Preventing Diabetes in the Deep South: Extending Partnerships and Adapting Interventions to Reach Rural Communities at High Risk

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Sponsor: NIH/NIDDK

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the local Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. 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 will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Preventing Diabetes in the Deep South: Extending Partnerships and Adapting Interventions to Reach Rural Communities at High Risk
Study Description:	Alabama has the 3rd highest rates of diabetes in the United States. The prevalence of diabetes is 14.1% compared with 9.4% nationally; in some areas of the Black Belt, the prevalence is over 20%, or 1 in 5 adults. Roughly 37% of people living in Alabama have pre-diabetes, but only 10% of these individuals know they have it. The Diabetes Prevention Program (DPP) is an evidence-based intensive lifestyle intervention that targeted weight loss and successfully reduced diabetes risk by 58%. However, the DPP was a resource intensive efficacy trial and was not designed to be directly deliverable in real world settings. Community-based adaptations of the Diabetes Prevention Program (DPP) can be feasible but typically fail to show the same benefit as the more intense original trial version of the lifestyle program. The aim of this study is to introduce innovative design elements to a community-based adaptation of the DPP to enhance research effectiveness. To reduce or delay the onset of diabetes among high-risk populations, the American Diabetes Associations recommends taking metformin. “Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI>30 kg/m2, those aged <60 years, and women with prior gestational diabetes mellitus.”1 We will compare two strategies, lifestyle modification alone versus lifestyle modification plus metformin recommendation, in a group-randomized controlled 2-arm trial.
Objectives:	Conduct a 12-month randomized control trial (RCT) to determine the feasibility of implementing a peer coach-facilitated DPP delivered by telehealth. The DPP will be compared to DPP with metformin therapy recommendations. The goal of the intervention is to prevent or delay the

	Type 2 diabetes among rural primary care patients with pre-diabetes and obesity at high for developing diabetes. The primary outcomes are body weight and HbA1 results at month 12. The RCT will test feasibility and provide data that will inform design and power for a future study to assess diabetes prevention as the main outcome measure.
Endpoints:	Percent change in body weight and HbA1 results at month 12
Study Population:	Enroll 100 adults with obesity (BMI >30kg/m^2) aged 19 to 65 years who receive primary care at one of four partnering clinics in rural Alabama.
Description of Study Intervention:	Condition 1. Receive lifestyle modification alone (DPP) Condition 2. Receive lifestyle modification with metformin therapy recommendations (DPP-recommendations)
Study Duration:	3 years
Subject Duration:	12-months

2 INTRODUCTION

2.1 SPECIFIC AIMS

Conduct a pilot study of an innovative lifestyle program (telehealth + community health workers) with and without metformin for diabetes prevention. This pilot trial is intended to consolidate and refine operations within the primary care coalition, and to develop data for a larger scale randomized trial evaluating a novel and sustainable approach for diabetes prevention that involves an innovative lifestyle intervention combined with metformin. The current revision application underscores the commitment of the DRC to partnerships and research that is directed at improving health in patients with diabetes and cardiometabolic disease in our communities with a particular emphasis on health disparities in rural communities. The primary care coalition is designed as a powerful resource for the study of mechanisms responsible for chronic disease disparities and developing interventions uniquely effective in these high-risk populations.

2.2 BACKGROUND AND SIGNIFICANCE

Alabama has the 3rd highest rates of diabetes in the U.S with 14.1% of adult living with diabetes compared with 9.4% nationally. Diabetes can be delayed or prevented for some people by making changes to their lifestyle. People at high risk for developing diabetes, often have prediabetes. Prediabetes is when a person has higher than normal blood sugars but do not yet have diagnosed diabetes. Roughly 37% of people living in Alabama have pre-diabetes, but only 10% of these individuals know they have it. Lifestyle interventions that include weight loss, increasing physical activity, and changing eating habits have been shown to prevent diabetes among some people. The Diabetes Prevention Program (DPP) provided a tested model of an intensive lifestyle intervention that targeted weight loss and successfully reduced diabetes risk by 58%. However, the DPP was a resource intensive efficacy trial and was not designed to be directly deliverable in real world settings. Community-based

adaptations of the DPP can be feasible but typically fail to show the same benefit as the more intense original trial version of the lifestyle modification program. The DPP demonstrated benefit from metformin therapy for prevention but to date limited effort has been made to promote the use of metformin therapy for diabetes prevention. Given the urgent need for novel ways to prevent or delay the Type 2 diabetes, this trial will combine the DPP with novel components including telehealth and peer coaches. PreventT2 is a CDC-adapted DPP implemented nationally at a variety of community locations including primary care offices, non-profits, and healthcare organizations (https://www.cdc.gov/diabetes/prevention/index.html) PreventT2 will be implemented in both arms of this study to assist participants at high risk of developing diabetes in making lifestyle modifications that may prevent or delay onset of Type 2 diabetes. In this trial, Condition 1 (lifestyle modification only) will be compared to Condition 2 which includes lifestyle modification with the recommendation that the primary care provider consider adding a prescription for metformin. The aim of this study is to introduce novel design elements including telehealth delivery, peer coaches, and daily weight checks to a community-based adaptation of the DPP to enhance research effectiveness. This approach may potentially prove to be a cost-effective and scalable approach to diabetes prevention in the Alabama Black Belt.

3 OVERVIEW OF STUDY DESIGN

This study is a cluster-randomized, two-arm controlled trial in primary care settings. A total of 4 primary care clinics in rural Alabama will be randomized to either 1) Receive lifestyle modification alone (DPP) or 2) Receive lifestyle modification with metformin therapy recommendations (DPP-recommendations). The sample will include up to 100 adults with obese (BMI 30-50 kg/m2) patients (4 clinics, 25 patients / clinic).

The primary aim of this trial is to conduct a 12-month randomized control trial (RCT) to determine the feasibility of implementing a peer coach-facilitated DPP delivered by telehealth. The DPP will be compared to DPP with metformin therapy recommendations. The goal of the intervention is to prevent or delay the Type 2 diabetes among rural primary care patients with pre-diabetes and obesity at high for developing diabetes. The primary outcomes are body weight and HbA1 results at month 12. The RCT will test feasibility and provide data that will inform design and power for a future study to assess diabetes prevention as the main outcome measure. All participants will receive the lifestyle intervention of the Diabetes Prevention Program (DPP) plus telemonitoring of their body weight using an Ideal Life body weight scale. The DPP is a 12-month intensive lifestyle modification intervention that include 16 group-based sessions over 6-months and 6 group-based session in the remaining 6-months. Consistent with the DPP, content includes fundamental components of evidence-based lifestyle interventions, including recommendations for dietary modification, increased physical activity, and behavioral strategies designed to promote treatment adherence. The current intervention includes two new features, a telemedicine platform and the participation of community health workers. Participants will be partnered with a Community Health Worker (CHW) who will facilitate the delivery of the group-based session delivered by a trained nurse or dietician joining via the telehealth platform. The CHW will assist participants in setting up the telemonitoring and conduct 16 brief weekly calls and 6 monthly calls over the 12-month intervention.

The primary outcome measures include feasibility assessment and the measurement HbA1c and body weight at baseline, 6 months, and 12 months. Demographic characteristics will be collected at screening and baseline. Participants will be enrolled for one-year period. This is a pilot trial designed to test feasibility for a larger scale randomized clinical trial that will evaluate effectiveness of an innovative lifestyle intervention combined with metformin in for diabetes prevention.

4 INCLUSION/EXCLUSION CRITERIA

Prevent T2 is a pragmatic trial to be conducted in primary care clinics. Thus, the inclusion criteria are broad and designed to capture a large cross-section of the target population.

4.1 INCLUSION CRITERIA

- Age 19 (the age of adulthood in Alabama) to 65 years
- A1c (A1c) 6.0% to 6.4%
- Body mass index (BMI) 30-50 kg/m2
- Receives care at one of the 4 participating primary care clinics
- Resides in one location at least 5 days each week
- Telephone line or Wi-Fi internet connection or cellular signal in home
- Willing or able to partner with a Community Health Worker
- Willing to attend group sessions

4.2 EXCLUSION CRITERIA

- Pregnancy or anticipating pregnancy
- Diabetes (A1c ≥6.5%, and/or chart value of fasting glucose ≥126 mg/dl, and/or diabetes medications)
- Unwilling or unable to do any of the following: give informed consent, accept random assignment, allow study staff to visit them at their primary care clinic for two follow-up visits
- Likely to relocate and no longer be seen at primary care clinic in the next 2 years
- Weight loss or gain ≥5% of body weight in past 6 months (other than postpartum)
- Prescription weight loss medications within the past 6 months
- Another household member already participating in the study
- Abnormal thyroid status
- eGFR ≤60
- not able to ambulate or have end-stage medical conditions with limited life expectancy

4.3 SCREEN FAILURES

Potential participant HbA1c less than 6.0 or greater than 6.5% or meets any of the above referenced inclusion criteria.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment from four primary care clinics in the AL Black Belt will be in a manner similar to that used for our previous trials implemented in primary care, including our ongoing Southeastern Collaboration to Improve Blood Pressure" in which we have currently enrolled 660 patients from 31 primary care clinics in the Black Belt. We will begin by conducting chart reviews and send direct mailings to practice lists of potentially eligible patients that include opt-out postcards providing a brief study description and contact information followed by recruitment phone calls after 2 weeks. In our experience, this strategy yields by far the highest return. We will also place flyers in accessible, high-traffic areas (e.g., waiting

room, exam rooms) and provide practice staff with simple and brief forms to refer patients. We will also conduct periodic 'lunch and learn' seminars for practice staff to facilitate referrals. Given our significant experience recruiting from primary care, the high prevalence of pre-diabetes and obesity in the rural south, and the strong interest in weight management programs in general, we do not anticipate difficulty recruiting and enrolling the required number of participants. The text of all announcements and advertisements and all recruitment methods will have IRB approval prior to use. Solicitation of information from candidates will be conducted in a HIPAA-compliant manner. A trained recruiter will follow up with the patient to assess their interest in participating and screen them for eligibility during a screening visit (SV) in which they will have a point-of-care A1c conducted and answer a screening questionnaire to determine their eligibility. Following the completion SV activities, if the patient is deemed eligible, he/she will provide written informed consent prior to participating in baseline measurements to formally enrolled in the study at the baseline visit. Patients who participate in the SV activities will not be considered enrolled in the study until they have provided informed consent and completed baseline measurements. Patients may choose to complete the baseline measurements at the SV or schedule an appointment to conduct baseline measurements.

A variety of approaches will be used to retain patients. Based on our experience, we understand the importance of creating a pleasant clinic environment and friendly and welcoming staff presence. We are also very clear from the initial screening session onward about what we expect from patients and what they can expect from us, as keeping patients well informed enhances adherence to the intervention and test schedules. All participants receive a tablet device (similar to Amazon Fire valued at up to $90) and upon study completion, a body weight scale (valued at 425). Finally, a total of $150/patient is budgeted for incentives related to the provision of outcome measures. All patients will be paid at the completion of each assessment visit ($40 at baseline, $50 at 6-months and $60 at 12-months).

5 RANDOMIZATION/BLINDING

Randomization. This is a cluster-randomized trial, and enrolled patients at a given clinic will receive the intervention assigned to their clinic. A total of 4 primary care clinics in rural Alabama will be randomized to either 1) Receive lifestyle modification alone (DPP) or 2) Receive lifestyle modification with metformin therapy recommendations (DPP-recommendations).

Blinding. Given that this trial is a small pilot randomized at the clinic level and the interventions are very distinct, patients will know their group assignment, as will clinic staff, CHWs, and research staff that are involved in delivering the intervention.

6 INTERVENTION METHODS

6.1 OVERVIEW OF INTEVENTION ARMS

The overall study design of Prevent T2 trial is a cluster-randomized, two-arm controlled trial with a total of 4 primary care clinics in rural Alabama will be randomized to either 1) Receive lifestyle modification alone (DPP) or 2) Receive lifestyle modification with metformin therapy recommendations (DPP-recommendations). Study staff will work with practices to recruit 25 participants from each clinic for a total 100 participants.

6.1.1 DESCRIPTION OF LIFESTYLE INTERVENTION ARM

All enrolled participants will receive lifestyle modification intervention. Participants will receive Diabetes Prevention Program Curriculum educational materials related to PreventT2 intervention that include evidence-based recommendations for dietary modification, increased moderate-intensity physical activity, and behavioral strategies designed to support these lifestyle changes to promote healthy weight loss to delay or prevent the development of type 2 diabetes.

Program materials were accessed and printed for study use from public sources: *https://www.cdc.gov/diabetes/prevention/resources/curriculum.html* *The* CDC Diabetes Prevention Program Curriculum (CDC DPP Curriculum) is based on the curriculum from the Diabetes Prevention Program (DPP) research study supported by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease *(*U01-DK48489). All participants will also receive a RM body weight scale, the Ideal Life Body Weight Scale. Participants will be asked to: (1) keep the scale in their bedroom, (2) weigh daily at the same time in light clothing, and (3) view and log their daily weight checks. Study staff will review with participants how to set-up and use the scale. Participants will receive a binder and additional program materials over the course of the 12-month program. Trained health educators will deliver the DPP intervention to all participants on a rolling schedule. The DPP is an evidence-based intensive lifestyle modification program to prevent or delay type 2 diabetes that asks that participants attend 26 group sessions over 12 months. Peer coaches will facilitate the delivery of the DPP. Participants are asked to attend 16 weekly group sessions, 4 bi-monthly sessions, and 6 monthly sessions over the course of 12 months. Group sessions will be held via Zoom.

Peer Coaches for this trial will be hired and supervised by community partner whose primary mission is to train, employ, and deploy CHWs, ConnectionHealth. Peer Coaches will complete over 20 hours of training in the peer coach study protocol. Study participants will be matched with a Peer Coach who will conduct brief scheduled telephone contacts with each participant over the course of 12 months to provide support for behavior modification and help participants problem solve to overcome barriers. The scheduled contacts with peer coaches will take place 1-10 days before each scheduled DPP group session. Peer coaches will facilitate make-up sessions for missed group session. Make-up sessions may be viewed on a private YouTube channel or at scheduled visit with the peer coach using a tablet.

6.1.2 DESCRIPTION OF LIFESTYLE INTERVENTION WITH METFORMIN THERAPY RECOMMENDATIONS ARM

Lifestyle intervention program (telehealth + peer coach) with metformin therapy recommendations (DPP-recommendations): Participants will receive the same lifestyle intervention as those in the DPP condition described above. In addition to the lifestyle intervention, they will receive a recommendation for metformin therapy for prevention of type 2 diabetes. Primary care providers at the practices randomized to the DPP-recommendations condition will attend an orientation session and evidence-based materials about low-dose metformin therapy recommendations for patients with pre-diabetes to prevent or delay the onset of type 2 diabetes. At the baseline assessment, study staff will provide participants with the patient education handout on “Understanding Metformin for Pre-diabetes” that details using metformin for prevention of type 2 diabetes. At the same time, the participant’s primary care provider will receive a recommendation to provide their patient with a prescription for Metformin for diabetes prevention. The communication between study staff and PCPs will be developed and

tailored to fit the work flow of each clinic. As described in the inclusion/exclusion criteria, participants without a charted eGFR or an eGFR<60 within the last 6-months will be excluded from the study.

7 DATA COLLECTION PROCEDURES

Data will be collected at chart review (CR), a screening visit (SV), a baseline visit (BV), and at 6- and 12-month visits. The physical measurements that that will be made as well as the questionnaires to be used are described below. All physical measurements will be recorded on the Measurements Form.

Chart Review and Screening Visit. Chart reviews will be conducted, and direct mailings will be sent to practice lists of potentially eligible patients that include opt-out postcards providing a brief study description and contact information followed by recruitment phone calls after 2 weeks to pre-screen patient for study eligibility. If eligible and interested, potential participants are scheduled for a Screening Visit (SV). A trained recruiter will assess patient interest in participating and screen them for eligibility during a screening visit (SV) in which they will have a point-of-care A1c conducted and answer a screening questionnaire to determine their eligibility. Following the completion SV activities, if the patient is deemed eligible, he/she will provide written informed consent prior to participating in baseline measurements to formally enrolled in the study at the baseline visit. Patients who participate in the SV activities will not be considered enrolled in the study until they have provided informed consent and completed baseline measurements. Patients may choose to complete the baseline measurements at the SV or schedule an appointment to conduct baseline measurements.

Finger-stick Blood Sample

Finger-stick blood samples will be used to measure hemoglobin A1c using a validated Bayer A1C Now+ point-of-care device at screening, month 6 and month 12 visits. The Bayer A1C Now+ is a small, portable analyzer that requires only a single drop of blood from a finger stick and eliminates the anxiety of a venipuncture. The research staff will clean the patient's fingertip with an alcohol wipe and obtain a drop of blood using a lancet. The blood is collected via specific tube and transferred to the A1C Now+ cassette. The results will available in less than five minutes, and will entered on the Measurement Form (see Appendix A) and data-entered by the research staff. Results will be entered onto the Health Report to be provided to the patient.

Baseline Measurements. After individuals have been recruited and screened, eligible patients will be invited to enroll and complete baseline assessments. This visit will include completing informed consent to participate in the study and completion of surveys. Baseline assessments will be conducted by trained recruiter at the patient's primary care clinic. Completion of the baseline assessment will take approximately 30 minutes to 60 minutes. Surveys may be completed in-person during the visit or at a later time over the phone. Upon completion of baseline assessments, they will receive specific information and materials relevant to the condition to which they have been assigned (described above). Study personnel will review these materials with participants during this study visit. It is anticipated that the review of intervention procedures and materials will take approximately 30 minutes to 60 minutes. Follow-up assessments will be conducted in a similar manner as described in bullet below.

Weight

Weight is the primary outcome for this study and will be measured with the patient in light indoor clothes without shoes to the nearest 0.1 kg using a digital scale at each assessment visit. Patients will be

instructed to stand still in the middle of the scale with head erect and eyes looking straight ahead. After the weight is recorded, the patient will step off of the scale and the research assistant will set the scale to zero, then repeat and record the second weight measurement. If the two readings differ by more than 0.5 kg, a third measurement will be obtained. The closest two measurements will be averaged for analysis. The accuracy of the scales will be checked at scheduled monitoring visits using standard weights. Weight will be measured at the baseline visit, and at the 6 and 12 month assessment visits.

Height

Height will be measured at the screening visit and the baseline visit using a portable stadiometer. The patient will be asked to remove their shoes and have their heels, buttocks and upper part of the back remain in contact with the stadiometer with their arms hanging naturally at their side. The patient is asked to inhale and hold their breath, while the technician lightly applies traction to the patient's head in order to maintain alignment with the Frankfort Plane. The slide is lowered until it reaches the vertex of the skull and the reading from the indicator is recorded to the nearest 0.1 centimeter. This process will be repeated, and if the two readings differ by more than 0.5 cm, a third measurement will be obtained. The closest two measurements will be averaged for analysis. Calibration of the portable stadiometer is not required, however the accuracy of the stadiometer will be checked at scheduled monitoring visits against a standard meter stick. It is not necessary for the stadiometer to be calibrated once all Baseline Visits are completed as height is not measured at follow-up measurement visits.

Questionnaires

All questionnaires will be interviewer administered and data-entered by research staff. Paper questionnaires will be used in the event of power or other equipment failure.

Baseline Demographic and Health History Questionnaire

A self-report demographic and health history questionnaire asks the patients about their age, sex, race/ethnicity, use of tobacco and alcohol, health insurance status, income and employment, education level, history of chronic diseases, and cellular phone ownership and internet use.

Change in Health History Questionnaire

A self-report questionnaire captures changes in health outcomes that have occurred across the 6 months of the intervention. This questionnaire is administered at the 6 and 12 assessment visits.

Patient-reported Quality of Life

PROMIS: Global Health, Physical Health, Mental Health, Physical Function, Social Isolation

PROMIS® stands for the Patient Reported Outcomes Measurement Information System (www.nihpromis.org), which is a system of highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being. The PROMIS items were developed using a rigorous methodology funded by the National Institutes of Health (NIH) with a goal to develop valid, reliable, and standardized questionnaires or tools to measure patient–reported outcomes. A previous study has shown that among people with disabilities, health-related quality of life was significantly lower among the obese as measured by the PROMIS scales as compared to the non-obese. The PROMIS measures will be administered at baseline, and at the 6 and 12 visits.

Dietary Intake Questionnaire

A questionnaire that assesses fruit, vegetable and alcohol intake is administered at baseline and at the 6- and 12-month assessment visits. The questionnaire contains scales derived from several sources. A standard 6-item fruit and vegetable screener developed by the NCI and National 5 a Day Program

grantees asks how often fruit and vegetables were consumed in the past month. One question related to the frequency of alcohol intake (beer, wine, hard liquor) in the past 30 days.

Simple Physical Activity Questionnaire – SIMPAQ
Physical activity levels are measured at baseline and at the 6 and12 month assessment visits using the SIMPAQ which asks questions related to physical activity performed over a representative 24-hour period from the previous 7 days. The SIMPAQ has acceptable reliability.

Perceived Competence: Maintaining a Healthy Diet and Exercising Regularly
The Perceived Competence Scale is designed to measure competence in different dimensions within lifestyle modification. For the purpose of this trial, only Maintaining a Healthy Diet and Exercising Regularly scales were administered at baseline, and at 6 and 12 month assessment visits.

Personal Health Questionnaire Depression Scale
Personal Health Questionnaire Depression Scale (PHQ8) is a screener designed to measure depressive symptoms in an adult population. PHQ8 consists of 8 items scored 4-point Likert scale. Higher scores indicate more depressive symptoms.

Perceived Stress Scale (PSS-4)
Perceived Stress Scale (PSS-4) is tool to evaluate control and confidence in handling stressful situations. The PSS-4 consists of 4 items scored on a 5-point Likert scale, with reverse coding for 2 items. Scores range from 0 to 16, with higher scores indicating higher levels of stress.

Follow-up Assessments. For follow-up assessments at month 6 and month 12, a trained staff will conduct measures of a point of care HbA1c, weight and surveys/questionnaires completed by participants. Patient-reported surveys/questionnaires may be completed in-person or over the phone prior to the in-person visit depending on participant preferences. For all in-person visits, telephone calls will be made to schedule these visits and provide reminders for upcoming visits. Reminder calls will occur 1-7 days prior to scheduled appointments.

Chart Review: Medical Record Data Collection
In addition to data collection of outcome measurements by the research staff, a chart review data collection effort will be done by utilizing the medical records at the participating clinics. For each of the participating patients in both arms, a retrospective chart review covering the period of the intervention will be done to abstract data on clinical variables of interest over the course of the intervention. The electronic medical records of the patients will be obtained, or in cases where electronic records are not available, paper medical records will be abstracted by hand and data-entered by research staff.

8 QUALITY ASSURANCE AND CONTROL

Quality assurance and quality control is of utmost importance in a randomized clinical trial. Standardized protocols for all measurements have been developed, and adherence to the written protocols is of paramount importance. All data collection personnel will be certified as competent to make the required measurements by trained experts. The following provides an outline of the quality assurance and control program developed for Prevent T2:

- Training and certification of all data collection personnel by experts
- Routine calibration of all equipment following manufacturers guidelines
- Performance of routine clinic site-visits and source document verification

- Setting realistic limits on data entry fields in REDCap
- Remote monitoring of data entry and missing data through REDCap
- Querying appropriate personnel regarding missing data
- Preparing quality control reports for personnel, investigators and medical monitor

9 DATA MANAGEMENT

Assessment (REDCap)

All data collected by the assessment team at SV, BV, and at month 6 and 12 assessment visits will be direct entered to the Research Electronic Data Capture (REDCap) system through data entry by study personnel. Paper forms will be used secondary if direct data entry unavailable (e.g. Internet service failure, power failure, or other equipment failure). REDCap is a secure, HIPAA-compliant, web-based application that can be utilized for electronic collection and management of research and clinical trial data. Study data and electronic data capture tools are housed in a secure data center at UAB, and all web-based information transmission is encrypted. The server is backed up nightly and is protected by an enterprise network security firewall. REDCap will be accessed through the UAB Department of Medicine's secure website, https://redcap.dom.uab.edu, where research personnel are required to enter user ids and passwords previously approved and set up by the UAB Department of Medicine REDCap Administrator.

The level of user access and privilege will be determined on an individual basis and will rely upon each user's role in the study and clinics they are associated with. Only select project management personnel will be able to edit participant record IDs or export data; the data collection staff will only be able to view and edit (not export) the participant data and run quality checks for the clinics with which they are associated, and investigators will only be able to view data collected at their site. Only select project management personnel will be able to edit participant record IDs or export data; the data collection staff will only be able to view and edit (not export) the participant data and run quality checks for the clinics with which they are associated, and investigators will only be able to view data collected at their site. All data entered will be run through multiple checks for internal consistency and biologic plausibility; these will be conducted in REDCap with either real-time error messages and data stoppage rules or user-initiated query reports, as well as with study-specific SAS programs designed by the data manager. Missing or questionable data will be assessed and corrected by research staff at the clinics or project management staff at UAB. All users will be thoroughly trained in the use of the REDCap data entry and validation system. Once it is determined that data collection, entry and verification is complete, the REDCap project will be locked so that users will no longer be able to edit the data, but investigators may still export and preserve it.

Intervention – Diabetes Prevention Program (REDCap)

All data collected by the Community Health Workers team over the 12-month intervention will be direct entered to the Research Electronic Data Capture (REDCap) system through data entry by trained Community Health Workers. Paper forms will be used secondary if direct data entry unavailable (e.g. Internet service failure, power failure, or other equipment failure). REDCap is a secure, HIPAA-compliant, web-based application that can be utilized for electronic collection and management of research and clinical trial data. Study data and electronic data capture tools are housed in a secure data center at Vanderbilt University, and all web-based information transmission is encrypted. The server is backed up nightly and is protected by an enterprise network security firewall. intervention delivery, treatment fidelity, scheduling of intervention visits with patients, and tracking of process measures for intervention delivery, such as attendance. REDCap is a secure, HIPAA-compliant, web-based application

that can be utilized for electronic collection and management of research and clinical trial data. REDCap will allow for tailoring the intervention to individual participants, and it will be used by the intervention team to quantify process measures related to intervention delivery. Specifically, it will be used to review participant attendance, goal setting progress, and adherence to the diet and exercise recommendations. These process data will be provided in reports generated and these data can be viewed at the study, clinic, CHW, and participant level.

10 SAFETY AND

This Human Subjects Research meets the definition of a clinical trial.

10.1 POTENTIAL RISKS TO SUBJECTS

Human Subjects Involvement, Characteristics, and Design: Participants will be women and men with obesity and prediabetes who receive care through a network of rural primary care providers and clinics that comprise in part the Primary Care Coalition organized by the UAB Diabetes Research Center. Eligible participants will be women and men aged 19-65 years with obesity (BMI >30) and an hemoglobin A1c (A1c) 6.0% to 6.4% who receive care through one of 4 primary care providers in the Alabama Black Belt. Randomization will occur at the clinic level where participants will be enrolled to either: (1) lifestyle condition only at two practice sites, or (2) lifestyle plus receive metformin 500 mg twice daily prescription from their provider at two different practice sites. All participants will receive the lifestyle intervention of the Diabetes Prevention Program (DPP) plus telemonitoring of their body weight using an Ideal Life body weight scale. The DPP is a 12-month intensive lifestyle modification intervention that include 16 group-based sessions over 6-months and 6 group-based session in the remaining 6-months. Consistent with the DPP, content includes fundamental components of evidence-based lifestyle interventions, including recommendations for dietary modification, increased physical activity, and behavioral strategies designed to promote treatment adherence. The current intervention includes two new features, a telemedicine platform and the participation of community health workers. Participants will be partnered with a Community Health Worker (CHW) who will facilitate the delivery of the group-based session delivered by a trained nurse or dietician joining via the telehealth platform. The CHW will assist participants in setting up the telemonitoring and conduct 16 brief weekly calls and 6 monthly calls over the 12-month intervention. This is a pilot trial designed to test feasibility for a larger scale randomized clinical trial that will evaluate effectiveness of an innovative lifestyle intervention combined with metformin for diabetes prevention.

Inclusion Criteria:

- Age 19 (the age of adulthood in Alabama) to 65 years
- A1c (A1c) 6.0% to 6.4%
- Body mass index (BMI) 30-50 kg/m^2
- Receives care at one of the 4 participating primary care clinics
- Resides in one location at least 5 days each week
- Telephone line or Wi-Fi internet connection or cellular signal in home
- Willing or able to partner with a Community Health Worker
- Attend group sessions

Exclusion Criteria:

- Pregnancy or anticipating pregnancy
- Diabetes (A1c ≥6.5%, and/or chart value of fasting glucose ≥126 mg/dl, and/or diabetes medications)
- Unwilling or unable to do any of the following: give informed consent, accept random assignment, allow study staff to visit them at their primary care clinic for two follow-up visits
- Likely to relocate and no longer be seen at primary care clinic in the next 2 years
- Weight loss or gain ≥5% of body weight in past 6 months (other than postpartum)
- Prescription weight loss medications within the past 6 months
- Another household member already participating in the study
- Abnormal thyroid status
- eGFR ≤60
- not able to ambulate or have end-stage medical conditions with limited life expectancy

Sources of Materials: All material obtained from participants will be used specifically for research purposes. Data to be gathered from participants include self-report questionnaires and weight and height measurements as outlined in the study protocol. A1c will be assessed by finger stick and point-of-care testing in the clinics using CLIA approved devices. We will conduct chart abstraction using the electronic medical records from the participating clinics in addition to data collection by our trained assessment team. Data will be collected from participants by the research team, by trained staff at the primary care clinics, and through the Ideal Life software interface (the scale manufacturer), where weights will be automatically recorded. Only the research team will have login credentials to access information. All data will be available only to trained research staff affiliated with this study.
All outcomes will be assessed using validated scales and tests where they exist. For example, height, and weight will be measured using standard procedures. In addition to direct health measures, several patient-reported outcomes will be measured by questionnaire, including quality of life, physical function, dietary intake, and physical activity.
The assessment team, peer coach, and data management staff will have access to personally identifiable private information about human subjects. All volunteers are assured of their confidentiality both verbally and in the informed consent form. The facilities are strictly limited to the staff of the research institution, clinics and to research volunteers. All medical records are locked in a secure area. Access to these areas is limited to the clinical support staff and the study investigators. Medical records are filed according to identification (ID) numbers. All forms in the chart, with the exception of the consent form and participant contact form, display only the ID number. Electronic data storage is similarly restricted with only the data management staff having access to the databases containing confidential records, i.e. those containing names or identifying information.

Potential Risks
This study does not involve major risks to participants. Efforts to minimize the potential risks of the assessment methods and outcome variables include frequent monitoring by the investigators to assure that no volunteer suffers any adverse effects from participating in the research. Our staff have performed similar testing procedures in many studies. Participants with known serious disease will be excluded from the study.
Potential risks associated with the study procedures include:

a) Body height and weight. There is minimal risk to participants from these measurements.
b) Finger stick blood sample. There is the possibility of pain and bruising on the finger where the finger prick is made. Aseptic (sterile) technique and trained personnel minimize these risks.

c) Diet. Patients may modify their diet based on intervention recommendations that is safe for humans and has been tested repeatedly in clinical trials.
d) Increased physical activity. Patients in the intervention arm will be counseled to increase physical activity to levels that are consistent with the recommendations for US adults (30 minutes of moderate intensity activity per day). There is the possibility of adverse events such as minor musculoskeletal problems, but risk is minimized by excluding potential participants with contraindications to exercise. Considering these types of events are expected in this trial they will not be recorded or reported unless they meet the definition of a Serious Adverse Event. Patients are counseled to secure physician approval before beginning any new exercise plan.
e) Gastrointestinal (GI) upset from taking metformin. For patients enrolled in the lifestyle plus metformin recommendations, we will ask patients to monitor their symptoms. Metformin is recommended by the American Diabetes Association for the prevention of diabetes among those at high-risk. To minimize nausea and GI upset, in the Orientation for providers and provider handout on metformin therapy recommendations, materials will describe how to start patients at low dose of 250mg daily and increase to 250mg twice daily after 2 weeks as tolerated. Enrolled participants who do not tolerate metformin (e.g., due to gastrointestinal symptoms) will continue to be followed for 12 months on an intent-to-treat basis. This is a minor risk and is reversible.

Adequacy of Protection against Risks

Recruitment and Informed Consent

The patients are volunteers that will be recruited through the primary care clinics. Potential subjects will then be screened in person to determine that they meet the initial recruitment criteria (such as age and BMI) and have no obvious contraindications to participating in the study. Screening of study participants will be conducted by a trained recruiter following a written manual of procedures. In a one-on-one, the potential participant(s) will be informed of the nature and requirements of the study, either via face-to-face interview or informed consent presentation. All patients will be given time to read the consent form and ask questions one-on-one with research staff. To continue, the participant must read and sign an informed consent to participate in further assessment and treatment.

Protection against Risks

This study will be required to have approval from the UAB Institutional Review Board as well as IRBs at partner institutions. UAB has full accreditation by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Efforts to minimize the potential risk of the assessment methods include frequent monitoring by the investigators to assure that no participant suffers any adverse effects. All volunteers are assured of their confidentiality both verbally and in the informed consent form. The clinical facilities are strictly limited to the staff of the research institution, clinics and to research volunteers. This is accomplished by a variety of stringent security measures. All medical records are locked in a secure area. Access to these areas is limited to the clinical support staff, director of clinical facilities, and the investigators. Volunteers' medical records are filed according to ID numbers. All forms in the chart, with the exception of the consent form, display only the ID number. Electronic data storage is similarly restricted with only data management staff having access to the databases containing confidential clinical records, i.e. those containing names or other identifying information.

Potential Benefits of the Proposed Research to the Subjects and Others

We cannot ensure direct benefits for patients in this study. However, it is likely that patients in both arms will experience health benefits associated with a healthier diet, increased physical activity and potential weight loss. The results of the study will provide important information about the

feasibility of an innovative intervention delivered through primary care that can be replicated in other regions of the United States.

Importance of the Knowledge to be Gained

This study proposes a comparative effectiveness trial of a pragmatic obesity intervention set within primary care. Thus, there is an urgent need to develop and test pragmatic treatment strategies in the primary care setting. There is a gap between current guidelines and what is currently implemented in clinical practice; thus, feasibility studies are required to change the way that primary care practitioners approach the patients at high risk for developing diabetes. This study directly addresses this gap by testing the feasibility of intensive lifestyle intervention combined with provider recommendations for prescribing metformin.

Pregnancy and Other Exclusions

If a participant experiences a pregnancy lasting beyond the first trimester, her data will be censured from the time of estimated conception, and she will be excluded from further participation. In the case of a miscarriage or pregnancy termination within the first trimester, or if a participant develops another exclusionary condition, such as cancer, unstable angina, or another condition for which weight loss or exercise might be contraindicated, further participation will be determined by the medical monitoring team.

11 SAFETY AND DATA MONITORING PLAN

11.1.1 STUDY IDENTIFICATION

Title: Preventing Diabetes in the Deep South: Extending Partnerships and Adapting Interventions to Reach Rural Communities at High Risk –
UAB IRB Protocol #: *IRB-300005012*
Principal Investigator: Andrea L. Cherrington, MD, MPH
Sponsor: NIH/NIDDK
National Clinical Trial (NCT) Identified Number: NCT0434387

11.1.1.1 STUDY OVERVIEW

Brief Description of the Purpose of the Study – This is a pilot and feasibility study featuring a randomized controlled trial of an adapted telehealth-delivered Diabetes Prevention Program augmented by Community Health Workers plus/minus pharmacotherapy (metformin). The intervention and measurement protocols pose minimal risk to participants given our plans for the protection of research volunteers. We anticipate no major adverse events or serious adverse events except for nausea in some patients taking metformin. The data and safety monitoring plan for this trial focuses on close monitoring by the PIs and research staff in conjunction with a data safety and monitoring board (DSMB), along with prompt reporting of excessive adverse events and any serious adverse events to the NIH and to the IRB at UAB. The study procedures pose little to no risk for human subjects. However, a medical monitor (MM) will review the protocol and monitor conduct of this study.

Adherence Statement - The Data Safety Monitoring Plan (DSMP) outlined below will adhere to the protocol approved by the UAB IRB

11.1.1.2 CONFIDENTIALITY

A. Protection of Subject Privacy – All volunteers are assured of their confidentiality both verbally and in the informed consent forms. The facilities are strictly limited to the staff of the research institution, clinics and to research volunteers. This is accomplished by a variety of stringent security measures. All medical records are stored in locked areas. Access to these areas is limited to the clinical support staff and the PI of the study. Volunteers' medical records are filed according to ID numbers. All forms on the chart, with the exception of consent form, display only the ID number.

B. Database Protection – Electronic data storage is similarly restricted with only the data management staff having access to databases containing confidential clinical records, i.e. those containing name or other identifying information.

C. Confidentiality during AE Reporting – Adverse events will be reported to the study PI, Project Manager, Medical Monitor, DSMB and Chair of the IRB throughout the trial. Adverse event data will be analyzed quarterly, but serious or life-threatening adverse events require immediate reporting and follow-up. AE reports and quarterly summaries will not include subject-identifiable material. Each will include the identification code only.

11.1.1.3 ADVERSE EVENT INFORMATION

A. Definition - An adverse event (AE) is any untoward medical occurrence in a subject temporally associated with participation in the clinical study. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.) or any combination of these. A Serious Adverse Event (SAE) is any adverse event that results in one or more of the following outcomes: death; a life-threatening event; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; a congenital anomaly or birth defect; important medical event based upon appropriate medical judgment.
B. Classification of AE Severity – AEs will be labeled according to severity which is based on their impact on the patient. An AE will be termed 'mild' if it does not have a major impact on the patient, 'moderate' if it causes the patient some minor inconvenience and 'severe' if it causes a substantial disruption to the patient's wellbeing. The Site Staff for this trial will be responsible for determining the 'severity' of AEs. Site Staff will also make an initial evaluation of the 'seriousness' of the AE in order to determine if the AE needs to be elevated to the MM immediately upon discovery. The MM will make the final and official determination of the 'seriousness' of an AE. We anticipate most adverse events will be "mild" and the participant will be able to resume daily activities within a day or two of reporting the event.

C. AE Attribution Scale – AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled as either related or unrelated to the study intervention, and this relationship will be confirmed by the Medical Monitoring Team (MMT) for this trial.
D. Expected Risks – This study does not involve major risk to screeners and trial participants. Efforts to minimize the potential risks of the assessment methods and outcome variables include frequent monitoring by the investigators to assure that no volunteer suffers any adverse effects from participating in the research. The expectedness of an AE will be determined by the Medical Monitoring Team (MMT).

The study procedures include:

a) Body height and weight. There is minimal risk to participants from these measurements.
b) Finger stick blood sample. There is the possibility of pain and bruising on the finger where the finger prick is made. Aseptic (sterile) technique and trained personnel minimize these risks.
c) Diet. Patients may modify their diet based on intervention recommendations that is safe for humans and has been tested repeatedly in clinical trials.
d) Increased physical activity. Patients in the intervention arm will be counseled to increase physical activity to levels that are consistent with the recommendations for US adults (30 minutes of moderate intensity activity per day). There is the possibility of adverse events such as minor musculoskeletal problems, but risk is minimized by excluding potential participants with contraindications to exercise. Considering these types of events are expected in this trial they will not be recorded or reported unless they meet the definition of a Serious Adverse Event. Patients are counseled to secure physician approval before beginning any new exercise plan.
e) Gastrointestinal (GI) upset from taking metformin. For patients enrolled in the lifestyle plus metformin recommendations, we will ask patients to monitor their symptoms. Metformin is recommended by the American Diabetes Association for the prevention of diabetes among those at high-risk. To minimize nausea and GI upset, in the Orientation for providers and provider handout on metformin therapy recommendations, materials will describe how to start patients at low dose of 250mg daily and increase to 250mg twice daily after 2 weeks as tolerated. Enrolled participants who do not tolerate metformin (e.g., due to gastrointestinal symptoms) will continue to be followed for 12 months on an intent-to-treat basis. This is a minor risk and is reversible.

E. SAE Reporting - SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Medical Monitoring Team and the UAB IRB in accordance with requirements. Anticipated SAEs or those unrelated to the study intervention will be reported to the same individuals/entities in accordance with requirements. Clinics will be required to report to the Medical Monitoring Team adverse events that are serious or in doubt about being serious within 24 hours of discovery. Other adverse events that are not serious but are unexpected and are associated with the study procedures will be reported within 10 days.

Data Quality and Safety Review Plan and Monitoring

A. Data Quality and Management – A Medical Monitor (MM) will be selected and will meet regularly throughout the study period. The MM will meet twice per year throughout the trial, and will be convened for a first meeting prior to recruitment of patients. A minimum of 1 meeting each year will be conducted. Prior to the start of recruitment the MM will give formal approval of the study protocol and informed consent.

Major Responsibilities of MM:

1. Sign and abide by a statement of confidentiality
2. Disclose any actual or potential conflicts of interest
4. Be familiar with the research protocol and plans for safety monitoring
5. Oversee safety of participants, which will include review of interim/cumulative data for evidence of study-related adverse events (including serious adverse events)
6. Review data quality, completeness, and timeliness (including recruitment)
7. Review adherence to the protocol
8. Review factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.)
9. Review reports of related studies, as appropriate

10. Review major proposed protocol modifications

Reports: Following each meeting, the MM will provide written documentation regarding findings for the study as a whole and any relevant recommendations related to continuing, changing, or terminating the study. All MM recommendations will be submitted to the Principal Investigator and/or his designee.

The MM will monitor and review recruitment, adverse events, data quality, outcome data, and overall awardee performance. The PI and Project Manager will regularly review all data collection forms and source documents on an ongoing basis for data completeness, accuracy, and compliance with the protocol. A statement reflecting the results of the review and describing any protocol deviations will be sent to the IRB in an annual report (non-competing continuation).

B. Subject Accrual and Compliance - Review of subject accrual, adherence to inclusion / exclusion criteria, and rates of study completion will occur quarterly. These data will be reviewed by the study PI and Medical Monitor.

C. Out of Range Data – _Laboratory and physical measurement reports will be reviewed weekly by the Medical Monitoring Team for the study. Out-of-range values for A1c will be reported to the patient as soon as possible so that they can follow up with their PCP.

Measure	**Alert Value**	**Notify Patient**	**Notify PCP**
A1c	≥6.5%	At Visit or Within 1 week or sooner as indicated by exact value and judgment of Medical Monitor	Provide letter to PCP with A1c value and instruct the patient to notify their PCP within 1 week or sooner as indicated by exact value and judgment of Medical Monitor

D. Stopping Rules - This study will be stopped prior to its completion if: (1) adverse effects that significantly impact the risk-benefit ratio have been observed; (2) study recruitment or retention becomes futile; (3) any new information becomes available during the trial that necessitates stopping the trial; and (5) other situations occur that might warrant stopping the trial. Because one of the most likely reasons for stopping the trial is the inability to recruit the study sample, the PI will include an assessment of recruitment futility in the annual progress report to funder and will consult with a biostatistician if necessary to assess the impact of significant data loss due to problems in recruitment, retention or data collection.

E. Safety Review Plan - The PI will monitor the progress of the study weekly, including reasons for attrition and whether all participants met entry criteria. Further, progress and safety will be reviewed quarterly. These progress reports will include information on recruitment, retention/attrition, and AEs and will be provided to the Medical Monitor quarterly. The Medical Monitor will also receive a yearly report that details data relevant to the possible early termination of the study. We will establish a DSMB and we will provide reports to the DSMB prior to each meeting on adverse events and recruitment.

F. Informed Consent
Patients are volunteers that will be recruited through primary care clinics. The UAB's Institutional Review Board (IRB) as well as the IRBs of the partner institutions will approve the study protocol and all consent forms. Trained recruiters will obtain informed consent from all participants as well as HIPAA authorization. All questions and concerns are clarified before any forms are signed.

11.2 INCLUSION OF WOMEN AND MINORITIES

Inclusion of Women - Women will be included in this intervention with equal probability as men as the inclusion criteria include both men and women.
Inclusion of Minorities - We have selected clinics with a high proportion of patients with low socio-economic status and African Americans; however, our inclusion criteria do not specify any specific ethnicity. Thus, we anticipate that the socio-demographic distribution of patients will follow closely the patient population in selected clinics.

11.3 INCLUSION OF CHILDREN

The focus of the Funding Announcement under which this study was funded is on diabetes prevention in adults therefore the patients in this study are mainly adults (19 - 65 years of age). The evidence-based intervention for lifestyle modification was trialed in adults and the treatment of childhood obesity and prevention of type 2 diabetes is beyond the scope of this intervention.

12 POWER AND SAMPLE SIZE

For this pilot study, the importance of sample size lies in establishing feasibility and the precision of estimated changes which will inform the design of future studies. We will recruit 25 participants at each of four clinics (2 clinics for each intervention), for a total of 50 per intervention, or 40 per intervention allowing for 20% attrition. The clustering of patients within practices, as measured by the intra-class correlation (ICC) may result in a reduced effective sample size. In considering to impact of the ICC, we relied on the ENCOURAGE study[49], our previous practice-randomized trial of diabetics in the Black Belt. ICCs were essentially negligible in that study; estimated ICCs were <0.01 and not statistically significant. The impact of the ICC is quantified by a design factor (D) defined as 1+ICC x (N-1) where N is the number of subjects per cluster. However, with an ICC of 0.01, the effective sample sizes per group are 40 (without attrition, D=1.24) and 33 (allowing for 20% attrition, D=1.19). This range of sample sizes will allow us to use to estimate changes in body weight with 95% confidence intervals that are ±0.28 standard deviations to ±0.35 standard deviations.

13 DATA ANALYSIS PLAN

Mixed models will be used to estimate the changes in outcomes by intervention with confidence intervals using practice as a random effect to account for clustering within practices. Secondary models will adjust for baseline values. In 2011, Katula et al. published 12-month results of randomized controlled trial comparing a community-based translation of a DPP lifestyle intervention conducted in a southern sample with usual care. Combined with data generated in our feasibility trial, this relevant study should further help inform our power assessments for a larger RCT. The change values observed in the control group in that project will serve as a reference for expected change in weight without any intervention and will be used to estimate the change due to the intervention.

Handling of Missing Data
Missing data are expected due to dropouts and missed visits. Weight loss is a subject-level variable and missing assessments would influence tests relative to treatment-by-time interactions. The primary analysis described above will employ restricted maximum likelihood using all data. No patients will be deleted from the analysis because of partial data. To assess the sensitivity of results, weight loss will be

analyzed using: 1) all patients irrespective of missing data to perform analysis of variance using mixed effects multi-level models with repeated measures; 2) only patients who have competed all assessment visits and have no missing data, to perform analysis of variance employing mixed effects multi-level models with repeated measures; 3) all patients, irrespective of missing data, to conduct analyses using mixed effects multi-level time trend models with random coefficients to capture individual time trends (does not require complete data across time); and 4) multiple imputation.

Multiple imputation will be employed to perform statistical inferences that properly account for statistical uncertainty due to missingness. Rubin's multiple imputation procedure replaces each missing value with a set of plausible values that represent the uncertainty about the appropriate value to impute.84 Missing values are imputed by drawing random samples, and the process is replicated to provide K data sets with pseudo-complete data. Estimates and corresponding confidence intervals will be plotted against K to determine the optimal K to use in subsequent sensitivity analyses. Mean weight loss is estimated for each data set, and the multiple imputation estimator is the average of the individual estimates. The variance of the estimator is estimated from between- and within-imputation variability. The SAS® procedure PROC MI provides four relevant options for imputation models and will be used in quantifying uncertainty due to missing data.

Statistical summaries will be compiled on the number of patients overall and by arm and who completed study per protocol, did not complete study per protocol, and reasons for not completing. Patient characteristics (age, sex, race, BMI) will be summarized similarly. Multi-level logistic regression will be used to investigate the significance of correlates of failure to complete the study per protocol.

14 TRIAL ORGANIZATION

The Principal Investigator will oversee and monitor progress to reach the milestones with decisions concerning short-term goals and the evaluation of longer-term progress being discussed with the research staff via weekly meetings. Broader management of the project will be undertaken by the Project Management Committee, as described below. The research team will be organized into sub-teams of investigators and staff. The overall organizational structure will be reviewed and amended as required.

Project Management Committee

The Project Management Committee will be comprised of the Principal Investigator, selected co-investigators, Project Manager and Community Coordinator. The Project Management Committee will be responsible for overseeing the day-to-day management of the trial, and the Principal Investigator will adjust the approach used by the team to achieve the milestones.

15 APPENDICES

Appendix A: Consent
Appendix B: PreventT2 Recruitment Materials

16 ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
GCP	Good Clinical Practice

HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LSMEANS	Least-squares Means
MM	Medical Monitor
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
UAB	University of Alabama at Birmingham
UP	Unanticipated Problem
US	United States