Mobile Diabetes Prevention for Hispanics Living in Rural Areas

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Table of Contents

STATEMENT OF COMPLIANCE 1
INVESTIGATOR'S SIGNATURE 2
1 PROTOCOL SUMMARY 3
1.1 Synopsis 3
1.2 Schema 3
1.3 Schedule of Activities 4
2 INTRODUCTION 6
2.1 Study Rationale 6
2.2 Background 7
2.3 Risk/Benefit Assessment 9
2.3.1 Known Potential Risks 9
2.3.2 Known Potential Benefits 9
2.3.3 Assessment of Potential Risks and Benefits 12
3 OBJECTIVES AND ENDPOINTS 13
4 STUDY DESIGN 14
4.1 Overall Design 14
4.2 Scientific Rationale for Study Design 15
4.3 Justification for Intervention 15
4.4 End-of-Study Definition 15
5 STUDY POPULATION 15
5.1 Inclusion Criteria 15
5.2 Exclusion Criteria 16
5.3 Lifestyle Considerations 16
5.4 Screen Failures 16
5.5 Strategies for Recruitment and Retention 16
6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) 17
6.1 Study Intervention(s) or Experimental Manipulation(s) Administration 18
6.1.1 Study Intervention or Experimental Manipulation Description 18
6.1.2 Administration and/or Dosing 19
6.2 Fidelity 19
6.2.1 Interventionist Training and Tracking 20
6.3 Measures to Minimize Bias: Randomization and Blinding 20
6.4 Study Intervention/Experimental Manipulation Adherence 20
6.5 Concomitant Therapy 20
6.5.1 Rescue Therapy 20
7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 20
7.1 Discontinuation of Study Intervention/Experimental Manipulation 21
7.2 Participant Discontinuation/Withdrawal from the Study 21
7.3 Lost to Follow-Up 21
8 STUDY ASSESSMENTS AND PROCEDURES 22
8.1 Endpoint and Other Non-Safety Assessments 22
8.2 Safety Assessments 23
8.3 Adverse Events and Serious Adverse Events 24
8.3.1 Definition of Adverse Events 24

8.3.2 Definition of Serious Adverse Events 24
8.3.3 Classification of an Adverse Event 24
8.3.4 Time Period and Frequency for Event Assessment and Follow-Up 25
8.3.5 Adverse Event Reporting 26
8.3.6 Serious Adverse Event Reporting 26
8.3.7 Reporting Events to Participants 26
8.3.8 Events of Special Interest 26
8.3.9 Reporting of Pregnancy 27
8.4 Unanticipated Problems 27
8.4.1 Definition of Unanticipated Problems 27
8.4.2 Unanticipated Problems Reporting 27
8.4.3 Reporting Unanticipated Problems to Participants 28
9 STATISTICAL CONSIDERATIONS 28
9.1 Statistical Hypotheses 28
9.2 Sample Size Determination 29
9.3 Populations for Analyses 29
9.4 Statistical Analyses 29
9.4.1 General Approach 29
9.4.2 Analysis of the Primary Endpoint(s) 30
9.4.3 Analysis of the Secondary Endpoint(s) 30
9.4.4 Safety Analyses 30
9.4.5 Baseline Descriptive Statistics 30
9.4.6 Planned Interim Analyses 30
9.4.7 Sub-Group Analyses 31
9.4.8 Tabulation of Individual Participant Data 31
9.4.9 Exploratory Analyses 31
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 31
10.1 Regulatory, Ethical, and Study Oversight Considerations 31
10.1.1 Informed Consent Process 31
10.1.2 Study Discontinuation and Closure 32
10.1.3 Confidentiality and Privacy 32
10.1.4 Future Use of Stored Specimens and Data 33
10.1.5 Key Roles and Study Governance 33
10.1.6 Safety Oversight 34
10.1.7 Clinical Monitoring 34
10.1.8 Quality Assurance and Quality Control 34
10.1.9 Data Handling and Record Keeping 35
10.1.10 Protocol Deviations 35
10.1.11 Publication and Data Sharing Policy 36
10.1.12 Conflict of Interest Policy 36
10.2 Additional Considerations 36
10.3 Abbreviations and Special Terms 36
10.4 Protocol Amendment History 38
11 REFERENCES 38

STATEMENT OF COMPLIANCE

(1) [The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 01/16/2026

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1 PROTOCOL SUMMARY

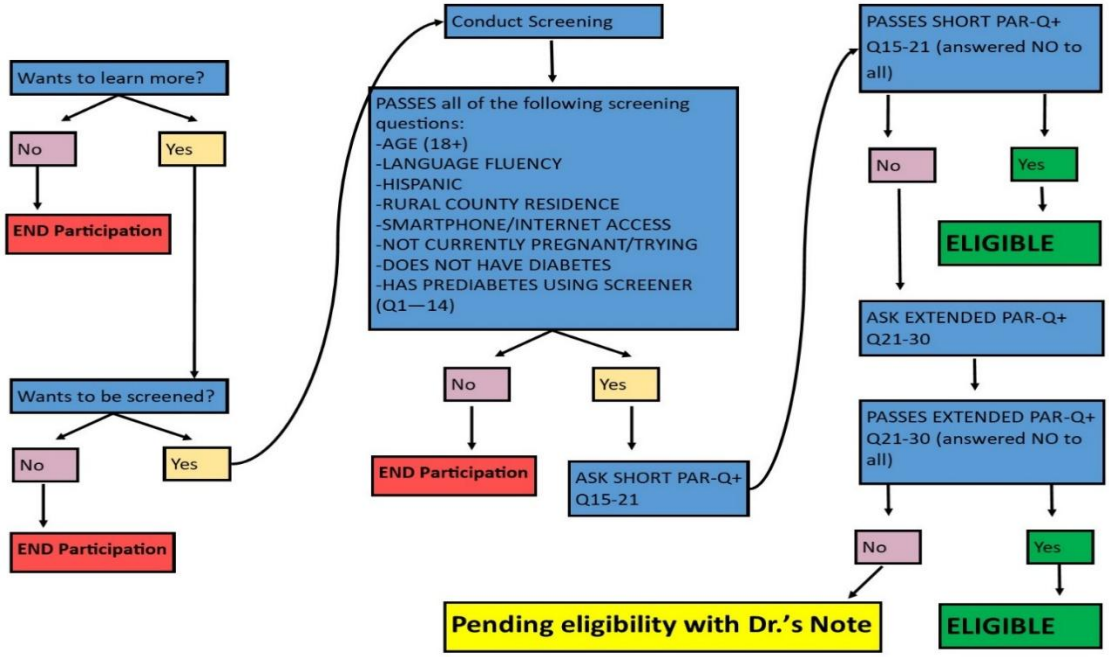
1.1 SYNOPSIS

Title:	Diabetes Prevention for Hispanics Residing in Rural Communities: A Mobile Web-based Approach
Grant Number:	R44MD014082
Study Description:	Two-arm, parallel-group randomized controlled trial comparing a tailored, mobile web app diabetes prevention program with usual care control to reduce diabetes risk by at 3 and 6 months among Hispanic adults who are at risk of developing Type II Diabetes.
Objectives*:	Objectives: Primary—evaluate the effect on percent weight loss . Secondary—evaluate effects on A1C, diabetes knowledge, eating patterns, and physical activity.
Endpoints*:	Endpoints: Primary—weight assessed at each study visit (baseline, 2 post visits). Secondary—validated scale scores at baseline and 2 follow-ups.
Study Population:	Hispanic adults aged 18+, with prediabetes, and smartphone owners in South Texas
Phase* or Stage:	Phase II clinical trial
Description of Sites/Facilities Enrolling Participants:	Single U.S. community health center in South Texas
Description of Study Intervention/Experimental Manipulation:	The study intervention includes a variety of education series with explanatory videos, interactive content, infographics, and engaging tools aimed at increasing diabetes risk knowledge, reducing risk behaviors, and improving overall health. Participants review the intervention across three months. Comparator: Usual care.
Study Duration*:	19 nb months
Participant Duration:	6 months

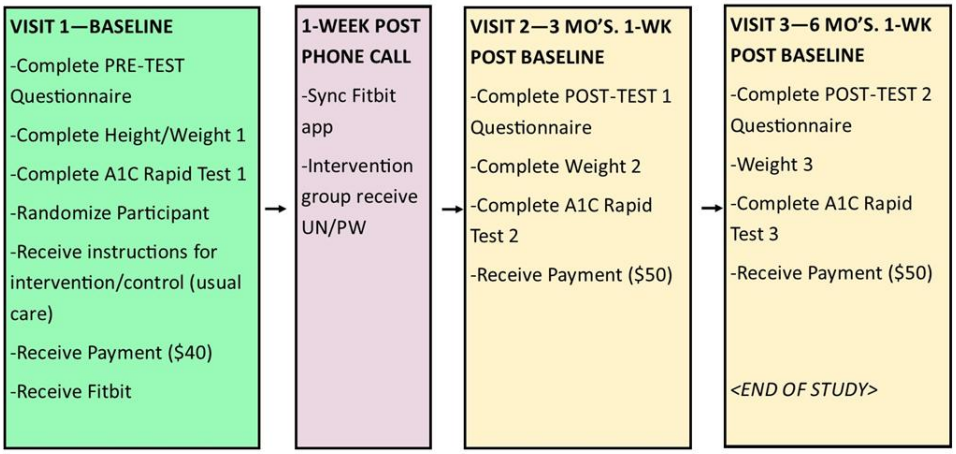
1.2 SCHEMA

Flow Diagram

Participant Flow Diagram 1.



Study Flow Diagram 2.



1.3 SCHEDULE OF ACTIVITIES

The schedule below is provided as an example and should be modified or replaced as appropriate.

	Pre-screening (Pre-consent)	Appointment 1 Day 1	Day 8-91	Appointment 2 Day 92	Appointment 3 Day ~175
Study information sent to potential participants	X				
Confirmatory eligibility screening	X				
Informed Consent		X			
Demographics		X			
Outcome Evaluation					
Weight measurement		X		X	X
A1C Measurement		X		X	X
Knowledge Questionnaire		X		X	X
Health Behavior Questionnaire		X		X	X
Randomization		X			
Control Intervention			X	X	
Experimental Intervention			X		
Adverse Events Reporting		X	X	X	X

2 INTRODUCTION

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections should include relevant background information and rationale for the clinical trial. This should be a brief overview (e.g., approximately 3-7 pages). Referring to relevant intervention manuals for more detail is appropriate. Text for Sections 2.1 and 2.2 may come from the Background and Significance section of the grant application.

2.1 STUDY RATIONALE

Behavioral interventions have been successful in reducing and delaying diabetes by targeting weight loss through modifiable behaviors (e.g., diet and exercise). There remain significant difficulties implementing Diabetes Prevention Programs (DPP) in certain populations due to access and resource availability. The health disparities seen between individuals living in rural communities versus metropolitan areas are evident. Rural communities have a 17% higher rate of type 2 diabetes compared to their urban counterparts.

Previous efforts to culturally adapt the DPP for Hispanics are vital, yet critical gaps remain. Specifically, insufficient attention has been paid to Hispanics living in rural settings and the formidable barriers these individuals face. We intend to fill this gap. ISA Associates, in partnership with the Community Action Corporation of South Texas (CACOST), has developed a mobile web-based diabetes prevention program for Hispanic Americans living in rural communities. ***STEPS****: Small Changes to Prevent Diabetes* will be designed to increase knowledge and skills to help change lifestyle factors associated with diabetes of Hispanics living in rural settings. ***STEPS*** will also place a strong emphasis on Hispanic cultural beliefs and will include themes of *familismo,* Mexican inspired recipes, and community health workers (*promotoras*). ***STEPS*** will deliver culturally tailored information to users following assessments of their needs and personal situation. The program provides users with the information, skills, and tools needed to promote health and reduce risk for the development of diabetes. Materials will be multi-modal in format (e.g., narration by a program 'coach', culturally-appropriate visuals, graphics, interactive assessments with feedback, and tailoring of information). The goal of the program will be to promote self-management of diet and physical activity and minimize risks associated with diabetes.

We plan to test the effectiveness of **STEPS** in a randomized controlled trial with 165 Hispanic adults. Participants will be randomly assigned to receive either the mobile **STEPS** intervention or usual care. Before, about 3-months post randomization, and about 6-months post randomization, we will assess anthropometric data including height, weight, a1c; demographic data, diabetes risk and knowledge, dietary intake, and self-report PA.

2.2 BACKGROUND

Over half of all U.S. population growth between 2010 and 2019[1] was among Hispanics, who are now the largest racial/ethnic minority group in the United States (U.S.).[2] While this expanding population faces a myriad of health challenges, none is bigger than diabetes and its cascading effects. More than half of all Latinos will develop diabetes in their lifetime.[3] And those that do are twice as likely to be hospitalized for end-stage renal disease compared to non-Hispanic whites[4], are more likely to suffer from diabetic retinopathy[5], and are at a greater risk of mortality from COVID-19.[6] Hispanics are also 50% more likely to die from diabetes than non-Hispanic whites.[7] Indeed, the problem is only intensifying for this growing population; the rate of new cases among Latinos is almost double that of non-Hispanic whites.[8]

Diabetes Lifestyle Risk Factors. Type 2 diabetes (T2D), which accounts for 90-95% of all cases, is largely preventable.[8] Consumption of a high fat and high diet caloric (including high caloric drinks); insufficient physical activity (PA); and prolonged sedentary time are all linked to the development of T2D.[9-20,23-28] Further, 52% of Hispanics do not meet the US weekly PA guidelines compared to 42% of non-Hispanic whites,[22] and get a higher proportion of their daily caloric intake from sugar-sweetened beverages.[28] Additionally, the risk of T2D increases as Hispanics modify their behavioral norms to be more consistent with the dominant culture.[29-31] Indeed, higher levels of acculturation among Hispanics predicts greater consumption of sugar-sweetened beverages, saturated fats, and fried food.[30,32-33] Consistent with this disparity in poor eating habits and insufficient PA, Latinos are also more likely to be overweight/obese as compared to whites.[34] Overweight and obesity is a significant risk factor for T2D, with virtually all diagnosed cases having a body mass index (BMI) of 25 or higher.[8,35-37] The degree of acculturation is also positively associated with BMI in Hispanics.[37,42]

Prediabetes. It is estimated that 88 million U.S. adults have prediabetes (i.e., a higher than normal blood sugar level);[8,43] a serious risk factor for developing T2D, heart disease, and stroke.[44] Indeed, 70% of individuals with prediabetes will go on to develop diabetes.[45] Similar to lifestyle risk factors, the rate of prediabetes is higher in Hispanics as compared to other non-Hispanic groups.[7,46]

Diabetes Prevention Program**.** Fortunately, a relatively modest reduction in body weight can significantly reduce the risk of developing T2D among those with prediabetes.[36] This was most clearly demonstrated by the Diabetes Prevention Program (DPP).[47-48] This landmark intensive behavioral intervention focused on healthy eating, PA, and stress management.[49] Over one year, participants attended 16-sessions (30-60 minutes in length) and bi-monthly in-person maintenance meetings after the active intervention phase. Each participant had access to a lifestyle coach and additional resources such as on-site PA sessions and food vouchers.[49] At 3-year follow-up, those who received DPP training lost between 5-7% of their total body weight and lowered their risk of developing diabetes by 58% compared to controls.[47] These effects persisted at 10-year follow-up.[48]

Cultural Adaptations of the DPP. Culturally sensitive behavioral health programs promote higher levels of acceptance, greater comprehension, and are more effective than generic programs for minority groups, including T2D prevention programs.[50-53] Ritchie et al[54] compared the effectiveness of the DPP for both English- and Spanish-speaking Hispanics to non-Hispanic whites. All groups lost weight, but Hispanics attended fewer sessions and were less likely to achieve recommended weight loss targets. As a result, it was recommended the DPP curriculum be further tailored, beyond language translation, to improve outcomes among Hispanics.[54]

To provide a framework for successful adaptations of T2D interventions, Lagisetty and colleagues[50] reviewed 34 culturally tailored diabetes programs. Overall, they found that interventions that were

more comprehensively tailored were also more successful. Indeed, they identified four essential tailoring domains: facilitators, language, location, and messaging. According to the FiLLM model ("Facilitating Interventions through Language, Location, and Message"), those who deliver the program should be community members who share core characteristics with the target population (e.g., community health workers). The program should also be delivered in the preferred language of participants and should be sensitive to literacy levels of typical end-users. Furthermore, access to the intervention should be convenient (e.g. community center, churches). Finally, the educational content (e.g. culturally tailored diet, family) and the mode of message delivery (i.e. communication channels most accepted by users) should be tailored to the intended audience.[50]

O'Brien et al[55] tailored a version of the DPP across the four FiLLM domains by using *promotoras* to deliver the training in a community-based organization, with cultural dietary components and concepts(e.g. *familismo*). Latinas with prediabetes who went through the intervention significantly lost weight, reduced waist circumference and LDL cholesterol, and lowered diastolic blood pressure. Similarly, Ockene et al[56] utilized community members as facilitators, tailored language and literacy levels to the target population, implemented the intervention at a community center, and tailored messaging content (e.g., modifying traditional recipes) through a preferred communication channel (e.g. telenovela). At 1-year follow-up, at-risk Hispanics in the intervention group experienced a myriad of significant salutary effects including weight and hemoglobin A1c (HbA1c) reduction compared to those in usual care. Overall, the evidence supports relying on the FiLLM framework to develop a culturally tailored diabetes intervention for optimal effectiveness.

Rural Hispanics: The Forgotten Group. Previous efforts to culturally adapt the DPP for Hispanics are vital, yet critical gaps remain. Specifically, insufficient attention has been paid to rural Hispanic populations and the formidable barriers these individuals face. This is an important group. Four million Hispanics reside in rural areas,[57] accounting for 46.2% of the growth in these communities.[58] Rural communities, in general, are facing significant health challenges.[59] Consistent with this, residents of rural communities have a higher incidence of T2D compared to urban dwellers.[60] Furthermore, Latinos who reside in rural settings have significantly higher mortality rates than Latinos living in metropolitan areas.[61] These morbidity and mortality disparities might be partially explained by the dearth of diabetes self-management education and support programs in nonmetropolitan counties.[62,63] Almost 2/3 of rural residents do not have access to these programs.[62] Indeed, access to quality health services, proper nutrition and weight status, and diabetes prevention were identified as the top 3 priorities among a national sample of rural health stakeholders.[64]

It is crucial that any rural T2D interventions account for the specific access and resource barriers facing these communities. Most prominently is a lack of readily available community and healthcare services, necessitating longer travel to obtain these services.[65] This becomes even more burdensome due to the lack of public transportation in these geographic areas.[66] Thus, multiple on-site sessions are impractical. Program curriculum must also be consistent with local resources. There is a lack of recreational facilities to engage in PA[68-71] and the density of grocery stores is low in rural areas thereby leading to cost and transportation barriers to healthful foods.[61,67-69]. The per participant cost for the initial year of DPP training is $1,399[72] (including a program coach).[49] While later interventions have reduced these costs (to as low as $553 per participant),[73] this remains impractical for most rural communities given their monetary and healthcare workforce shortages.[74]

An often-overlooked aspect to rural programming are the cultural factors that are particularly germane to T2D prevention. Research demonstrates that rural women are more likely to be discouraged from exercising by others compared to urban women,[67,75-76] thereby leading to a social norm against

PA.[77-78] This cultural barrier is only reinforced when rural women see their neighbors exercising less often compared to urban women.[78-79]

Some DPP adaptations have relied on web-based approaches, mobile phones, and videoconferencing to overcome these access and resource barriers and have yielded average weight loss ranging from 3.3% to 4.7%.[80] While clinically meaningful and comparable to in-person programs,[81] the modal participant across these studies have been white females with higher levels of education.[80] To address this shortcoming, Omada Health recently developed and evaluated a digital version of the DPP for an urban, multi-ethnic/racial Medicaid population.[82] Participants in the intervention group lost, on average, 4% of their total body weight. Examining only those who completed 9 or more sessions yielded even greater weight loss. Overall, these findings suggest that an online version of the DPP can benefit low-income multi-ethnic/racial populations.[82] While the program was offered in Spanish, additional cultural tailoring for the needs of rural Hispanics remain unaddressed. The lack of diabetes prevention programs targeting this high-risk, underserved population is a major weakness in the fight against T2D.[52-53,80] We intend to address this weakness.

During Phase I, we developed an early version of a culturally-tailored, theoretically-driven mobile web-based T2D prevention program for rural Hispanic adults. By digitizing our program, we are reducing access barriers and providing diabetes prevention straight to the fingertips of an at-risk population who otherwise would be unexposed to this resource. We aim to increase knowledge about diabetes risk, enhance skills to prevent new cases, and improve self-efficacy to deploy those new skills by interweaving both Hispanic and rural cultural components into our intervention. For example, cultural values like *Familismo*[83] will be incorporated by involving *la familia* in healthy cooking nights utilizing traditional Hispanic recipes (e.g. *enchiladas with chicken and low-fat cheese*). PA regimens will be taught in a way that are consistent with rural constraints such as walking at local track fields or being active at home.[77] Our intervention will capitalize on the strong social support seen among *comadres/compadres*[84] to encourage healthful behaviors and change social norms on rural exercise.[78-79] Further, interactive tools that promote self-regulation (e.g. goal setting tool) will provide motivation to end-users and increase self-efficacy to adopt and maintain healthy eating and PA. In developing an mHealth diabetes prevention program, we are providing a scalable resource that can make a significant impact on Hispanic health, thus, presenting vast commercialization potential across rural America.

2.3 RISK/BENEFIT ASSESSMENT

The following subsections should include a discussion of known risks and benefits, if any, to human participants. Text from the corresponding sections of the Human Subjects section of the grant application, and/or IRB package may be used here.

2.3.1 KNOWN POTENTIAL RISKS

There are minor risks to human subjects from participating in this project, however, protocols have been developed to further reduce risk for all participant.

Participation. There are some minor risks associated with participating in the study. Participants will be told that participation is completely voluntary and that there are no consequences associated with choosing not to participate. Additionally, participation within the Fitbit and Text Message components of

the study are also voluntary and participants can opt-out of these components without hindering their participation in the full study. When completing any type of study questionnaire or biometric data, participants will be told answers are not tied to any indefinable information and that they may skip any question or test they do not wish to answer or complete. It is possible that, as a result of hearing or talking about diabetes, a participant may become concerned about his or her own diabetes risk. This realization may be accompanied by distress. If this should occur, participants will be given contact information for the CACOST Health center and will be instructed to contact their primary care provider for additional assistance. Participants can stop participating at any time, and their care at CACOST will not be affected. They will continue to receive the same level of services from CACOST.

Physical Activity. There are some minor health risks associated with participating in physical activity via the STEPS program. To minimize risk, ISA has instituted several protocols to protect participants and reduce their risk related to physical activity. To begin, it is an eligibility criteria that participants must PASS the PAR-Q+ Physical activity screener AND if yielded from the screener, receive a doctor's note indicating that they are medically cleared to exercise. Additionally, once in the program, there are disclaimers in the physical activity modules that remind participants that if at any point they are questioning engaging in physical activity due to health or have concerns they will need to contact their primary care provider. Contact information for the CACOST Health Center will be included. If a participant reaches out to ISA Staff at any point to indicate injuries with physical activity, ISA Staff will advise to stop all physical activity until further discussed with their primary care provider. Further, ISA Staff will report to the PI and a report will be made.

A1c Test. There are some minor health risks associated with conducting and obtaining information from a rapid A1C test. The use of a rapid A1C test is no more of a risk than using a blood glucose meter. It does not require blood to be drawn, in large amounts, or using a syringe. It also does not require a medical professional to complete. An A1C self-check will be conducted by the participant after being provided with instructions by ISA Staff. ISA Staff will monitor to ensure the participant is following directions. This test requires a droplet of blood only slightly larger than a traditional glucose monitor test. Participants will do the step-by-step instructions and then show ISA Staff their A1C reading. If a participant does NOT want to participate in doing the test, they will not be required to. There are minimal risks associated with the test. To alleviate the risks, ISA Staff will implement the following procedures for the following associated risks.

First, even though ISA Staff will be instructing the participant to self-test, they will wear a new set of latex gloves with each reach in the case they need to assist the participant. They will also throw all supplies in a sharps container once the test is completed. They will disinfect the area where the test is conducted as well.

While the blood sample is just a droplet of blood, there might be participants who have anxiety about blood and/or may feel light-headed at the sight of blood. Therefore, all participants will be required to be seated while they conduct the self-test. Additionally, if a participant feels unwell due to the blood

droplet, ISA STAFF will immediately call CACOST Health Center Staff to come assess the participant. While highly unlikely, in the case that there is a medical emergency, ISA Staff will immediately contact first responders. After the incident has been handled and cleared, ISA Staff will immediately contact the PI to inform them of the event and will document details.

Additionally, there may be associated risks with the participant learning their A1C levels. If a participant's A1C level is in the diabetes range, they will be provided with a sheet with information on A1C levels and information about how to contact their primary care physician about their results. This sheet will provide CACOST Health Center contact information as well.

Data. There are some minor risks associated with data safety, however, we have several protocols in place to protect the data of all participants. With the exception of the contact forms, consent document, and signatures on a receipt log used to track participant payment, ISA will not be collecting written, identifiable information from participants. ISA staff will keep these forms in a locked cabinet. Further, contact forms will be shredded once the research study is complete. Consent documents and the receipt logs will be kept in a sealed envelope and in the possession of ISA Staff when not at ISA. After returning from the data collection, the documents will be stored in a locked filing cabinet to minimize any opportunity for breaches in confidentiality. Given the fact that no identifying information will be recorded on any anthropometric data and surveys, and that strict security procedures will protect participants personal information gathered on the contact form, consent forms, and receipt logs, the protections against any possible breach of confidentiality are likely to be quite successful. To further protect against any breaches of confidentiality, all project staff proposed to work on this project have received or will receive training on the protection of research risks and are or will be well versed in the Code of Federal Regulations (including 45 CFR 46 and 42 CFR) and the Belmont Report. ISA continually obtains information from the Office of Protection from Research Risks at NIH on new regulations regarding the protection of human subjects, which is disseminated to all staff.

2.3.2 KNOWN POTENTIAL BENEFITS

Include a discussion of known potential benefits from either clinical or nonclinical studies. For behavioral or social intervention studies, relevant published literature should provide relevant benefits information. For studies including a licensed or approved product, a package insert or device labeling should be used as a primary source of benefits information. If the study includes an investigational product, the Investigator's Brochure (IB) should be a primary source of the benefits information.

Describe any physical, psychological, social, legal, or any other potential benefits to individual participants or society in general, as a result of participating in the study, addressing each of the following:

- *Immediate potential benefits*
- *Long-term potential benefits*

Note that payment to participants, whether as a non-coercive inducement to participate or as compensation for time and inconvenience, is not considered a "benefit." Provision of incidental care is also not to be considered a benefit. For details of compensation see ***Section 5.5, Strategies for Recruitment and Retention****.*

There are several benefits to participating in the proposed research to both the research participants and others. There are a number of benefits to participating in the proposed research for both the participants and others. All participants will have access to a state-of-the-art diabetes prevention program that can help them improve health behaviors, reduce diabetes risk, and improve overall health. This information should not only be of interest to participants but also help them understand the importance of prevention behaviors in protecting their health. This research also has the potential to benefit many other Hispanic adults, since ISA will test the effectiveness of this mHealth intervention. If found to be successful, this program can help better meet the needs of Hispanic adults and better provide them with information and training in how to prevent diabetes. Given that the potential risks are minimal, the risk to participants seems quite reasonable in relation to the benefits. Given that the potential risks are very small, the risk to participants seems quite reasonable in relation to the benefits.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Include an assessment of known potential risks and benefits, addressing each of the following:

- *Rationale for the necessity of exposing participants to risks*
- *A summary of the ways that risks to participants were minimized in the study design*
- *Justification as to why the value of the information to be gained outweighs the risks of participation in the study*

As indicated above, the risks to study participants are small. ISA will protect against any potential risk and ensure the confidentiality of the data using multiple methods. First, to protect against psychological risk or discomfort in completing the survey, participants will be informed of the confidentiality of the surveys (i.e., they will contain no personally identifying information) and the secure nature of the computer-based survey tool. In addition, questions will be phrased in a way to minimize discomfort and participants will be free to skip questions they do not wish to answer. No one outside the study team will have access to the data. Moreover, participants will be told specifically that if, because of reviewing their assigned materials or completing the research surveys, they are feeling distressed about their physical health, they should discuss their concerns with a CACOST Staff Member. They will also be provided with a list of resources in the informed consent that can provide information about diabetes.

To maintain confidentiality of all data collected, no names or other identifying information will be included on the survey, or as part of STEPS or the control materials. As noted earlier, the file that will link the participant name to the user ID and study phone number will be maintained on a password protected computer that will not house the survey data. The only people that will have access to the linking file will be the Principal Investigator and her staff. Finally, we will utilize strict security protocols – described previously – to protect the confidentiality of all information stored on our secure server as part of the STEPS intervention.

To protect against any breaches of confidentiality, all project staff proposed to conduct the data collection have received or will receive training on the protection of research participants and are or will be well

versed in the Code of Federal Regulations (including 45 CFR 46 and 42 CFR) and the Belmont Report. ISA continually obtains information from the Office for Human Research Protections (OHRP) at NIH on new regulations regarding the protection of human subjects, which is disseminated to all staff.

After all participants have completed follow-up surveys, the linking file housed on the ISA computer – the only file that contains participant's personal information (e.g., name, phone number) – will be deleted. In addition, the Windows Eraser program will be used to completely remove (i.e., "wipe") the linking file from the computer by overwriting it several times using government-sanctioned deletion algorithms. Deidentified participant research data from the baseline and follow-up surveys will be retained for 3 years from the submission of the final financial report to NIH, in keeping with guidelines described in the NIH Grants Policy Statement.

The Phase II evaluation will provide very important information about the efficacy of the STEPS intervention to improve the health of Hispanic adults residing in rural areas. This data is critical to developing a successful program that can help Hispanic adults reduce their risk of Diabetes. Knowledge gained from this field test will be integrated into the final program prior to marketing to FQHCs and other health care organizations. We believe that the risks associated with this Phase II effort are reasonable in relation to the valuable information we will receive.

3 OBJECTIVES AND ENDPOINTS

Provide a description of the study objectives and endpoints, as well as a justification for selecting the particular endpoints, in the table format included below. This will provide clear articulation of how the selected primary and secondary endpoint(s) are linked to achieving the primary and secondary objectives and an explanation of why endpoint(s) were chosen. Data points collected in the study should support an objective or have a regulatory purpose. Therefore, careful consideration should be given prospectively to the amount of data needed to support the study's objectives.

*An **objective** is the purpose for performing the study in terms of the scientific question to be answered. Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., feasibility, acceptability, engagement of the intervention target, identifying mechanisms of action, mediation, moderation, efficacy, effectiveness, dissemination, implementation).*

*A study **endpoint** is a specific measurement or observation to assess the effect of the study intervention. Study endpoints should be prioritized and should correspond to the study objectives and hypotheses being tested. Give succinct and precise definitions of the study endpoints used to address the study's primary objective and secondary objectives (e.g., specific diagnostic tests that define safety or efficacy, clinical assessments of disease status, assessments of psychosocial characteristics, patient reported outcomes, behaviors or health outcomes). A full description of study endpoints, including administration, scoring, psychometrics, adjudication of endpoints, etc., belongs in **Section 8**, **Study Assessments and Procedures**.*

A putative mechanism of action is the theorized explanation for how the intervention functions.

Consider whether primary and secondary endpoints should be adjusted for multiple comparisons, family-wise error rates, alpha inflation, etc. Details of any such adjustments should be included in ***Section 9.4.2, Analysis of the Primary Endpoint(s)*** *and* ***Section 9.4.3, Analysis of the Secondary Endpoint(s)****.*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate whether the intervention increases percent weight loss in Hispanic adults.	• Weight measured by the research staff at each study visit	Tests causal mechanism
Secondary		
To evaluate whether the intervention improves A1C levels, diabetes knowledge, and improves health behaviors.	• A1c levels measured by research staff at each study visit • Diabetes knowledge • Eating pattern behaviors • Physical activity behaviors	Tests causal mechanism or potential moderating effects

4 STUDY DESIGN

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

4.1 OVERALL DESIGN

This is a Phase II single-site randomized, 2-arm between-subjects study examining differences in diabetes risk and knowledge between participants randomized to the experimental intervention and those randomized to the attention control condition (usual care). Outcomes were assessed at baseline, three months 1 week post baseline, and again at 6-months 1 week post-baseline. We hypothesized that experimental participants would have higher rates of percent weight loss and improved knowledge and behaviors to reduce diabetes risk than control participants. Participants were assigned to conditions by an algorithm programmed into the study computer using a permuted blocks randomization scheme. Blocks of size 4 and 6 were used. Assignments within blocks were to be random but balanced among the two conditions and the order of the blocks (4 vs 6) also was random. This procedure will ensure that the number of participants randomized to each condition was equal, that any imbalance among the conditions at any point during the recruitment and randomization was modest, and that it would be very difficult to guess the assignment of the next participant. Randomization was administered via computer-based admin system and triggered by the study coordinator.

The intervention, STEPS, combines educational videos and content, as well as skill development exercises to provide diabetes education, reduce risk of developing Type II Diabetes.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Those in the control condition will receive UC. Due to the lack of adequate resources for T2D prevention in rural communities,[62-63] we designed the control to provide the most intensive diabetes prevention education a patient could expect from their primary care doctor.[118,149] This method has been used in prior RCTs examining the effects of T2D prevention programs for Hispanic adults.[118,149] This study design was chosen to allow for a comparison between the STEPS intervention and what is commonly available to Hispanics in rural areas.

4.3 JUSTIFICATION FOR INTERVENTION

The STEPS intervention is an effective, affordable, and scalable intervention to reduce diabetes risk among Hispanic adults. Principles from the Social Cognitive Theory (SCT),[53,84,117] Theories of Social Networks and Social Support[117] will guide development of **STEPS**. For example, self-regulation is a core concept of SCT[117] and a key component of T2D prevention.[98] As such, **STEPS** will include interactive tools to help end-users set PA and eating goals, monitor progress towards meeting those goals, and reinforce success through feedback. Additionally, outcome expectations related to T2D diagnosis and outcomes will be examined through a cultural lens. There will be substantial observational learning opportunities through videos and interactive activities that will also reinforce self-efficacy in healthy eating and PA. Additionally, the Theories of Social Networks and Social Support[117] will provide a framework to mobilize social resources at both the individual and community levels. Our tool, Connect with Comadres/Compadres, will encourage social network appraisal and help users solicit instrumental support to meet their health goals. Lastly, the FiLLM[50] model will guide cultural tailoring of **STEPS** to meet the needs of rural Hispanics.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment and the 6-month follow-up assessment.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. 18 years of age and older

3. Able to read and write in English or Spanish
4. Hispanic
5. Resides in rural area
6. Has access to a smartphone and internet access
7. Does not have diabetes
8. Has prediabetes as per screener
9. Not currently pregnant
10. Can participate in physical activity as per screener

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Less than 18 years of age
2. Not able to read and write in English or Spanish
3. Resides in a metropolitan area
4. Does not have access to a smartphone and internet
5. Has been diagnosed with diabetes
6. Cannot participate in physical activity as per screener

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Re-screening is permitted if circumstances change.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited from Community Action Corporation of South Texas (CACOST) health centers through a collaborative effort between CACOST health center employees and the onsite ISA Research Assistant. CACOST is a non-profit organization that aims to improve the health and wellness of the people of South Texas and includes several health services including primary care, women's health, dental, and mental health services. As key healthcare providers in the South Texas region, CACOST is the leading health provider to over 16,000 patients annually. Almost 70% of their patient population is over the age of 18 and 87% of patients identify as Hispanic.

Similar to our successful Phase I recruitment process, recruitment will occur at CACOST clinics and also via CACOST social media platforms. Specifically, Patient Care Coordinators will hand out study flyers prior to patient visits with their primary care physician. The Patient Care Coordinators will instruct interested participants to contact the on-site research assistant for more information about the project and will provide a room number, a telephone number, and hours in which the research assistant is available. Additionally, contact information for the on-site ISA Research Assistant will be listed on study flyers (i.e. online and in person). The same study flyer will also be posted on CACOST social media platforms to further reach the target audience. We successfully used this strategy to recruit rural Hispanic adults from CACOST for focus groups and feasibility testing for the prototype of our proposed diabetes prevention program.

To maximize retention, this study will employ several techniques that have proven successful in previous research projects conducted by ISA with similar populations. First, the on-site ISA Research Assistant will collect as much contact information as the participant feels comfortable providing (e.g., additional phone numbers, email address, preference for calls v. text messages). This will include asking about secondary contacts – these are alternate phone numbers where the participant can be reached, such as the number of a parent, spouse, or friend. To protect participant's privacy, the on-site Research Assistant will record how the project should be identified when calling each secondary contact (e.g., "the diabetes project" v. "the phone study"). We have successfully retained participants whose personal phones were temporarily unavailable (e.g., the phone was broken or disconnected, the participant got a new number) using this strategy. Second, we will offer reminder texts or calls the day before a scheduled appointment. Third, if a participant misses a scheduled appointment, the on-site Research Assistant will implement the retention protocol with the goal of rescheduling the missed appointment. Specifically, the on-site Research Assistant will contact the participant via their preferred contact method the day of the missed appointment and – if they are not reached – every two business days thereafter for one week. If the participant is not reached within a week, the ISA Research Assistant will begin calling the alternate contacts' phone numbers. If the participant is not reached after calling each alternate contact once, the Research Assistant will continue contacting the primary number every two days for an additional week. If the participant is not reached after two weeks, the on-site Research Assistant and the Principal Investigator will meet to determine whether additional contacts are warranted or if the participant should be categorized as "lost to follow up."

In general, we expect the retention rates to be high. CACOST is well regarded in the South Texas region and many participants visit regularly for medical care or other services. We believe the proposed study will have similarly favorable retention rates.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

STEPS is an effective, affordable, and scalable intervention to reduce Type II Diabetes risk in Hispanic adults. Principles from the Social Cognitive Theory (SCT),[53,84,117] Theories of Social Networks and Social Support[117] will guide development of **STEPS**. For example, self-regulation is a core concept of SCT[117] and a key component of T2D prevention.[98] As such, **STEPS** will include interactive tools to help end-users set PA and eating goals, monitor progress towards meeting those goals, and reinforce success through feedback. Additionally, outcome expectations related to T2D diagnosis and outcomes will be examined through a cultural lens. There will be substantial observational learning opportunities through videos and interactive activities that will also reinforce self-efficacy in healthy eating and PA. Additionally, the Theories of Social Networks and Social Support[117] will provide a framework to mobilize social resources at both the individual and community levels. Our tool, Connect with Comadres/Compadres, will encourage social network appraisal and help users solicit instrumental support to meet their health goals. Lastly, the FiLLM[50] model will guide cultural tailoring of **STEPS** to meet the needs of rural Hispanics.

The **STEPS** 12-week curriculum closely follows the sequence and topics of the original DPP intervention.[49] Van Name et al[118] conducted an RCT on a shortened (14-wk) version of the DPP. At 12-month follow up, participants who received this modified DPP yielded a 6% weight loss as compared to controls. Building off this success, we intend to incorporate all core behavioral learning components of successful intensive lifestyle intervention for T2D.[98] The first seven modules will focus on building foundational knowledge, setting and then working towards diabetes preventive goals, and enhancing self-monitoring skills. The latter five modules will focus on maintenance of behavior change. All module content will address the psychological, social, and motivational benefits and barriers to regular PA and healthy eating specifically among rural Hispanics.

Self-monitoring and social support are integral components of self-regulation, and are critical to effective diabetes prevention.[98] The *Goal Setting* tool will utilize a simple interface with drop down options and buttons to easily help users define specific and attainable PA and healthy eating goals.[98] Specifically, end-users will be able to 1) name their goal, 2) type in the behavior (e.g., walk two laps at the track), and 3) select the frequency (e.g., 3 times per week) and duration (e.g., 4 weeks) of the desired behavior. The *Goal Setting* tool will then finalize their goal (e.g., "*I will walk two laps at the track 3 times a week for 4 weeks.*") This tool will allow users to easily monitoring their goals (e.g. indicate goal progression and completion). Once a goal is achieved, users will receive a virtual trophy icon by their goal to indicate success. The ***STEPS** Tracker* is a highly interactive tool that is synced with a Fitbit wearable and allows for self-monitoring of PA, diet, and weight. Within the tool, users can set their daily steps goal, will see visuals on their progress (via the Fitbit web API), and will receive notifications for achievements. Additionally, users can manually enter their weight and daily dietary consumption by selecting foods from a library of common and cultural foods. Users will receive summary statistics and figures displaying calories and fat per food item and each day's consumption, aligned with the original

DPP curriculum.[49] The ***STEPS*** *Tracker* will provide visual feedback with charts and easy to understand diagrams (e.g. total steps walked per day and per week). The *Connect with Comadres /Compadres* tool will allow users to create friend groups within the **STEPS** program and then exchange support, motivation, and successes by using pre-designed messages (e.g. "You've got this", "Great job"). In addition, users will be able to post their daily steps from the ***STEPS*** *tracker* tool within their friend groups to show successes and encourage others in their PA endeavors. The *Health Text Messages* tool will deliver 46 text messages across the intervention. A meta-analysis examining the effects of text-messaging for health promotion found that message frequency moderated the effect of health interventions.[120] Specifically, interventions that decreased the frequency of text messages had larger effects than those that relied on low-fixed or high-fixed messaging frequency. Thus, **STEPS** users will receive 5 messages per week during week 1, 4 messages per week during weeks 3-8, and 3 messages per week during weeks 9-12. Topics will cover healthy eating, PA, stress, motivation, and reminders to use the program. Examples of text messages include: "*Make tonight a healthy eating night con la familia! Check out the healthy arroz con pollo recipe in* ***STEPS****: <weblink>"; "Stand up and walk in place for 5 minutes!"; and "Take a minute to do belly breathing. Try this exercise in* ***STEPS*** *<weblink>"*.

The control group will receive usual care.

6.1.2 ADMINISTRATION AND/OR DOSING

Participants in the intervention arm receive a fully automated, mobile web app that videos, text, animations, and interactive activities. It is entirely accessible on a mobile device. The curriculum phase consists of twelve modules that are adapted from the DPP and also align with Effective components of Lifestyle Interventions to Reduce Diabetes Risk. These effective components include: Commit to Program; Set Goals, Self-monitor (diet, weight, PA); Reduce overall calorie intake; Build healthier eating patterns; Increase PA, reduce sedentary time; Self-regulate energy balance; Manage environmental cues (stimulus control); Problem Solving; Manage self-defeating thoughts, lapses; Manage social cues, build social support; and Manage motivation, stress, health overall.

Curriculum frequency/intensity. The curriculum comprises 12 modules; for dose accounting, we treat each module as a "session," yielding ~12 sessions for a full curriculum dose (with additional tools available or usage).

There are **no live interventionists** and **no participant-to-participant interaction** after randomization. All contact is and web-based and a pre-recorded Community Health Worker hosts the videos. There is no face-to-face or group sessions conducted.

Control arm receives usual care.

6.2 FIDELITY

No text is to be entered in this section; rather it should be included under the relevant subheadings below. This section refers to efforts made to confirm that the intervention is appropriately conducted by the

*interventionist(s). It is distinct from the content of **Section 6.4, Study Intervention Adherence**, which is intended to capture a study participant's adherence to an intervention.*

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

The intervention is conducted entirely by the curriculum hosted on the mobile web-app. Therefore, there is no additional fidelity checks required to ensure the interventionist is conducting the intervention as intended. However, the research staff do review the administrative dashboard to ensure the mobile web-app is functioning appropriately. All issues are noted and resolved within 24 hours.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be assigned to conditions by an algorithm programmed into the computer-based research portal. Randomization will utilize a permuted-blocks randomization scheme. Blocks of size 4 and 6 will be used. Assignments within blocks will be random but balanced among the two conditions and the order of the blocks (4 vs 6) also will be random. This procedure will ensure that the number of participants randomized to each condition will be equal, that any imbalance among the conditions at any point during the recruitment and randomization will be modest, and that it will be very difficult to guess the assignment of the next participant. Because the intervention and control materials are inherently different, participants and research staff cannot be blinded to assignment.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participants' adherence is tracked entirely through mobile website administration page. Participants are given full and immediate access to all 12 modules and mobile web tools. Adherence is assessed by module access (dichotomy), number of logins, number of pages visits, and number of minutes in each module and tool for the mobile web-app. Control-arm adherence (e.g., usual care) is not collected.

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from the intervention but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). The data to be collected at the time of study intervention discontinuation will include the following: the reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Lost-to-follow up; unable to contact subject
- Participant withdraws consent for further participation and/or data use.
- Safety concerns: any SAE or AE judged related to participation that warrants removal, per the Data and Safety Monitoring Plan and IRB reporting rules.
- Ineligibility discovered post-enrollment, duplicate enrollment, or other protocol violations that compromise data integrity.
- Investigator decision that continued participation poses undue burden or risk (e.g., credible threats of harm), consistent with IRB policies.

The reason for participant discontinuation or withdrawal from the study will be recorded on a dedicated Case Report Form (CRF). Participants who withdraw or are discontinued after randomization will not be replaced; enrollment continues until the target sample size is reached.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to respond for the 6-month follow-up call and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to respond for a required study appointment:

- The site will attempt to contact the participant, reschedule the missed baseline or follow-up appointment, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls including to a secondary contact number). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

This individually randomized, remote trial evaluates a mobile, web app diabetes prevention program versus a usual care control. All study activities are conducted in person with a trained research coordinator. The research coordinator obtains only weight and instant A1C measures if participant has agreed to the measures, and the remaining data is collected via a participant initiated questionnaire.

Screening, eligibility, and enrollment

- **Eligibility confirmation window.** Up to 30 days prior to enrollment. Research coordinator assesses eligibility and pending eligibility (from physical activity readiness questionnaire). For those with pending eligibility, the research coordinator must receive a doctor's signed form allowing participation in physical activity for the study.
- **Consent.** Participants complete electronic informed consent.
- **Baseline survey.** Immediately post-consent, participants complete a baseline questionnaire.
- **Randomization.** After baseline completion, participants are assigned to intervention or control.

Interventions begin (initial administration conditions)

- **Intervention arm.** Participants are told to immediately wear their fit bit for one week to get baseline physical activity measure. One week post baseline visit, they are provided their username and password to login and commence the intervention.
- **Control arm.** Participants are told to immediately wear their fit bit for one week to get baseline physical activity measure. They are also told they are in the usual care group and will receive access to the intervention post-study.

Measures and assessments (non-safety)

Baseline (pre-randomization)

- Demographics and contact details (mobile number required for delivery).
- Diabetes knowledge questionnaire
- Health behavior questionnaire
- A1C and weight biometrics

During intervention (process/dose)

- The administrative platform will provide all utilization details including login, page numbers, minutes used, and additional utilization statistics. These are used for exposure/dose summaries and adherence monitoring (not safety).

Follow-up (primary outcome window)

- **Primary outcome ascertainment:** Weight measure is utilized for future calculation of percent weight loss.
- **Follow-up questionnaire:** Repeat weight measurement at each follow up visit is used for percent weight loss.

Outcome definitions (non-safety)

- **Percent weight loss:** Calculated between weight at three different time points. This is used to calculate a percent weight loss in the participant.
- **Exposure/dose metrics:** Number of modules completed; number of minutes in the intervention; and number of times interactive tools utilized.

Administration, scoring, and data quality

- **Administration.** All questionnaires are self-administered via computer or tablet.
- **Scoring.** Multi-item scales are scored per codebook (sum or mean of valid items; higher scores reflect greater endorsement or knowledge, as defined). Missing-data rules (e.g., minimum items required) are pre-specified.
- **Data capture.** Survey responses are time-stamped and stored on the study platform'

Qualified personnel

- **In person visit biometrics:** Conducted by trained study staff.

8.2 SAFETY ASSESSMENTS

The current study gathered two biometric data points: (1) weight and (2) A1C levels using a rapid at-home assessment. Given the A1C test, the study followed the following protocol.

A1C Protocol for Safety Assessment. There are some minor health risks associated with conducting and obtaining information from a rapid A1C test. The use of a rapid A1C test is no more of a risk than using a blood glucose meter. It does not require blood to be drawn, in large amounts, or using a syringe. It also does not require a medical professional to complete. An A1C self-check will be conducted by the participant after being provided with instructions by ISA Staff. ISA Staff will monitor to ensure the participant is following directions. This test requires a droplet of blood only slightly larger than a traditional glucose monitor test. Participants will do the step-by-step instructions and then show ISA Staff their A1C reading. If a participant does NOT want to participate in doing the test, they will not be required to. There are minimal risks associated with the test. To alleviate the risks, ISA Staff will implement the following procedures for the following associated risks.

First, even though ISA Staff will be instructing the participant to self-test, they will wear a new set of latex gloves with each reach in the case they need to assist the participant. They will also throw all supplies in a sharps container once the test is completed. They will disinfect the area where the test is conducted as well.

While the blood sample is just a droplet of blood, there might be participants who have anxiety about blood and/or may feel light-headed at the sight of blood. Therefore, all participants will be required to be seated while they conduct the self-test. Additionally, if a participant feels unwell due to the blood

droplet, ISA STAFF will immediately call CACOST Health Center Staff to come assess the participant. While highly unlikely, in the case that there is a medical emergency, ISA Staff will immediately contact first responders. After the incident has been handled and cleared, ISA Staff will immediately contact the PI to inform them of the event and will document details.

Additionally, there may be associated risks with the participant learning their A1C levels. If a participant's A1C level is in the diabetes range, they will be provided with a sheet with information on A1C levels and information about how to contact their primary care physician about their results. This sheet will provide CACOST Health Center contact information as well.

Further safety procedures consist of: (1) AE/SAE identification and follow-up; (2) monitoring for distress potentially triggered by educational content; (3) privacy/technology safeguards (e.g., wrong-number texting, shared phones). AEs are any unfavorable or unintended psychological or practical effect temporally associated with participation in the study's activities (videos, , surveys), whether or not considered related. Examples include: heightened anxiety/distress about diabetes risk, perceived breach of privacy (e.g., texts seen by others on a shared device), escalation of medical mistrust that prompts clinical concern, and elevated A1C measures that require further doctors assessments. SAEs would be rare in this context and are defined per IRB policy (e.g., death, life-threatening event, hospitalization) regardless of attribution.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

8.3.1 DEFINITION OF ADVERSE EVENTS

An AE is defined as an event that is unexpected, related or possibly related to research participation, and suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is defined as an event that results in death, is life-threatening, results in inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect, or may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed based on temporal relationship. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

A member of the research team with appropriate expertise will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study appointments.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, assessment of severity,

relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The study coordinator will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Any AE or SAE, whether or not related to study intervention, will be reported to the IRB, NCI, and the Office for Human Research Protections (OHRP). SAE's will be reported to the IRB within 24 hours and AEs will be reported to the IRB within 72 hours. All SAE's and AE's will be reported to NCI and OHRP within two weeks. The initial report will be followed by submission of a completed report to all institutions.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Any AE or SAE, whether or not related to study intervention, will be reported to the IRB, NCI, and the Office for Human Research Protections (OHRP). SAE's will be reported to the IRB within 24 hours and AEs will be reported to the IRB within 72 hours. All SAE's and AE's will be reported to NCI and OHRP within two weeks. The initial report will be followed by submission of a completed report to all institutions.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 24 hours and to the funding agency within two weeks of the investigator becoming aware of the event

- Any other UP will be reported to the IRB within 72 hours and to the funding agency within two weeks of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within two weeks of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s):

We hypothesize that, compared to participants who receive usual care, participants who receive the tailored mobile web-app, STEPS, will have a higher percentage of weight loss at 6 months post-randomization. Alternatively, our null hypothesis is that there will be no difference between arms in screening completion at 6 months.

- Secondary Endpoint(s):

A1C (3 and 6 months):
We hypothesize that the intervention arm will report a lower A1C at 3 and 6 months than the control arm; the null hypothesis is that there will be no difference between arms.

Diabetes Knowledge (3 and 6 months):
We hypothesize that the intervention arm will report higher diabetes knowledge (higher total score) at 3 and 6 months than the control arm; the null hypothesis is that there will be no difference between arms.

Eating Patterns (3 and 6 months):
We hypothesize that the intervention arm will report better eating patterns aligned with weight loss and management (total score) at 3 and 6 months than the control arm; the null hypothesis is that there will be no difference between arms.

Physical activity (3 and 6 months):
We hypothesize that the intervention arm will report higher amounts of physical activity at 3 and 6 months than the control arm; the null hypothesis is that there will be no difference between arms.

9.2 SAMPLE SIZE DETERMINATION

We examined power using treatment effects from two sources: 1) a meta-analysis examining the overall effectiveness of mobile device interventions on weight loss[154] and 2) a digital diabetes prevention program for low-income patients.[85] First, a meta-analysis examining the effects of mobile device interventions on weight loss found an average effect size of Cohen's d: 0.43 (95% CI:0.252-0.609; p<0.01) across 11 mobile-based intervention studies.[154] This indicates an overall medium effect size. Second, Kim et al[82] developed and tested a mobile-based diabetes prevention program for a multi-racial/ethnic population. This study yielded a mean weight loss of 4.4% (SD 7.7%) at 12 months. This finding is associated with a Cohen's d=0.57, which is considered a medium effect size. To ensure our study is fully powered, we conducted our power analysis using the smaller effect size (Cohen's d=0.43) from Lyzwinski et al.[154], who examined the effects of mobile-based interventions on our primary outcome, participant weight loss.

We estimated power for the paired t-test for %weight loss (primary outcome). The G*Power 3.1 program[157] was used to determine that a Cohen's d of 0.43 and an α error probability of 0.05 requires a final sample size of 136 to be sufficiently powered (1 - β error probability) at 0.80. Presuming a 20% attrition rate, randomizing a final sample size of 164 participants should be sufficient to detect significant differences in % weight loss across the two survey time points (i.e., at baseline and 3 months after the end of the intervention).

9.3 POPULATIONS FOR ANALYSES

Because randomization carries the expectation of creating treatment groups equivalent with respect to known and unknown prognostic factors, removing randomized participants from the analysis runs the risk of tampering with this balance and introducing bias into the treatment comparisons. As a result, an intention-to-treat analytic approach will be followed such that all participants randomized into the study will be included in all analyses irrespective of protocol violations post randomization. Even with our best efforts, we can expect some missing data. For the primary outcome, missing data will be limited to cases where we are unable to receive a weight as per participant request. Because we allow participants to opt out of any biometric or question, there is the possibility that there is missing data for the primary outcome. However, very little missing data is anticipated. For secondary measures, missing data will consist of those who fail to complete the 3 or 6-month follow-up survey. We will conduct an initial evaluation of missingness by performing a series of logistic regression analyses where the indicator of missing data is the outcome and potential explanatory variables (e.g., condition, screening status, demographic characteristics) serve as predictors. We will then use imputation to manage missing data.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

A paired t-test will be the main analytic technique for the primary measure (percent weight loss) and all continuous outcome measures. The test of the intervention effect will be the t-test for the

regression coefficient for condition, which will estimate the adjusted difference between the two conditions at posttest. That test will be two-tailed with a type I error rate of 5%. Chi-square testes will be used for all categorical outcome data.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary outcome is percent weight loss, and secondary outcomes include: HbA1c levels, diabetes knowledge, dietary intake, and self-reported physical activity. All but the weight and HbA1C measures (assessed by the research coordinator) will be self-reports using established scales that have evidence of reliability (internal consistency and/or a test-retest reliability) and validity. A paired t-test will be the main analytic technique for the primary measure (percent weight loss) and all continuous outcome measures. The test of the intervention effect will be the t-test for the regression coefficient for condition, which will estimate the adjusted difference between the two conditions at posttest. That test will be two-tailed with a type I error rate of 5%. Chi-square testes will be used for all categorical outcome data. We will perform the analysis using SAS PROC GLM, Version 9.1.[148] We will perform these analyses in collaboration with our statistical consultant, Dr. Kaplan.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The primary outcome is percent weight loss, and secondary outcomes include: HbA1c levels, diabetes knowledge, dietary intake, and self-reported physical activity. All but the weight and HbA1C measures (assessed by the research coordinator) will be self-reports using established scales that have evidence of reliability (internal consistency and/or a test-retest reliability) and validity. A paired t-test will be the main analytic technique for the primary measure (percent weight loss) and all continuous outcome measures. The test of the intervention effect will be the t-test for the regression coefficient for condition, which will estimate the adjusted difference between the two conditions at posttest. That test will be two-tailed with a type I error rate of 5%. Chi-square testes will be used for all categorical outcome data. We will perform the analysis using SAS PROC GLM, Version 9.1.[148] We will perform these analyses in collaboration with our statistical consultant, Dr. Kaplan.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

All analyses will control for any confounding variables not managed through randomization (i.e., group difference $p < .10$).

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Study intervention is only for men.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

10.1.1 INFORMED CONSENT PROCESS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

When a participant arrives for their first visit, they will complete the informed consent procedure. Specifically, ISA research staff will explain the research project, the purpose of the mobile phone-based

program and how it works, the role of participants in testing this product, and the voluntary nature of participation. Our staff will also explain that, although information of a sensitive nature may be raised in program materials or while taking the survey, they will have the option to skip any questions that make them uncomfortable. ISA Staff will also point out the additional consent areas of *Fitbit* and *Text Messaging*. Participants will also be informed about monetary incentives related to participation in the study. Participants will be given the consent document, which will detail in writing all pertinent information about the study and the participant's rights. All participants will be encouraged to ask ISA Staff any questions prior to signing the consent form. Participants who agree to participate will sign the consent form before taking the first questionnaire and before collection of any health-related data. A copy of the consent document will be given to each participant.

All participants will be given the opportunity to have the consent form read to them. However, if they choose to read the consent form themselves, we will not assume that they understood the main points of the study. Instead, we will summarize those points before the participant signs the consent form. Moreover, they will be asked if they have any questions before they sign the consent form.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study appointment schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (ie, significant protocol violations)
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, , or other relevant regulatory or oversight bodies (OHRP).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable

information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

To maintain confidentiality of all data collected, no names or other identifying information will be included with the survey data and in-app interactives. As noted earlier, the file that will link the participant name to the user ID and study phone number will be maintained on a password protected computer that will not house the survey data. The only people that will have access to the linking file will be the Principal Investigator and her staff. Finally, we will utilize strict security protocols – described previously – to protect the confidentiality of all information transmitted via the web-app.

To protect against any breaches of confidentiality, all project staff proposed to conduct the data collection have received or will receive training on the protection of research participants and are or will be well versed in the Code of Federal Regulations (including 45 CFR 46 and 42 CFR) and the Belmont Report. ISA continually obtains information from the Office for Human Research Protections (OHRP) at NIH on new regulations regarding the protection of human subjects, which is disseminated to all staff. Further, participants will have the MRR procedure explained to them and will be asked to complete a medical release form before any medical records are extracted. In addition, any ISA staff proposed to work on the MRR and EHR extraction are or will be trained in all applicable HIPAA regulations.

After all participants have completed follow-up surveys, the linking file housed on the ISA computer – the only file that contains participant's personal information (e.g., name, phone number) – will be deleted. In addition, the Windows Eraser program will be used to completely remove (i.e., "wipe") the linking file from the computer by overwriting it several times using government-sanctioned deletion algorithms.

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Deidentified participant research data from the baseline and follow-up surveys will be retained for 3 years from the submission of the final financial report to NIH, in keeping with guidelines described in the NIH Grants Policy Statement.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor or Independent Safety Monitor. Update table heading to remove non-relevant role.

Principal Investigator
Debra M. Rios, DrPH
ISA Associates, Inc.
4501 Fairfax Dr, Ste 601 Arlington, VA 22203
703-739-0462
DRIOS@isagroup.com

10.1.6 SAFETY OVERSIGHT

Debra M. Rios, DrPH, the PI, has the responsibility for assessing adverse events (AEs) and serious adverse events (SAEs) and the ultimate responsibility for all data and safety monitoring. She will conduct weekly reviews of any problems related to quality of data collection, transmission, or analyses and of any AEs and SAEs that occurred in the past week. Further, she will conduct annual reviews of SAEs associated with renewal of IRB approval.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

We will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Baseline and follow-up survey data will be captured directly in the study database.

Intervention Fidelity — Intervention is delivered electronically. Periodic monitoring will check for errors.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

10.1.9 DATA HANDLING AND RECORD KEEPING

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the study staff under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source data will be completed electronically to ensure legibility.

10.1.9.2 STUDY RECORDS RETENTION

Deidentified participant research data from the baseline and follow-up surveys will be retained for 3 years from the submission of the final financial report to NIH, in keeping with guidelines described in the NIH Grants Policy Statement. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations will be

addressed in study source documents. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 10 years after the completion of the primary endpoint by contacting ISA.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CFR	Code of Federal Regulations

CLIA	Clinical Laboratory Improvement Amendments
DPP	Diabetes Prevention Program
CRF	Case Report Form
DHHS	Department of Health and Human Services
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IRB	Institutional Review Board
ITT	Intention-To-Treat
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale
n/a	n/a	n/a	n/a

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