COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: Effect of Behavioral Lifestyle Intervention on Frailty in Older Adults With Diabetes

NCT number: NCT04440449

IRB Approval Date: 10/20/20

Unique Protocol ID: HSC20190019H

Form CT
UTHSA Clinical Trial Description
This form is not mandatory. Other documents are acceptable if equivalent information is provided.

UTHSCSA Tracking Number *(internal use only)*	HSC20190019H	**1. Original Version Date**	
		1.1. Revision Date(s) *add rows as needed*	

2. Background
Briefly discuss the important literature relevant to the trial and that provides background for the trial. Include the importance of the trial and any relevant treatment issues or controversies.

Type 2 Diabetes (T2D) is a significant problem in older adults and is known to increase the risk of future frailty. More than 25% of the U.S. population aged ≥ 65 years has T2D; and, recent projections suggest that the number of cases of diagnosed T2D in those aged ≥65 years will increase by 4.5-fold (compared to 3-fold in the total population) between 2005 and 2050. Although the burden of T2D is often described in terms of its impact on working-aged adults, the disease also affects longevity, disability, and common geriatric syndromes such as frailty, which ultimately leads inability to maintain independence. The combination of the T2D epidemic and increasing population of older adults call for innovative healthcare strategies and communication technology such as mobile health (mHealth) that can play a significant role in modifying the lifestyle behaviors of older adults in order to improve frailty characteristics and manage T2D. It has been supported that mHealth can facilitate behavior promotion (diet, physical activity), improve self-management, self-efficacy, and medication adherence in older adults. Research indicates that older adults have positive attitudes toward the use of mHealth interventions and applications and confident in their ability to self-manage their T2D suggesting that the benefits of technology outweigh the costs of adapting its use in this population.
To the best of our knowledge, no study has reported on the impact of behavioral lifestyle interventions for overweight/obese older adults with T2D on improvements of frailty characteristics. For this pilot study, we will conduct a randomized controlled trial to determine the feasibility and compare the preliminary efficacy of a behavioral lifestyle intervention and its impact on frailty-related measures in overweight/obese community-dwelling older adults with T2D. We will be using mHealth tools to enhance self-monitoring of multiple behaviors (diet and physical activity) and to manage T2D. Our overall goal is to test the hypothesis that the implementation of behavioral lifestyle interventions to promote physical activity and dietary modifications will help older adults with T2D to improve frailty characteristics and manage the disease, which may eventually lead to healthy aging. Such intervention would include the use of self-monitoring of diet and physical activity.

3. Objectives and Endpoints *All data points collected in the study should support an objective or have a regulatory purpose.*
Complete the table – add rows as needed.

3.1. Objective(s) *Clearly and concisely define the primary and secondary outcomes.*	**3.2. Endpoint** *Clearly define the endpoints. (endpoints are the basis for concluding that the objective has been met).*	**3.3. Justification for Endpoint** *Briefly explain why the endpoint(s) were chosen.*
Determine the feasibility of the lifestyle intervention using a smartphone for self-monitoring of diet and physical activity for the improvement of frailty measurements	Results from this study will provide the first information regarding the efficacy of a behavioral lifestyle intervention using a smartphone in the	Behavioral lifestyle interventions using a smartphone for self-monitoring to improve frailty measurements, body weight, and glycemic control in overweight/obese older adults with T2D.

(primary outcome) and on weight management and glycemic control (secondary outcomes) in overweight/obese older adults with T2D.	improvement of frailty measurements in community-dwelling older adults with T2D.	

4. Rationale
Briefly state the reason for conducting the clinical trial.

Despite the significant prevalence of T2D among older adults and/or those with multiple comorbidities, these populations have been excluded from randomized controlled trials of treatments for T2D and its associated conditions. Based on the prevalence of T2D, its related complications, implementation of cost-effective treatment and up to date (or less burdensome) self-monitoring strategies for overweight/obese older adults with T2D, this study is needed.

5. Study Design: Randomized controlled trial

5.1. Number of Groups/Arms	1	**Group name(s)**	mHealth+ group Intervention group

5.2. Overall Design
Select all applicable

☐	**Randomization**		☐	**Cluster Randomized**			
☐	**Group-Sequential**		☐	**Adaptive Design**			
☐	**Parallel Design**		☐	**Placebo-Controlled**			
☐	**Superiority**		☐	**Equivalence**	☐	**Non-inferiority**	
Device	☐	Pilot	☐	Pivotal	☐	Post-Approval	

Drug/Biologic	☐	Phase 1	☐	Phase 1/2	☐	Phase 2	☐	Phase 2/3	☐	Phase 3	☐	Phase 4

☐	**Dose escalation**	*If yes, details →*	
☐	**Dose ranging**	*If yes, details →*	
☐	**Sub-studies**	*If yes, details →*	

5.3. Other Design Details: This will be a 6-month randomized controlled trial. The study will start after the approval from UT Health San Antonio IRB department. All study visits will be performed in the UT Health School of Nursing.

6. Study Population:

6.1. Study Population(s) Label/Name	6.2. Identify the criteria for inclusion	6.3. Identify the criteria for exclusion
To add more populations – select a row, copy & paste	*The criteria that every potential participant must satisfy, to qualify for study entry.* All individuals in this study population must meet all of the inclusion criteria in order to be eligible to participate in the study	*The characteristics that make an individual ineligible for study participation.* All individuals in this study population meeting any of the exclusion criteria at baseline will be excluded from study participation.

Overweight/obese community-dwelling older adults with T2D	Community-dwelling Age 65 and older Men and women of all ethnic groups Self-reported of provider-diagnosed with T2D for at-least 6 months. Received basic diabetes self-management education Stable medication regimen and no medication changes are expected over the next 6 months. Overweight/obese (BMI ≥25 kg/m2 Able to read and write in English Own a smartphone At PI discretion, participant is willing/able to comply with the protocol requirements	Unsafe to walk using EASY criteria or clinical judgement of the PI. History of severe psychiatric disorders or cognitive impairment which interferes with active participation in the study Residence of long-term care facility History of substance abuse in the past year Unwilling to be randomized in a mHealth+ individual intervention group

6.4. Will screen failures be allowed to re-screen at a later date?	☒	**No**	☐	**Yes**	*If yes, describe criteria below ↓*

7. Study Intervention(s) being tested or evaluated

This can include prevention, diagnostic or therapeutic interventions (e.g., drug or device) or educational, health services or basic science interventions (e.g., educational program, health care delivery model, or examining basic physiology)

Behavioral lifestyle intervention: Participants (N=40) will be randomized to the mHealth+ group Intervention group (Group A; n=20)and mHealth+ individual intervention group (Group B; n=20) group using a block randomization table. (1) The mHealth+ group Intervention group (Group A) will receive a modified Look AHEAD behavior lifestyle intervention with smartphone-based self-monitoring of diet and physical activity. This comprises ten group sessions for lifestyle intervention in 6-months. The group will receive three weekly classes in the first month and then bi-weekly classes for month 2-3, and three monthly session in month four, five, and six. The frequency and layout of these classes will allow participants to master new skills gradually, then eventually wean off, and adopt the modified lifestyle as the part of their daily lives. (2) The mHealth+ individual intervention group (Group B) will receive an abbreviated behavior lifestyle intervention with smartphone-based self-monitoring of diet and physical activity in one face-to-face individual session at the beginning of the study. In addition, participants will receive self-study materials, from Look Ahead modules, and a monthly follow-up phone calls for the duration of the study (6-months). The goal for these follow up phone calls are to assess understanding of the modules, to promote continued engagement with the study material, and to provide clarification on materials as needed. Participants in the mHealth+ group Intervention group (Group A) and mHealth+ individual intervention group (Group B will receive instruction on how to download an app to help them record their diet and physical activity at the beginning of the study. (see updates to study protocol dated below)

Fitbit offers a simple, easy-to-use tool for tracking food and physical activity. It helps set daily calorie budget, and set and work towards goals for nutrient intake, weight loss, exercise, and more. https://www.fitbit.com/inspire

04.12.20: Due to COVID-19 and social distancing order, we are adding hemoglobin Hba1c home test for our eight participants who are finishing the study on April 20, 2020. We have called all 8 participants and informed them about Hba1c home testing kit that will be delivered to their house after the final and tenth virtual session on April 20, 2020. We have confirmed their home address over the phone to mail the kit. Participants have been informed that the PI will explain and run the test individually with all 8 participants. Our next study group will finish the study in 2nd week of June, 2020. We will continue to follow our study participants and provide monthly behavioral educational sessions

in the group intervention, virtually, until the social distancing order will be lifted. Our study is not enrolling any new participants at this time.

On April 20, 2020, eight participants will finish the study and we will collect focus group questions virtually. We will also collect their individual questionnaire virtually to collect end of study assessments. Once the social distancing order will lift, we will collect face to face blood test and frailty assessments.

10.20.20: we finished our participants (N=20) in the group intervention and due to COVID-19 restrictions we were not able to enroll our participants for the control group (Group B). We talked with IRB staff and study team and decided to stop enrolling participating for the control group (group B) as the risk was higher based on the inclusion criteria for our study participants than the benefits for the control participants. Modification due to Pandemic, forgoing control arm, and worked with the interventional participants still worked with the study data to meet study aim-the deviation related to COVID-19 did not impact subject rights, safety, welfare, or the overall integrity of the science of the study.

8. Protocol-Directed procedures, items, services or tests

List all procedures directed by the study plan - including items or services provided as part of routine or conventional care and those needed to diagnosis or treat research related complications.

Important Note – The protocol directed procedures listed must match those in the Schedule of Activities (attachment)

8.1. Drugs *(trade and generic, dosage, route of administration)*

N/A

8.2. Devices

N/A

8.3. Biologics

N/A

8.4. Laboratory Tests

Laboratory tests: Complete blood count, chemistry with liver function tests, lipid profile, HbA1c, and inflammatory markers (CRP, IL6) will be collected from all participants. Approximately 28 ml of blood will be collected at baseline and at end of study for clinical labs and quantifying proteins of interest. Approximately 16 ml of blood will be collected in a serum separating tube and will be used for clinical lab values (complete metabolic panel, lipids and A1c). The remaining 12 ml of blood will be collected in an EDTA tube and will be used to quantifying circulating cytokines.

04.12.20: Due to COVID-19 and social distancing order, we will be adding hemoglobin Hba1c home test for our eight participants who are finishing the study on April 20, 2020. We will continue to our virtual behavioral education session and will collect other end of study assessments virtually.

8.5. Imaging Procedures

N/A

8.6. Other Research Procedures *(e.g., other safety and efficacy assessments.)*

Frailty assessment: We will conduct the assessment at the baseline and then at the end of the study. Frailty is defined as the presence of ≥3/5 of characteristics 1) self-reported unintentional weight loss of ≥10 pounds in last year, 2) self-reported exhaustion, 3) low physical activity based on the Minnesota Leisure Time Physical Activity Questionnaire, 4) weak handgrip, 5) and slowness on a 10-foot walk at the usual pace. These measures have been standardized in SALSA study [7,21] and will be used in this study. Pre-frailty is defined as 1 or 2 of these characteristics and Non-frailty is defined as the presence of 0 characteristics. As a measure of lower extremity function, we will use the Short Physical Performance Battery (SPPB).[22] All participants regardless of frailty status are eligible for study inclusion.

History and Physical Assessment: We will document participants' medical history regarding his/her diagnosis of T2D, length time having T2D, and use of any glucose-lowering medications and/or insulin. Height, weight, waist circumference, and vital signs (blood pressure, heart rate, temperature, and respiration) will be measured.
Patient-Reported Outcomes Measurement Information System (PROMIS): PROMIS-Global Health (GH) and PROMIS-57 questionnaires, and a single-item Binge eating question will be completed by all participants at the baseline and end of study visit. In addition, all participant will complete focus group questionnaires at the end of study visit.
For this study, we will recruit 20 participants for group intervention. All participants will receive a baseline and end of study visit. Participants in the group intervention will receive 10 behavioral education sessions We will have 4-8 participants in each group intervention The focus group will be conducted at the end of study visit and procedures (session 10, visit 11) for the group intervention population. Participants will be informed in the consent and once again before the focus group that their responses will be audio-recorded. Participants will be informed that no personally identifiable information will be discussed or recorded as part of the focus groups, and that questions will be centered on improving the program and evaluating its successes and areas for improvement. Risks of the focus groups would include discomfort answering questions and/or discomfort from participating in a group setting and breach of confidentiality. Participants do not have to answer or discuss any questions that make them uncomfortable, and that confidentiality will be protected by maintaining the audio recordings in a secure, locked location.
The PI will conduct the focus group using the following questionnaires.
Focus Group Questions

As we are currently going through lifestyle changes due to the corona virus, tell me the impact of it on your day to day on self-monitoring of diet, physical activity, and diabetes management. (04.12.20)
What behavioral strategies have been most helpful to you in making the changes?
Behavioral strategies that have worked for you?
Behavioral strategies that have not work for you?
What are your plans for staying on track in the absence of these group sessions?
Since joining the program, what are the health-related benefits that you have experienced?
Since joining the program, what are the appearance-related benefits that you have experienced?
How would you say these benefits have influenced your quality of life?

8.7 Attach a Schedule of Activities (SOA) Excel File [Download the Template here: *Schedule of Activities]*	*Check to indicate that the SOA Excel File is attached →*	☒

9.	**Preparation/Handling/ Storage/Accountability of Investigational Drug, Biologic, or Device**
☒	*N/A - This study does not include any investigational products (e.g. drugs, devices or biologics)*
☒	*N/A - An Investigator Brochure is attached*
☒	*N/A - A Drug/Device Manual is attached*

9.1. Acquisition and accountability

State how the study intervention and control product will be provided to the investigator. Describe plans about how and by whom the study intervention will be distributed, including participation of a drug repository or pharmacy, and plans for disposal of expired or return of unused product.

N/A

9.2. Formulation, Appearance, Packaging, and Labeling

Describe the formulation, appearance, packaging, and labeling of the study intervention and control product, as supplied. Information in this section can usually be obtained from the IB or the package insert, or device labeling. This section should include the name of the manufacturer of the study intervention and control product.

N/A

9.3. Product Storage and Stability

Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and control product. For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).

N/A

9.4. Preparation

Describe the preparation of the study intervention and control product, including any preparation required by study staff and/or study participants. Include thawing, diluting, mixing, and reconstitution/preparation instructions in this section. For devices, include any relevant assembly or use instructions.

N/A

10. Study Intervention Additional Details

10.1. Measures to Minimize Bias: Randomization and Blinding

This section should contain a description of randomization and blinding procedures (if applicable to the study design). It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that blinding or randomization might be compromised. Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind. Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for serious adverse evets (SAEs)). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

The PI will not be blinded by the study mHealth+ group Intervention group and mHealth+ individual intervention group.
Participants (N=40) be randomized into two groups using a block randomization table to receive behavioral lifestyle educational intervention. Everyone will receive a baseline and end of study visits.

We divided our future participants into 4 groups (10 - (group A):10- (group A):10- (individual B):10 (individual B) and with the help of computer generated program, we will start our intervention group (Group A - n=20) first followed by our control group (Group B - n=20). (see updates dated below)

Participant in **mHealth + group intervention** (Group A) you will receive a total of 10 group sessions in 6-months. The group will receive 3 weekly classes in the first month and then bi-weekly classes for month 2-3, and three monthly session in month four, five, and six.

10.20.2020: we completed up to three face to face group intervention sessions (Group A) over WebEx due to COVID-19 restrictions.

10.20.20: we finished our participants (N=20) in the group intervention and due to COVID-19 restrictions we were not able to enroll our participants for the control group.

After discussing with IRB person and mentors, we decided to not to enroll participants for the Group B due to high-risk for COVID-19. We were able to receive enough information from the Group A intervention participants and to finish enrolling participants for the pilot study. Modification due to Pandemic, forgoing control arm, and worked with the interventional participants still worked with the study data to meet study aim-the deviation related to COVID-19 did not impact subject rights, safety, welfare, or the overall integrity of the science of the study.

10.2. Study Intervention Compliance

Define how adherence to the protocol (e.g., administration of study intervention, use of device,) will be assessed, and verified (if applicable, e.g., plasma assays, electronic monitoring devices, daily diaries).

The project is limited because we are enrolling only older adults from the community with T2D who carry a smartphone. In addition, given the significant commitment necessary to participate in the group sessions for the intervention group an attrition is an inherent potential issue. We will take several steps to minimize attrition including providing reimbursement and collecting multiple contact information (cell phone, home phone, email addresses) from the participants in order to remind them of the scheduled group sessions. We will also provide periodic updates to providers to remind them of the study and the importance of their support. The information gained from the pilot project will inform future interventions using mHealth tools toward community-dwelling older adults with T2D.

10.3. Permitted Concomitant Therapy

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints).

N/A

10.4. Rescue Medicine

List all medications, treatments, and/or procedures that may be provided during the study for "rescue therapy" and relevant instructions.

☒ *N/A, no rescue medicine*

11. Study Intervention Discontinuation

11.1. Discontinuation of Study Intervention

Describe the criteria for discontinuing the study intervention (e.g., halting rules), including any monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the study intervention (e.g., type and quantity of adverse events), clearly stating the length of time, if applicable, and describe the data to be collected at the time of study intervention discontinuation and approaches for restarting administration of or re-challenging with study intervention.

Participants will be allowed to discontinue from the study (mHealth+ group Intervention group) anytime.

11.2. Continued Follow-up Discontinuation of Study Intervention

Describe efforts that will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Reasonable efforts must be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AE), serious adverse events (SAE), and unanticipated problems involving risks to subjects or others (UPIRSOs).

Participants will be allowed to discontinue from the study (mHealth+ group Intervention group) anytime.

12. Statistical Considerations

12.1. Statistical Hypotheses

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

Behavioral lifestyle interventions using a smartphone for self-monitoring to improve frailty measurements, body weight, and glycemic control in overweight/obese older adults with T2D.

12.2. Sample Size Determination

Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants.

Because the POCL model is complex and this is a pilot study, it is not practical or feasible to do a power analysis for the given experimental design but based on the work of Drs. Espinoza and Wang, we believe at least 20 participants in the group (mHealth+ group Intervention group) are needed. The effect of the intervention on the change in frailty category and/or frailty scores will be used to calculate power and sample size estimation for a future, larger study.

12.3. Populations for Analyses

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each).

The impact of the intervention on frailty status (non-frail, pre-frail, frail) and frailty score (0, 1, 2, 3, 4, or 5) over the 6-month period (from baseline to follow-up) will be assessed by proportional odds cumulative logit (POCL) model to assess the log-odds of frailty as an indicator of being exposed to the intervention. The initial POCL model will adjust only for the baseline value of frailty status. A subsequent model will adjust for baseline age, sex, ethnic group, BMI, and Hba1c, to determine potential covariate interactions with the intervention. Continuous secondary outcomes including fasting glucose, Hba1c, and BMI will be assessed using linear regression with intervention, baseline frailty, sex, and ethnic group as categorical predictor variables and baseline age, BMI, and Hba1c as continuous predictor variables. The categorical outcomes SPPB and PROMIS scores will also be evaluated using the POCL model.

12.4. Statistical Analyses

Include analysis of primary efficacy endpoints, secondary endpoints, safety analyses, and any planned interim analyses

The impact of the intervention on frailty status (non-frail, pre-frail, frail) and frailty score (0, 1, 2, 3, 4, or 5) over the 6-month period (from baseline to follow-up) will be assessed by proportional odds cumulative logit (POCL) model to assess the log-odds of frailty as an indicator of being exposed to the intervention. The initial POCL model will adjust only for the baseline value of frailty status. A subsequent model will adjust for baseline age, sex, ethnic group, BMI, and Hba1c, to determine potential covariate interactions with the intervention. Continuous secondary outcomes including fasting glucose, Hba1c, and BMI will be assessed using linear regression with intervention, baseline frailty, sex, and ethnic group as categorical predictor variables and baseline age, BMI, and Hba1c as continuous predictor variables. The categorical outcomes SPPB and PROMIS scores will also be evaluated using the POCL model. Because the POCL model is complex and this is a pilot study, it is not practical or feasible to do a power analysis for the given experimental design but based on the work of Drs. Espinoza and Wang, we believe at least 20 participants in the group (mHealth+ group Intervention group) are needed. The effect of the intervention on the change in frailty category and/or frailty scores will be used to calculate power and sample size estimation for a future, larger study.