not. Both intervention and control participants will receive a text message each week asking them to respond with how they rate their diabetes management. A feedback text response will be sent back to participants based on their diabetes management rating. IVR calls allow patients to receive information and respond using their mobile or landline telephone. Additionally, for the intervention participants we will develop IVR messages that inquire about follow-up with resources and ease of access, and automated messages back to the study team if the participant reports needing additional help in navigating resources. IVR calls will be placed on days and times that the intervention participant indicates are convenient, with automatic call-backs in the event that the call is not completed. Each call will take less than 5 minutes to complete, depending on patients' responses. In prior studies, patients have completed more than 80% of weekly IVR assessments over the course of a year.[25-28] Both IVR and text messaging will be supported by the HIPAA-compliant platform within the University of Michigan Health System.

Pilot Amendments: Amendment 00086864/Amendment 00088719

We will first develop a prototype of CareAvenue refinements and pilot results with a group of 5 participants with type 1 or type 2 diabetes. Participants will be recruited from the UM Health Research Participant Registry and will have varying literacy levels. Participants will be recruited by phone. One-on-one interviews will be conducted with participants at the Ypsilanti District Library. Participants will be asked to complete 3 one-on-one interviews. The 3 interviews will test the CareAvenue prototype for the following:

1. Using the Health-IUEM framework [36], we will then assess error prevention, information needs, memorability, learnability, and flexibility/customizability.
2. We will also evaluate the acceptability of the IVR telephone and text messaging administration and content in order to verify the suitability of our content and estimate IVR call length.
3. We will also assess the acceptability of the CareAvenue website in regards to resource content and user experience.

All participants recruited for assessing user-centered design for the refinements of CareAvenue will be given a $25 MasterCard gift card per interview. Based on their feedback, refinements to CareAvenue will be made.

6.4 Survey

Through the baseline, 6-month (-2 weeks/+4 weeks) and 12-month (-2 weeks/+4 weeks) surveys, we will ascertain key demographic data, health insurance coverage, income, other household information, self-report of unmet basic needs, and resources for addressing financial burdens currently being utilized. Via self-report measures, we will also assess communication with health care professionals, navigation and uptake of resources, and financial management behaviors.[5,39] We will also obtain self-report information about participants' clinical history, including polypharmacy. We will also include validated survey measures to assess depressive

symptoms and diabetes-related distress (DDS[54]), and health literacy. All other measures are identified throughout the surveys. Primary and secondary outcomes are shown below in Table 2.

Research staff will collect survey data via a computer-assisted interview. In-person interviews will take place in a private room located at Domino's Farms or other University of Michigan location. Patients will be provided with detailed directions to the space. Interviews conducted as a virtual appointment will take place via phone. All research staff will complete PEERRS and Good Clinical Practice training as well as training on best practices in data collection from the study Project Manager and Recruitment Coordinator. Through the use of trained research staff to administer the study, we anticipate being able to collect the most complete data possible. We do not anticipate any foreign language concerns in administering the survey. All efforts will be made to ensure that study materials including the survey are in plain language. Additionally, the survey will be administered by research staff, so no reading of the survey will be required by patients.

	Measures	Outcome
Primary Outcomes	HbA1c	• Change in HbA1c will be measured at baseline, 6 months, and 12 months using HbA1c machine. HbA1c is a measure of the average level of glucose in blood over the past 3 months measured as a percentage.
Secondary Outcomes	Blood Pressure	• Change in blood pressure will be measured at baseline, 6 months, and 12 months using an automated blood pressure machine. Blood pressure is measured as systolic blood pressure/diastolic blood pressure in millimeters of mercury (e.g., 120/80 mm Hg).
	Cost-related nonadherence behaviors with prescribed treatment regimens related to diabetes	• Cost-Related Non-Adherence (CRN) Behaviors related to diabetes will be measured at baseline, 6 months, and 12 months by 4-items adapted from the Medicare Current Beneficiary Survey and 2 items adapted from the National Health Interview Survey that look at diabetes. The items are measured with a 4-point Likert scale. Participants answering "often" or "sometimes" to any of the items are indicated as exhibiting CRN.
	Cost-related nonadherence behaviors with prescribed treatment regimens related to other conditions being managed	• Cost-Related Non-Adherence (CRN) Behaviors related to other conditions being managed will be measured at baseline, 6 months, and 12 months by 4-items adapted from the Medicare Current Beneficiary Survey and 2 items adapted from the National Health Interview Survey that look at other health conditions being managed. The items are measured with a 4-point Likert scale. Participants answering "often" or "sometimes" to any of the items are indicated as exhibiting CRN.
	Perceived financial burden	• Perceived Financial Burden will be measured at baseline, 6 months, and 12 months by the 12-item measure Comprehensive Score for Financial Toxicity (COST) – Functional Assessment of Chronic Illness Therapy (FACIT). The items are measured with a 5-point Likert scale. The higher the score the better the Financial well-being.
	Unmet Social Risk Factors	• Change in Unmet Social Risk Factors will be measured at baseline, 6 months, and 12 months by 20 items adapted from the Accountable Health Communities Health-Related Social Needs Screening Tool, the Health Leads Social Needs Screening Toolkit, and the Kaiser Permanente Your Current Life Situation Questionnaire. The item values are binary (yes/no). Number of "yes" responses indicates number of unmet social risk factors.
	Unmet Social Risk Factors	• Change in Unmet Social Risk Factors will be measured at baseline, 6 months, and 12 months by 3 items from the Accountable Health Communities Health-Related Social Needs Screening Tool and 1 item adapted from the National Health Interview Survey. The items each have three response options, in which a positive response indicates an unmet social risk factors.

7 DATA COLLECTION AND MANAGEMENT PROCEDURES

7.1 Data collection

Participants will complete 3 data collection appointments. Each appointment will last approximately 90 minutes and will consist of a survey assessment, an HbA1C test, and two blood pressure readings. Participants enrolled prior to AME00101220 were enrolled in-person and completed surveys and assessments in-person; following AME00101220 all surveys and assessments for all participants are conducted virtually via phone. The baseline survey will be

given to participants prior to randomization. At the baseline appointment participants randomized to the intervention group will be asked to engage with the CareAvenue website on a tablet provided for use on-site or on own personal devices for virtual appointments. They will be asked to complete the website, which will take up to 20 minutes, and will also be provided a unique username and ID to login to the website on their own time.

Trained research staff will collect survey data via a computer-assisted interview through the use of Qualtrics software. We will assess HbA1c with an HbA1c machine. For in-person appointments research staff will be trained in best practices for HbA1c assessment by staff of the University of Michigan Department of Pathology. Once trained, research staff can train additional staff on use of the HbA1c machine. The HbA1C reading will be entered into Qualtrics. We will take the participant's blood pressure readings using an automatic blood pressure monitor. The blood pressure readings will also be entered into Qualtrics. Participants completing virtual appointments will obtain these measurements using at-home testing supplies provided by the study team.

All data will be downloaded from Qualtrics into a CSV file. This file will then be uploaded into SAS to create the study database.

7.2 Process evaluation

On a regular basis once the intervention is deployed, a research staff member will monitor resources being promoted. We will measure program engagement by completed IVR calls and web analytics data (e.g. unique log-ins, time on page, click throughs, etc).

We will also assess experience with the program with a purposive sample of intervention participants selected based on differing levels of engagement with the intervention.

7.3 Data Safety

The Data Manager will audit data collection processes on a weekly basis in order to ensure study procedures related to data safety are being followed. Any issues will be reported to the Project Manager and PI within 24 hours of identifying the problem. Weekly meetings will be held between the Project Manager and research staff and data collectors to provide an opportunity for discussing general interviewing issues and issues of confidentiality. The Project Manager will report directly to the PI on a weekly basis or per the adverse event timeline available in the DSMP in Appendix 5.

Only the Project Manager, Data Manager, and Recruitment Coordinator will have access to data and participant identifiers. All other research staff, including the data collection staff, and the investigators will only have access to specific and select information on an 'as needed' basis in order to conduct recruitment, data collection, or the intervention.

All data collected will be coded so that no direct participant identifiers are linked with the data. Access to the code that links data with participant identifiers will be held only by the Data Manager and Project Manager. All electronic files will be stored on the U:\ drive, the HIPAA-compliant MiStorage service with the Common Internet File System (CIFS) protocol on storage appliances from NetApp and EMC, maintained by the University of Michigan Information and Technology Services at the University of Michigan in the Michigan Academic Computing Center (MACC). The MACC is a highly secure data center with advanced facility security systems including card scanning systems, cameras, closed circuit television, and monitoring to restrict access to appropriate Data Center Operations personnel and approved faculty and staff. Physical access to the server is limited to trained and authorized system administrator employed by ITS.

Participant data for IVR calls will be maintained by a HIPAA-compliant platform within the University of Michigan Health System. All participant data collected and transmitted through the intervention website will be sent encrypted via TLS/SSL secure transfer.

SMS participant data will be stored on HIPAA-compliant University of Michigan servers. In order to send and receive SMS messages, the SMS platform will transmit and receive messages through Twilio. Messages will be automatically redacted on Twilio's servers, to ensure that participants' messages and identifiable data such as phone numbers are not stored in Twilio's logs.The CareAvenue website will not have access to any participant identifiers. The website will only collect responses to content questions and progress of website completion. Progress of website completion will be securely transmitted through an application programming interface hosted on a HIPAA-compliant server within University of Michigan Health System and will be encrypted using TSL or SSL encryption.

Some virtual appointments may be conducted with a HIPAA-compliant tele-meeting program used at the University of Michigan. The virtual study appointments will be audio only; no audio content of the call will be saved.

When data must be shared for study purposes (e.g. potential Diabetes Registry patient lists, reports to the DSMB), it will be shared through the University of Michigan School of Public Health secure, HIPAA-compliant fax line or stored virtually via a secure, HIPAA-compliant web application hosted by the University of Michigan, DropBox at U-M, or through MiShare, a secure virtual file transfer system hosted by Michigan Medicine Health Information Technology & Services (HITS).

To the extent that logbooks or paper records for individual participants need to be maintained for purposes of data collection or conducting the intervention, they will be kept locked in file cabinets in a locked room accessible to research staff only. All consent forms will be stored in the same manner. All participant identifiers will be destroyed as soon as it is no longer needed for completion of study related activities.

8 DATA ANALYSIS

All primary analyses will be intention-to-treat. From our prior work, we expect low rates of missing data. We will use multiple imputation on any variables with >5% missingness in linear mixed-effects models. We will apply the inverse probability weighting method to GEE models to handle dropout cases to perform complete case analysis. We will conduct sensitivity analyses to assess any impact of missing data.

8.1 Preliminary analyses

We will examine baseline clinical differences between study arms and use them as model covariates as appropriate to address potential uncontrolled confounding. We will use t-tests and analysis of variance (ANOVA) to assess effects of covariates (e.g., gender, age, education, health insurance type) on continuous outcomes (e.g., HbA1c). For categorical variables, we will calculate two-way contingency tables (e.g. % improved by arm), and use odds ratios and chi-square tests to evaluate differences in proportions by study arm. These results will be used to guide multivariate regression analyses.

8.2 Regression models

For the primary outcome (HbA1c), we will fit a longitudinal mixed-effects model to all repeated measurements during the pre-randomization baseline period and the one-year intervention period. The model will have the intervention (yes/no) as the main independent

variable and HbA1c accounted for as a repeated measure within patients. Thus, we will model HbA1c as a function of fixed effects for the treatment arm (the intervention group vs. the control group), the observation period (baseline vs. one-year intervention period), and a treatment-by-time period interaction term, with adjustment for confounding covariates (age, gender, race, income, health insurance type, comorbidities, health literacy). For this model, the coefficient of the treatment-by-time period interaction effect estimates the key parameter of interest: changes in HbA1c levels. Random effects are included in the model to adjust for HbA1c variation over time within patients. We will take a similar modeling approach to secondary outcome measures (CRN behaviors, perceived financial burdens, perceived stress of unmet SDHs). We will also dichotomize outcomes based on standard thresholds (eg., baseline HbA1c 8-9% vs > 9%) and use similar mixed-effects logistic regression models to test differences in HbA1c, CRN behaviors, perceived financial burdens, and perceived stress of unmet SDHs across treatment arms.

Among those randomized to CareAvenue in Aim 1, we will assess the change in magnitude of the outcome coefficient's association with the intervention before and after the adjustment of mediators of interest (see Figure 1, conceptual model). We will examine the Lagrange Multiplier and Wald Tests to consider the deletion or inclusion of paths based on our hypotheses.[56] Once the model is identified, we will test for group differences (i.e. intervention vs. control) in latent constructs and in the paths between these constructs. This method will allow us to estimate the intervention effects on the constructs directly as well as their relationships to one another.[56] We will follow guidelines for adequate reporting of SEM using three goodness-of-fit indices: Bentler-Bonnet's Normed Fit Index (NFI), Bentler-Bonnet's Non-Normed Fit Index (NNFI), and the Comparative Fit Index (CFI). We will also verify the root mean-square error of approximation (RMSEA) as an index of misfit. Well-fitting models will have fit indices of.90 or higher and <.06 for RMSEA.

9 QUALITY CONTROL AND QUALITY ASSURANCE

The Data Manager in collaboration with the study PI and study biostatistician will be responsible for data quality assurance. The Data Manager will audit all data collected on a weekly basis to identify data discrepancies such as missingness, significant outliers, input errors, skip patterns errors, etc. All discrepancies will be documented and communicated to the PI on a weekly basis. The Data Manager will work with the PI to resolve discrepancies on a rolling basis throughout the study with resolutions being noted in the data discrepancy documentation. At the discretion of the PI, the study biostatistician will be consulted if there are data discrepancies that have the potential to significantly impact the study's primary or secondary outcomes.

10 STATISTICAL CONSIDERATIONS

The calculations used to determine study sample size for detecting differences between study arms at follow-up in our primary outcome of HbA1c are based on early data collected in the study. The hypothesis to be tested is that the intervention will lead to uptake of low-cost resources for health and unmet basic needs and reductions in CRN, thus leading to medication/regimen adherence and intensification. We expect the beneficial impacts from improved access to treatment recommendations and unmet basic needs can lead to improved HbA1c management and control. A 0.5 or greater reduction in HbA1c, after adjusting for

confounding covariates, is considered a clinically meaningful change in stabilizing or improving HbA1c control.[54] We designed the study to have 80% power at an alpha level of 0.05 to detect a change difference of 0.53 unit change in hemoglobin HbA1c between study arms, and a standard deviation of 1.46. This is based on early data collected in the study.[55] We will need a total of 510 participants (255 per arm) with outcome data to show a 0.53 unit difference in HbA1c. With this sample size, we will also have sufficient power to detect differences in our other self-reported secondary outcomes.

Intervention participants will be asked to give their provider their CareAvenue-generated action-plan to alert them of their needs and possibly receive additional support in accessing services. Although the intervention is targeted at the individual, physicians may change their behavior based on their interaction with treatment group patients and begin to better address unmet needs with control patients, thus raising the issue of contamination. That is, due to interactions with intervention patients, providers may alter "usual care." This could diminish the effect size between intervention and control patients. One solution to this problem would be to conduct a cluster-randomized trial, which would obviate such contamination. We concluded, however, that because of the large number of unique providers seeing patients in the Diabetes Registry, the likelihood that a doctor will have patients in each arm is low. Further, some cross-over is inevitable because many patients in the Diabetes Registry see both a specialist and primary care provider, who may be randomized to different arms. Finally, a cluster randomized design would have required a large increase in sample size and cost. Although potential contamination lowers the treatment effect, we consider our design a strength of the study compared to a cluster randomized trial because baseline and follow-up assessments will allow us to quantify how much the control group also benefited from increased communication about low-cost treatment options with providers in the absence of the e-Health tool (comparing pre- and post- data among control patients within providers). This will demonstrate a generalized effect for the whole practice. We have increased the sample size by 3% to account for the potential that physicians' behavior will spill over onto control patients. To account for a potential 12% loss to follow-up, we will recruit 600 participants. Based on our preliminary data from the pilot study and co-investigators' prior studies with this population, we expect the following survey response rates: recruitment (72%), baseline (87%), follow-up 1 (94%), and follow-up 2 (80%).

11 REGULATORY REQUIREMENTS

11.1 Informed Consent

Participants who meet inclusion criteria will be consented over the phone or in-person prior to their baseline assessments (survey, HbA1C, and blood pressure testing) by trained study staff. All consenting will take place in private rooms (University of Michigan offices or research exam rooms located at Domino's Farms or other University of Michigan location). All potential participants will be given a copy of the consent form to read before consenting or research staff will read the entire consent form aloud (if requested by the participant). Potential participants will be allowed to ask any questions they have and the voluntary nature of the study will be emphasized. The study team will always use the most current IRB-stamped and approved consent form.

11.2 Participant Confidentiality

The researchers will take steps to minimize the risk of breach of patient confidentiality through data safety procedures as outlined in this protocol, section 7.3 Data Safety.

In order to efficiently and cost-effectively enroll large enough pool of eligible participants to show meaningful difference in study outcomes, we will obtain participants' diabetes diagnosis and most recent HbA1C levels from the DRR and DataDirect. This information will only be used for recruitment purposes and will not be stored for analysis.

This study evaluates change in outcomes over time, therefore, participants contact information must be retained in order to reach them throughout the study. This information must be linked to the data in order to evaluate outcomes at the 3 different data collection points.

A certificate of confidentiality is included as it is an NIH funded study. All NIH studies are automatically issued a Certificate of Confidentiality as part of the terms of the award.

11.3 Reporting Adverse Events, Other Reportable Events and Occurrences, and Unanticipated Problems

See Appendix 5 for the studies Data Safety Monitoring plan which outlines reporting and oversite for all AEs, ORIOs, and UaPs. This project will be overseen by a Data Safety Monitoring Board. The DSMB Charter is attached in Appendix 3 of the DSMP.

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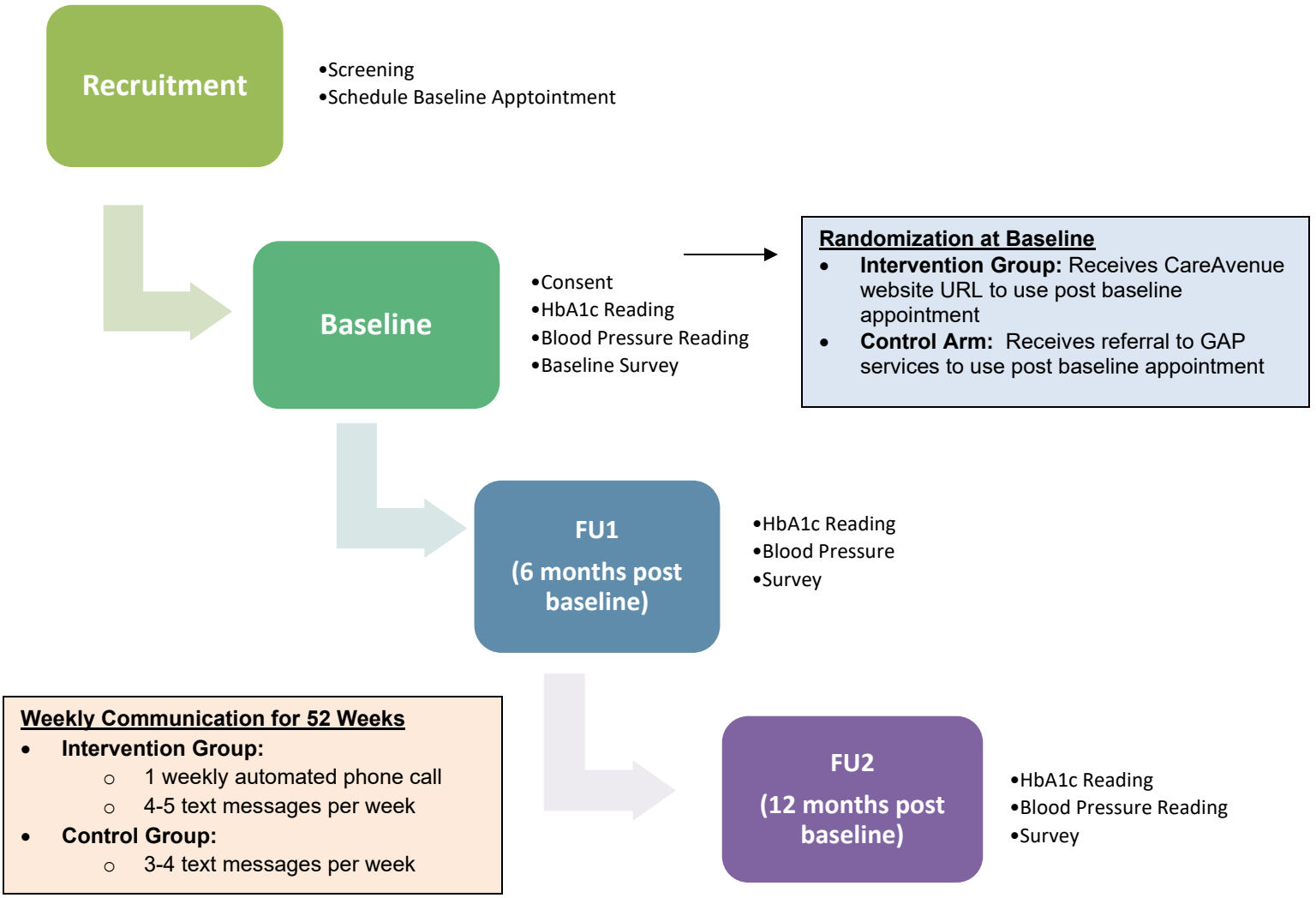
APPENDICES

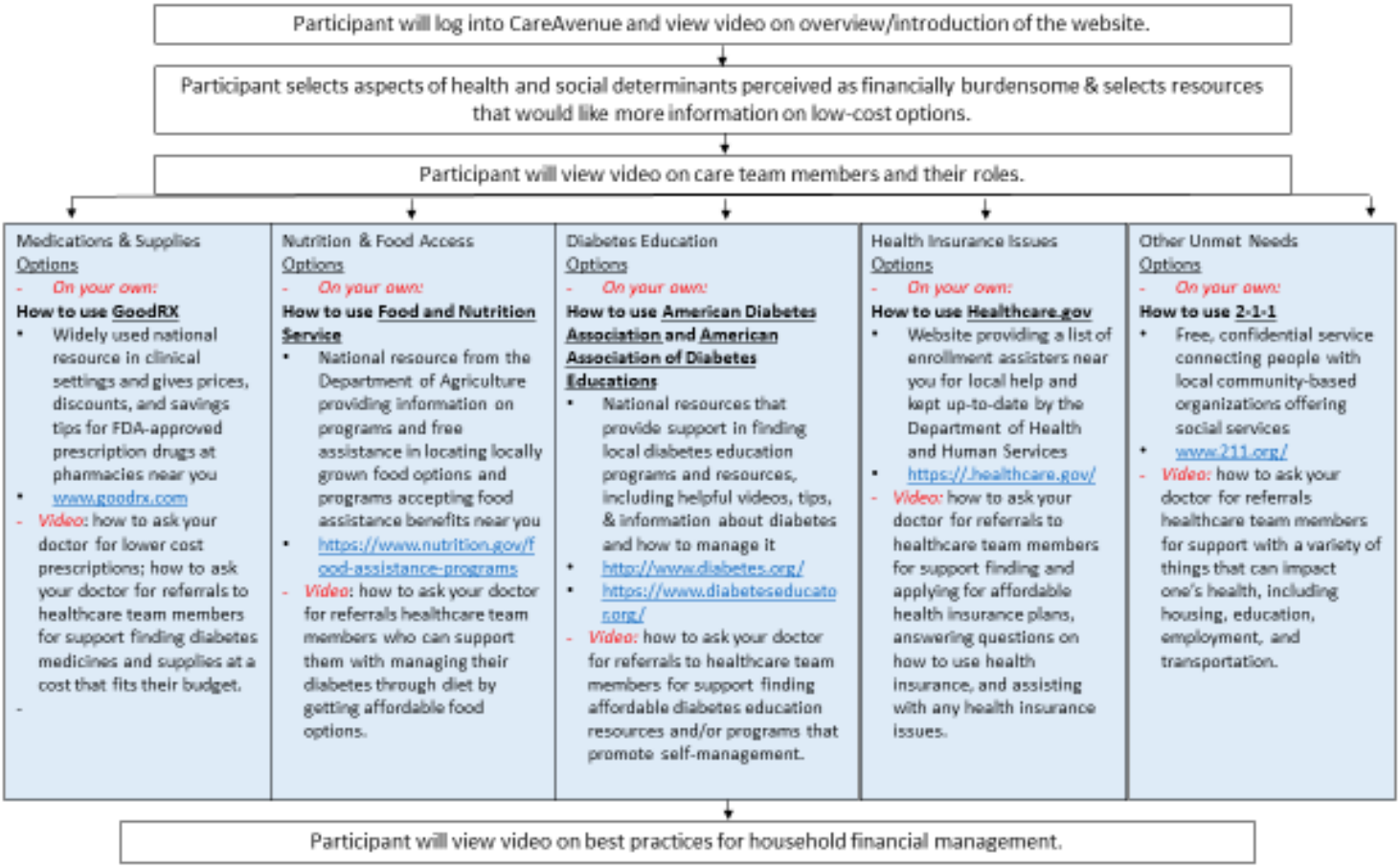
Appendix 1: Study Timeline

	Year					
	Pre-Award	**1**	**2**	**3**	**4**	**5**
Finalize protocol	●					
Clinicaltrials.gov registration	●					
Institutional Review Board Approval	●					
Agreement set up with Diabetes Registry	●					
Refine and finalize intervention		●				
Recruit participants and implement the intervention		●	●	●		
Enrollment of first participant		●				
25% of project recruitment			●			
50% of project recruitment			●	●		
75% of project recruitment				●		
100% of project recruitment				●		
6-month follow-up			●	●	●	●
12-month follow-up				●	●	●
Completion of data collection					●	●
Data cleaning and entry			●	●	●	●
Interim analysis				●	●	
Primary and secondary data analyses					●	●
Prep for dissemination					●	●
Manuscript preparation; grant submissions						●
Reporting results in clinicaltrials.gov						●
Publication of primary trial results						●

Appendix 2: Participation Flowchart



Appendix 3: CareAvenue Intervention Website Overview Diagram



Appendix 4: Data Safety Monitoring Plan

Data and Safety Monitoring Plan

NIH Study Number: 1 R01 DK116715-01A1

Title: Improving diabetes outcomes and health disparities through a patient activation intervention addressing unmet resource needs

Principal Investigator: Minal R. Patel, Phd, MPH

I. Overview

A. Study Purpose

The purpose of this study is to determine the extent to which activating diabetes patients to address health-related financial burdens that impact treatment adherence and unmet social risk factors improves disease control, and the mechanisms through which primary and secondary outcomes are achieved. The goal of this study is to evaluate CareAvenue on health outcomes- an automated, e-health screening, feedback and skills training intervention that addresses health-related financial burden and unmet SDHs.

B. Adherence Statement

The Data and Safety Monitoring Plan (DSMP) outlined below for (1 R01 DK116715-01A1) will adhere to the protocol approved by the University of Michigan Institutional Review Board (IRBMED), National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), and the study Data Safety Monitoring Board (DSMB).

C. *Data and Safety Monitoring Board (DSMB)*

The purpose of the study DSMB is to monitor the safety and conduct of the study. The responsibilities of the DSMB are outlined in the charter.

II. Adverse Events, Other Reportable Incidents and Occurrences, and Unanticipated Problems

A. Assessment of Participant Risks

Potential risks for this study include:

- A common side effect of the finger stick blood draw is localized discomfort or bruising
- In rare cases, infection may occur as a result of the capillary blood collection
- In rare cases, fainting may occur as a result of the capillary blood collection

Discomfort, bruising, fainting, infection, or any other unexpected adverse reactions to the capillary blood collection will be documented. All identified risks are addressed in the study protocol and have been outlined in the study consent form.

All research staff will undergo training in line with university and federal guidelines. Staff of the University of Michigan Department of Pathology will thoroughly train research staff on taking HbA1c assessment using established protocols that emphasize sanitation, cleaning the site of the prick with alcohol before and after, and properly disposing of gloves and fingersticks after each assessment. Once trained, research staff can train additional staff on use of the HbA1c machine. All research staff will undergo Biosafety Training for Laboratory Personnel offered by the University of Michigan Institutional Biosafety Committee. First aid will be available onsite site at the location of testing. Study HbA1C testing protocols can be found in Appendix 1.

i. *Adverse Events*

Adverse Events (AEs) are events that involve physiological, social, economic, or psychological harm to subjects. They may include symptoms, abnormal test results, a response to the study procedures, or any combination of these. Adverse events may also indicate risks of harm to other

subjects or others who are not study subjects but may be affected directly or indirectly. AEs include harmful effects that are both expected and unexpected.

The study will rely on self-reporting by study participants of adverse events. All participants will be provided with contact information for the project manager and study PI. Both in the study consent form and through verbal instructions from data collection staff, participants will be instructed to contact the project manager and PI if they experience any of the expected potential adverse events or experience any other events, symptoms, or occurrences that are unusual for them to experience whether they believe they are related to the study or not. Additionally, the study team will formally assess for Adverse Events/Serious Adverse Events at the Follow-up 1 (6 months-post baseline) and Follow-up 2 (12-months post baseline) data collection time points. The study team will utilize case report forms to collect this information from participants. Specific safety data the study team will assess includes:

- Discomfort, bruising, infection, fainting or unexpected adverse reactions to the capillary blood collection for the HbA1c measurement
- Negative outcomes related to use of the CareAvenue website (intervention group), Guest Assistance Program services (control group), receiving IVR calls (intervention group), or receiving text messages (intervention and control groups). This includes participant concerns related to privacy and safety of their information.
- Events resulting in inpatient hospitalization, prolongation of existing hospitalization, or emergency department visits
- Death (reported to the study team by an individual acquainted with the participant)
- Other non-specified events the participant shares

In addition to self-reporting, all data collectors will be instructed to report any indicators of adverse events to the project manager as soon as possible and not more than by the end of the business day. Indicators of adverse events may be observations of study subjects during data collection or reports made by study subjects directly to data collectors during routine study contact. Once the event has been reported to the project Manager, the project Manager will inform the PI. The PI will review the event and make a determination on the expectedness and relatedness of the event to the study using the University of Michigan Medical School Office of Research guidelines (see Appendix 2). This will occur within 24 hours of the initial report of the adverse event.

ii. Other Reportable Incidents and Occurrences

Other Reportable Incidents and Occurrences (ORIOs) are events in which no one suffered actual harm but indicate that there is a potential for future adverse events to occur. This includes events that may increase risk, alter the risk-benefit assessment, affect a participant's willingness to participate in the study or any departure from the human subject protection regulations and policies set forth by the IRB, NIDDK, or in this DSMP.

iii. Unanticipated Problems

Unanticipated Problems (UaPs) are events that are unexpected, related or possibly related to the study, and suggests that participation in the study places the participant or others at a greater risk of harm than was previously thought. Unanticipated problems do not include events in which harm has already occurred (which would be classified as an adverse event) or events in which potential harm or risk to subjects occurs (which would be classified as an ORIO). UaPs may happen to participants or non-participants who are affected by a person taking part in the study.

B. AE reporting

1. All adverse events whether expected/unexpected or related/unrelated that are reported to the study team including: research associates; data collectors; study staff; and investigators will be documented.
2. An adverse event report will be generated for each event. The report will include: a description of the event; when the event occurred; how it was reported; any documentation that corroborates the event; and the likely relatedness of the event to the subjects' involvement in the study.
3. Adverse event reports will be sent to the study DSBM and IRBMed based on the study reporting timeline. Any actions taken by IRBMed will be reported to the NIDDK program officer. A summary of adverse events will be presented to the NIDDK program officer during annual reporting.
4. This study will use the University of Michigan Medical School Office of Research Adverse Event Reporting Timeline (see Appendix 2).
5. Any action resulting in a temporary or permanent suspension of this study, such as actions by IRBMed, the study DSMB, or investigators, will be immediately reported to the appropriate NIDDK program official.

C. ORIO reporting

1. All other reportable incidents and occurrences that are reported to the study team including: research associates; data collectors; study staff; and investigators will be documented.
2. The PI will determine if the event should be reported to the IRB immediately or at the scheduled continuing review (SCR) using the University of Michigan Medical School Office of Research guidelines for ORIOs (see Appendix 2).
    a. If the ORIO requires reporting to the IRB within 7 days, the event will also be reported to the DSMB.
    b. If the ORIO is reported to the IRB at the annual SCR, the event will be reported to the DSMB at their meeting prior to the CSR.
3. Any action resulting in a temporary or permanent suspension of this study, such as actions by IRBMed, the study DSMB, or investigators, will be immediately reported to the appropriate NIDDK program official.

D. UaP reporting

1. All unanticipated problems whether expected/unexpected that are reported to the study team including: research associates; data collectors; study staff; and investigators will be documented.
2. The PI will determine when the event should be reported to the IRB using the University of Michigan Medical School Office of Research guidelines for reporting UaPs:
    a. Serious UaPs will be reported within 7 calendar days.
    b. Non-serious UaPs will be reported within 14 calendar days.
3. All serious and non-serious UaPs will be reported to the DSMB within one week of reporting to the IRB.
4. Any action resulting in a temporary or permanent suspension of this study, such as actions by IRBMed, the study DSMB, or investigators, will be immediately reported to the appropriate NIDDK program official.

III. Safety Review Plan and Monitoring

Oversight of subject safety includes review of adverse events as well as study progress, data integrity and study outcomes.

A. Justification of sample size

We propose to enroll 600 subjects in this study. The hypothesis to be tested is that the intervention will lead to uptake of low-cost resources for health and unmet basic needs and reductions in CRN, thus leading to medication/regimen adherence and intensification. We expect the beneficial impacts from improved access to treatment recommendations and unmet basic needs can lead to improved HbA1c

management and control. A 0.5 or greater reduction in HbA1c, after adjusting for confounding covariates, is considered a clinically meaningful change in stabilizing or improving HbA1c control.[1] We designed the study to have 80% power at an alpha level of 0.05 to detect a change difference of 0.53 unit change in hemoglobin HbA1c between study arms, and a standard deviation of 1.46 based on early data collected in the study. [2] We will need a total of 510 subjects (255 per arm) with outcome data to show a 0.53 unit difference in HbA1c. With this sample size, we will also have sufficient power to detect differences in our other self-reported secondary outcomes.

Intervention subjects will be asked to give their provider their CareAvenue-generated action-plan to alert them of their needs and possibly receive additional support in accessing services. Although the intervention is targeted at the individual, physicians may change their behavior based on their interaction with treatment group subjects and begin to better address unmet needs with control patients, thus raising the issue of contamination. That is, due to interactions with intervention subjects, providers may alter "usual care." This could diminish the effect size between treatment groups. One solution to this problem would be to conduct a cluster-randomized trial, which would obviate such contamination. We concluded, however, that because of the large number of unique providers seeing patients in the Diabetes Registry, the likelihood that a doctor will have patients in each treatment arm is low. Further, some cross-over is inevitable because many patients in the Diabetes Registry see both a specialist and primary care provider, who may be randomized to different arms. Finally, a cluster randomized design would have required a large increase in sample size and cost. Although potential contamination lowers the treatment effect, we consider our design a strength of the study compared to a cluster randomized trial because baseline and follow-up assessments will allow us to quantify how much the control group also benefited from increased communication about low-cost treatment options with providers in the absence of the e-Health tool (comparing pre- and post- data among control patients within providers). This will demonstrate a generalized effect for the whole practice. We have increased the sample size by 3% to account for the potential that physicians' behavior will spill over onto control subjects. To account for a potential 12% loss to follow-up, we will recruit 600 subjects.

B. Safety and study progress reviews

Adverse events, ORIOs, and UaPs will be reviewed by the study PI as soon as they are reported. The DSMB will review all reported AEs, ORIOs, and UaPs annually at regularly scheduled meetings. Ad hoc meetings will be held to review serious adverse events, ORIOs, and UaPs. All AEs, ORIOs, and UaPs will be reported to and reviewed by the IRB based on the timeline in Appendix 2.

Adherence to recruitment and retention protocols will be reviewed by the PI on a regular basis through reports made by the project manager. Additionally, the DSMB will review adherence on an annual basis.

The annual report provided to NIDDK will include the following information:

- A summary of AEs, SAEs, ORIOs, and UaPs
- A comparison of AEs rates with those anticipated at the study outset
- Statement regarding any loss of confidentiality that occurred, if applicable, and remedial steps taken
- Any protocol deviations and remedial steps taken
- Any communications with the IRB
- Recruitment and retention over the reporting period including the reason for subject drop out
- Study progress toward stated aims
- A comparison of study progress to the timeline set at the outset of the study

C. DSMB guidelines for recommending action

The DSMB will monitor the safety and conduct of the study. The board will make recommendations to the study team which may include study protocol modification, study suspension, or study termination. The

recommendations will be made at the DSMB's discretion and in accordance with the following specific guidelines:

- If study recruitment is more than 50% behind the recruitment timeline
- If participants report repeated AE/SAE directly related to the study intervention or their study involvement
- If there are consistent breaches of patient confidentiality either at the data collection site or through storage of data
- The DSMB will request unmasking of closed session reports at its discretion and if analyses indicate:

Half of participants experience a significant increase in HbA1c levels through the course of the study as measured by the HbA1c collected at follow-up data collection time points

IV. Informed Consent

Informed consent will be obtained from each subject at entry into the study. Informed consent will be treated as an ongoing process. The process will begin with recruitment and continue throughout the subjects' involvement in the study. Subjects will be provided with the consent form prior to baseline data collection. Subjects will be given time to thoroughly read the consent form and ask any questions prior to signing the form. Data collectors will offer to read the entire consent form aloud to the subject. At subsequent data collection points, data collectors will reiterate that participation is voluntary and that subjects may withdraw at any point in time from the study.

V. Data Quality and Management

A. *Data collection review*

All screening and survey data will be downloaded on a weekly basis for auditing and to identify and address any data discrepancies. All data will be collected and entered by research staff. The data manager will be responsible for downloading and auditing all data. In addition to review of data collection by the data manager, the DSMB will review the data on an annual basis and ensure that protocols are being followed in data collection and the quality of the data is not compromised. Internal interim monitoring will occur on a regular and continuous basis in the form of data collection auditing and safety data monitoring throughout the study. As noted in the charter, the unmasked biostatistician will prepare reports on a semi-annual basis.

B. Measures to insure data integrity and protection of databases.

All data will be collected through Qualtrics which uses Transport Layer Security to encrypt information. Data will be downloaded and audited for data quality on a weekly basis by the Data Manager. The Data Manager will store all downloaded data in a secure, password protected, encrypted University of Michigan drive. Back up databases will be stored before a new download is initiated. No databases will ever be overwritten. Access to the drive storing the databases will be restricted to the PI, Data Manager, project manager, and study biostatistician.

VI. Confidentiality

In order to maintain subject confidentiality, all study staff will be trained in Good Clinical Practice and Responsible Conduct of Research. The Data Manager will audit data collection processes on a weekly basis in order to ensure study procedures related to data safety are being followed. Any issues will be reported to the project manager and PI. Weekly meetings will be held between the project manager and research staff and data collectors to provide an opportunity for discussing general interviewing issues and issues of confidentiality. The project manager will report directly to the PI on a weekly basis or per the timeline listed above in the case of adverse events.

All recruitment and data collection activities will take place in private rooms to help protect subjects'

privacy.

All data collected will be coded so that no direct subject identifiers are linked with the data. Access to the code that links data with subject identifiers will be held only by the Data Manager and project manager. All other research staff, including the data collection staff, and the investigators will only have access to specific and select information on an 'as needed' basis in order to conduct recruitment, data collection, or the intervention. The coded database will be password protected and stored on a secured, encrypted University of Michigan drive.

When data must be shared for study purposes (e.g. potential Diabetes Registry subject lists, reports to the DSMB), it will be shared through the University of Michigan School of Public Health secure, HIPAA-compliant fax line or stored virtually via a secure, HIPAA-compliant web application hosted by the University of Michigan, DropBox at U-M, or through MiShare, a secure virtual file transfer system hosted by Michigan Medicine Health Information Technology & Services (HITS).

Participant data for IVR calls will be maintained by a HIPAA-compliant platform within the University of Michigan Health System. All participant data collected and transmitted through the intervention website will be sent encrypted via TLS/SSL secure transfer.

SMS participant data will be stored on HIPAA-compliant University of Michigan servers. In order to send and receive SMS messages, the SMS platform will transmit and receive messages through Twilio. Messages will be automatically redacted on Twilio's servers, to ensure that participants' messages and identifiable data such as phone numbers are not stored in Twilio's logs.

The CareAvenue website will not have access to any participant identifiers. The website will only collect responses to content questions and progress of website completion. Progress of website completion will be securely transmitted through an application programming interface hosted on a HIPAA-compliant server within University of Michigan Health System and will be encrypted using TSL or SSL encryption.

To the extent that logbooks or paper records for individual subjects need to be maintained for purposes of data collection or conducting the intervention, they will be kept locked in file cabinets in a locked room accessible to research staff only. All consent forms will be stored in the same manner. All data with subject identifiers will only be destroyed as soon as it is no longer needed for completion of study related activities.

References

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Data Safety Monitoring Plan Appendix 1

Testing Protocols for HbA1C and Blood Pressure

Brief Hemoglobin HbA_1C and Blood Pressure Testing Protocol

1. **Prior to Participant Appointment**
    - Turn on HbA1c machine – requires 8 minutes to warm up
    - Open cartridge
        - Scan barcode
    - Open NEW capillary pack
    - Other supplies
        - Gloves
        - Alcohol wipes
        - NEW lancet
2. **Take Blood Pressure Twice**
    - Decide which cuff to use for blood pressure and hook up to machine
    - Place cuff on participant's upper arm with tubes coming down from midline
    - Press start on the machine
    - Record the measurement in the survey and on the participant's lab sheet
    - Wait one minute and repeat previous steps to perform the second blood pressure reading on the same arm

***If BP > **180/120** → wait one minute and take second blood pressure reading.
If BP remains > 180/120 terminate interview and encourage to go to Urgent Care ***
If both readings, or only the second reading, are >180/120, terminate the interview and encourage to go to Urgent Care.
The >180/120 threshold was derived from the American Heart Association

NOTE: Both numbers do not need to meet 180/120. If systolic is above 180 OR diastolic is above 120, the participant should be encouraged to go to Urgent Care immediately. Provide list of nearby Urgent Care centers.

3. **Finger Stick**
    - Ask participant if there is a finger they prefer to have poked
    - Wipe fingertip with alcohol
    - Put on gloves
    - Poke fingertip with lancet
    - Wipe off first drop of blood with gauze pad

4. **Run DCA**
    - Suck blood up into capillary
    - Insert capillary into cartridge
    - Place cartridge inside the machine
    - Pull foil tap out of cartridge while bracing it in the machine
    - Close machine window

5. **Clean Up**
    - Offer participant gauze to wipe off finger and band aid
    - Remove gloves and discard in the biohazard bin
    - Record HbA1C measurement in the survey and on the participant's lab sheet.
    - Open HbA1c machine window, press down button, push cartridge to the right, & remove
    - Dispose of cartridge, capillary (do not pull out plunger) and lancet in the sharps container
    - Dispose of all other materials in the biohazard bin

Data Safety Monitoring Plan Appendix 1 Continued

Testing Protocols for HbA1C and Blood Pressure

Upper Arm Blood Pressure Detailed Testing Protocol

Preparation for the Blood Pressure Measurement:

1. Ask participant to remove tight-fitting clothing or tight rolled up sleeve from their left upper arm.
2. Have the participant sit upright on a chair with their feet flat on the ground. The participant's arm should rest on a table so that the arm cuff is at the same level as their heart.
3. Ask the participant to remain still and refrain from speaking while the blood pressure measurement is taken.

Preforming the Blood Pressure Measurement:

1. Insert the arm cuff air plug into the air jack, located on the left side of the automatic blood pressure machine.
2. Wrap the arm cuff firmly around the participant's left upper arm and secure the cuff using the fabric fastener.
    a. The bottom edge of the arm cuff should be about ½ inch above the elbow
    b. The air tube attached to the arm cuff should be located inside the participant's arm and should align with their middle finger.
3. Press the START/STOP button located on the bottom right of the blood pressure machine's visual display. The arm cuff with start to inflate automatically.
    a. The irregular heartbeat symbol will be displayed at the top of the display screen if the monitor detects an irregular rhythm two or more times during the measurement.

    b. The movement error symbol will be displayed at the top of the display screen if the participant moves during the measurement. Remove the arm cuff and wait 2-3 minutes before attempting another measurement.

4. Record the participant's blood pressure
    a. The blood pressure machine displays the systolic blood pressure above the diastolic blood pressure. The smaller number indicates the participant's pulse.

5. Once the arm cuff has completely deflated, remove the arm cuff and press the START/STOP button to turn the monitor off.
6. Record the measurement in the survey and on the participant's lab sheet.

Data Safety Monitoring Plan Appendix 1 Continued
Testing Protocols for HbA1C and Blood Pressure

Hemoglobin A_{1c} Detailed Testing Protocol

Materials Needed:

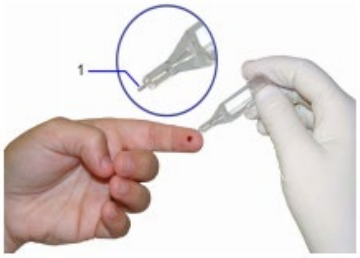
- Disposable Gloves
- Sharps/Biohazard Container
- Alcohol Wipes/Swabs
- HbA1c Machine
- Reagent Cartridge
- Capillary Holder
- Lancet Device
- Adhesive bandage
- Blue pad

Preparation for Hemoglobin A_{1c} Test:

1. Take out a new **reagent cartridge pack** from refrigerator for each new participant.
    a. Remove Reagent Cartridge from its foil package and let sit for 5-10 minutes at room temperature
2. Turn power switch to On (I) position on the **HbA1c machine**. Allow approximately 8 minutes for the device to warm up.
3. Take out a new **capillary holder pack** and inspect that all materials are present and in good condition: absorbent pad, glass capillary and a properly working latching mechanism. A new capillary holder pack will be used for each new test.

Preforming Hemoglobin A_{1c} Test:

1. Put on disposable latex gloves**.**
2. Scan **reagent cartridge.** In a smooth, quick motion, slide the reagent cartridge down past the dot. A beep will sound to signal a successful scan has occurred.
3. Clean participant's fingertip with an **alcohol wipe.** Let dry.
4. Use a new **lancet device** to prick the participant's finger (see picture, right)
    a. If necessary, squeeze fingertip until blood pools.
    b. Wipe away first drop of blood. Re-squeeze fingertip if necessary



5. Hold the capillary holder at an angle and touch only the tip of the capillary to the small drop of blood on the finger until the capillary is filled.
    a. *Once the capillary is filled, the test must be performed within 5 minutes*
    b. Inspect the glass capillary for any air bubbles. If bubble(s) are present, repeat the procedure using a new capillary.
6. Carefully insert the capillary holder in the reagent cartridge until the holder snaps into place (see picture below).

Analyzing the Sample:

1. Make sure the HbA1c machine display reads "READY: SCAN BARCODE."

2. Hold the reagent cartridge so the barcode is facing right, insert the reagent cartridge above the dot on the barcode track, and slide cartridge down past dot until hear beep to signal successful scan has occurred.
3. Open the cartridge door of the machine and insert the reagent cartridge with the barcode facing right into the compartment until a subtle snap is heard/felt.
4. In a smooth, quick motion, pull the flexible pull-tab out of the reagent cartridge.
5. Close the cartridge door. Within 5 seconds, a beep should sound indicating the assay is in progress.
    a. *The test takes approximately 7 minutes to complete.*
6. Results will show up on the display.
7. Record the measurement in the survey and on the participant's lab sheet.

Removing the Reagent Cartridge:

1. Open cartridge door.
2. Locate the button on the right side of cartridge door. Push and hold it down with your right hand.
3. With your left hand, gently push the tab on the cartridge to the right. This action releases and unlocks the cartridge.
4. Pull the reagent cartridge out of the compartment.
5. Discard the reagent cartridge in the proper container, according to standard operating procedures.

*****Be sure to dispose of all sharps (lancets) and biohazardous materials (capillary & cartridge) in the appropriate disposal containers*****

Data Safety Monitoring Plan Appendix 2

We will follow the guidelines for classifying Adverse Events and the timeline for reporting Adverse Events as outlined by the University of Michigan Medical School Office of Research found here: *https://az.research.umich.edu/medschool/guidance/adverse-event-reporting* and in accordance with the study DSMP.

We will follow the Adverse Events, Other Reportable Information and Occurrences, & Other Required Reporting guidelines outlined by the University of Michigan Medical School Office of Research found here: *https://az.research.umich.edu/medschool/guidance/adverse-events-aes-other-reportable-information-and-occurrences-orios-other* and here https://az.research.umich.edu/medschool/guidance/adverse-events-aes-other-reportable-information-and-occurrences-orios-other and in accordance with the study DSMP.

Appendix 3: Data Safety Monitoring Board Charter

Data and Safety Monitoring Board (DSMB) Charter

Improving Diabetes Outcomes and Health Disparities through a Patient Activation Intervention Addressing Unmet Resource Needs

This charter defines the roles and responsibilities of the Data and Safety Monitoring Board (DSMB) for the study: Improving Diabetes Outcomes and Health Disparities through a Patient Activation Intervention Addressing Unmet Resource Needs. This study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

The DSMB will serve in accordance with the guidelines set forth in this charter. DSMB members will review and agree to the charter at the initial meeting. If changes to the charter are necessary, the DSMB will review and affirm their agreement with the changes. Their concurrence will be noted in the DSMB meeting summary.

DSMB RESPONSIBILITIES

The first responsibilities of the DSMB will be to review the final protocol, informed consent documents, and plans for data and safety monitoring and provide input to the investigators on major changes that should be made. Ultimately, the DSMB will approve the clinical study named above so the study can begin enrolling patients.

After initial approval, and at periodic intervals during the course of the study, the DSMB responsibilities are to:

- Provide input to the investigators on the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the study sites, and other factors that may affect study outcomes
- Review serious adverse events and other safety reports and make recommendations regarding protection of the safety of study participants
- Ensure data integrity and confidentiality
- Provide input to assist the investigators in protecting the safety of the study participants
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study
- Provide input to the investigators on modification of the study protocol or possible early termination of the study because of attainment of study objectives, safety concerns, low likelihood of showing a benefit of the intervention, or inadequate performance (such as enrollment and retention problems)

MEMBERSHIP

The members have been appointed by the investigators and approved by NIDDK. Members of the DSMB have no financial, scientific, or other conflict of interest with the study. Members will

be required to attest to their lack of interest in the study using a conflict of interest form (see Appendix 1).

Collaborators or associates of the investigators in this study are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest will be provided by the DSMB members on an annual basis, and also if there is a change in investigators.

The investigators will appoint a DSMB chairperson. They will be responsible for overseeing the meetings and developing the agenda in consultation with the principal investigator.

VOTING DSMB MEMBERS

1. **Patrick J. Heagerty, PhD**
   Gilbert S. Omenn Endowed Chair Biostatistics
   Professor and Chair
   Department of Biostatistics
   heagerty@u.washington.edu

2. **Ranak Trivedi, PhD**
   Assistant Professor of Psychiatry and Behavioral Sciences (Public Mental Health and Population Sciences) at the Palo Alto Veterans Affairs Health Care System
   ranakt@stanford.edu

3. **Ann-Marie Rosland, MD, MS**
   Associate Professor, Internal Medicine
   Research Scientist, VA Center for Health Equity Research and Promotion
   roslandam@pitt.edu

DSMB MEETINGS

The DSMB will typically meet once a year, or as deemed necessary. A quorum of more than half of the DSMB members is required in order to convene a meeting of the DSMB. Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended, when appropriate, by the principal investigator (PI) and members of her staff, as well as the study statistician. Meetings may be convened as conference calls or webinars, as well as in person. In special circumstances, the meetings may also be conducted by email. An emergency meeting of the DSMB may be called at any time by the DSMB chairperson or PI should questions of patient safety arise.

REPORTS TO THE DSMB

Reports will be prepared by the unmasked biostatistician on a semi-annual basis as decided by the investigators and the DSMB. The reports will be distributed to the DSMB at least 10 days prior to a scheduled meeting. These reports shall be provided by access to a secure cloud sharing device.

Data reports for the randomized clinical study will consist of two parts: an Open Report and a Closed Report.

Open Session Report
This portion of the report provides information on study aspects such as accrual, baseline characteristics, and other general information on study status. This report is shared with all investigators involved with the clinical study. The reports contained in this section will include:

- Comparison of Target Enrollment to Actual Enrollment by Month
- Overall Participant Status including: Participants Screened, Enrolled, Active, Completed and Terminated
- Demographic and Key Baseline Characteristics by Group
- Treatment Duration for Participants who Discontinue Therapy

Closed Session Report
This report will contain data on study outcomes, including safety data, and Adverse Events/Serious Adverse Events by participant. Data will be presented by masked treatment groups; however, the DSMB may request that the treatment groups be unmasked to ensure that there are no untoward treatment effects. The Closed Session Report is considered confidential and will be destroyed at the conclusion of the meeting. Data files to be used for interim analyses will have undergone established editing procedures to the extent possible. This report will not be viewed by any members of the clinical study except the designated unmasked study statistician.

MEETING FORMAT
An appropriate format for DSMB meetings consists of an open, closed, and executive session. This format may be modified as needed.

Open Session
Members of the DSMB, the PI, staff members of the PI and the study biostatistician may attend the open session. Issues discussed will include the conduct and progress of the study, including patient recruitment, data quality, general adherence and toxicity issues, compliance with protocol, and any other logistical matters that may affect either the conduct or outcome of the study. Proposed protocol amendments will also be presented in this session. Patient-specific data and treatment group data may not be presented in the open session.

Closed Session
The closed session will be attended only by DSMB members, and the unmasked study biostatistician. The discussion at the closed session is completely confidential. All materials from the closed session will be destroyed at the end of the meeting. Analyses of outcome data are reviewed by masked treatment groups, including baseline characteristics, primary and secondary outcomes, adverse events, adherence and dropouts, and examination of any relevant subgroups. The DSMB may request unmasking of the data for either safety or efficacy

concerns. Procedures to accomplish unmasking of either individual or treatment group data are to be specified in the Data and Safety Monitoring Plan.

Executive Session

The executive session will be attended by DSMB members only, who will discuss the information presented during the closed and open sessions and provide input on the continuation or termination of the study, protocol modification or other changes to the conduct of the study. The DSMB can be unmasked at any time if trends develop either for benefit or harm to the participants.

The DSMB will make a recommendation for either continuation or termination of the study. Sound rationale for either decision (continuation or termination of the study) should be presented. Termination may be suggested by the DSMB at any time. Reasons for early termination include:

- Serious adverse effects in entire treatment group or in a dominating subgroup
- Greater than expected beneficial effects
- A statistically significant difference by the end of the study is improbable
- Logistical or data quality problems so severe that correction is not feasible

DOCUMENTATION OF DSMB MEETINGS

Meeting Summaries

A formal summary containing the DSMB's input on the conduct of the study and their recommendation regarding continuation of the study will be prepared by the DSMB Executive Secretary. Each DSMB summary will include the DSMB's recommendation regarding continuation or termination of the study and/or any recommended protocol changes related to patient safety. The DSMB meeting summary will not include unmasked data, discussion of the unmasked data, or any other confidential data.

The report will include:

- Summary of AEs and SAEs, including a brief discussion of any unanticipated and/or related events, and any steps taken to deal with these;
- Statement regarding any loss of confidentiality that occurred, if applicable, and remedial steps taken.

Once completed, the summary is sent to the DSMB members for their review and concurrence. When the summary is satisfactory to the DSMB members and concurrence with the summary is received, the summary will be sent to the PI. It is the responsibility of the PI to distribute the summary to all co-investigators. It is the responsibility of the study investigators to assure that the DSMB summary is submitted to all the Institutional Review Boards (IRBs) associated with the study. The PI will notify the NIDDK of any actions taken by the IRB.

The PI will provide the DSMB summary to NIDDK during annual performance reports along with the following information:

- The tracking and review process used
- Recruitment and retention over the reporting period

- Any protocol deviations and remedial steps taken
- Any communications with the IRB

CONFIDENTIALITY AND OBJECTIVITY

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality. All members will sign a confidentiality agreement (see Appendix 2). Closed session meeting materials will be stored, transmitted, and destroyed in a manner compliant with the study protocol for data safety and security. This includes:

- Storing closed session materials in locked file cabinets and/or on password protected computers in locked offices
- Transmitting information through the University of Michigan secure "DropBox at U-M" cloud storage system
- Destroying paper copies of materials in a secure manner (shredding) following each meeting

In order to maintain their objectivity, DSMB members are expected not to discuss the study with the investigators except during DSMB meetings.

Data Safety and Monitoring Board Conflict of Interest Attestation Form

Conflict of Interest Statement

NIH Study Number: 1 R01 DK116715-01A1

Title: Improving diabetes outcomes and health disparities through a patient activation intervention addressing unmet resource needs

Principal Investigator: Minal R. Patel, Phd, MPH

I agree to the following statements:

- Protect the interests and safety of study participants;
- Uphold the integrity of the research process, including data collection and analysis, to be as free from bias and preconception as I am able;
- Adhere to the highest scientific and ethical standards, comply with all relevant regulations, and eliminate or disclose, during my involvement with the proposed clinical research project, any real or apparent conflicts of interest.

In addition:

- I declare that I, my spouse or dependent children, or organization with which I am connected, do not have any financial interest in the Improving diabetes outcomes and health disparities through a patient activation intervention addressing unmet resource needs study, where financial interested is defined by the U.S. Department of Health and Human Services (DHHS), as anything of monetary value, including but not limited to, salary or other payments for services (for example, consulting fees or honoraria); equity interests (for example, stocks, stock options or other ownership interests); and intellectual property rights (for example, patents, copyrights and royalties from such rights).

The financial interest term does not include various items which can be found in The Federal regulation, Public health Service (PHS), DHHS Part 50: Policies of General Applicability, Subpart F: Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought.

For federal employees, financial interests that are allowable and require disclosure are:

Financial Interest Disclosure: Financial interest that require disclosure are stock holdings in pharmaceutical firms, medical device manufacturers, and biotechnology companies

Allowable Financial Interests: In a company that produces a product that is being evaluated by a study, participants may hold up to $15,000 of stock: and, up to an aggregate of $25,000 of the stock of that company and its competitors who produce that (or a similar) product. As an alternative to individual stock holdings, participants may hold up to an aggregate of $50,000 in sector mutual funds-including pharmaceutical/health care sectors.

- I agree not to withhold any data related to the Improving diabetes outcomes and health disparities through a patient activation intervention addressing unmet resource needs study or to interfere

with the analysis or publication of the study's results.

- I will not engage in activities that could be viewed as real or apparent conflict of interest, including but not limited to:

  - Having a part-time, full-time, paid, or unpaid employee status of any organizations that are: (a) involved in the study under review; (b) whose products will be used or tested in the study under review, or whose products or services would be directly and predictably affected in a major way by the outcome of the study;
  - Being an officer, member, owner, trustee, director, expert advisor, or consultant of such organizations;
  - Being a current collaborator or associate of the principal investigator;
  - Having a scientific interest beyond that required for my role, for which scientific interest is defined as having influence over the protocol, the study design, conducting the study analysis, or any reporting related to the investigation

_____	_____	_____
Signature	Printed Name	Date

Data Safety and Monitoring Board Certificate of Confidentiality

Data and Safety Monitoring Board Confidentiality Agreement

NIH Study Number: 1 R01 DK116715-01A1

Title: Improving diabetes outcomes and health disparities through a patient activation intervention addressing unmet resource needs

Principal Investigator: Minal R. Patel, Phd, MPH

I understand that I will be provided with information from the study sites or similar organizations for the Improving diabetes outcomes and health disparities through a patient activation intervention addressing unmet resource needs study, including proprietary and confidential information.

I understand that I will have access to these records in order to participate in the Data and Safety Monitoring Board for the Improving diabetes outcomes and health disparities through a patient activation intervention addressing unmet resource needs study.

In my role as a DSMB member, I hereby agree that I shall not release, publish, or reproduce these records. I further agree that I shall not make any use of these records except for the limited purpose of participation in the Data and Safety Monitoring Board for the Improving diabetes outcomes and health disparities through a patient activation intervention addressing unmet resource needs study.

I will take reasonable precautions to prevent access by any other persons to these confidential records or to work products that result from review of those records. I will retain any confidential documentation until the conclusion of the study and will return the documents and all related materials to the Project Manager for this study.

I have read the terms of this agreement and agree to abide by its terms.

_____	_____	_____
Signature	Printed Name	Date