Effectiveness and Cost-Effectiveness of Fully-Automated Digital vs. Human Coach-Based Diabetes Prevention Programs

Protocol Number: IRB00265873

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Principal Investigator: Nestoras Mathioudakis, MD MHS

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STATEMENT OF COMPLIANCE

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

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- ICH E6

All key personnel (all individuals responsible for the design, management and conduct of this trial) have completed Human Subjects Protection Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, 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 participants who provided consent, using a previously approved consent form.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principle Investigator:

Nestoras Mathioudakis, MD MHS

Signed: _____ Date 04-05-2021

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Effectiveness and Cost-Effectiveness of Fully-Automated Digital vs. Human Coach Based Diabetes Prevention Programs

Study Description: This study will be a Phase 3, parallel group, open-label, 12 month multicenter non-inferiority trial to compare the effectiveness of the Sweetch fully-automated digital diabetes prevention program (dDPP) to a standard of care control group consisting of a human coach-based diabetes prevention program (hDPP) delivered via in-person or via distance learning modalities. A total of 368 participants will be randomized in a 1:1 ratio (N=184 per arm) to receive the Sweetch digital health kit (dDPP) or referral to a CDC recognized lifestyle change program (hDPP). The primary endpoint will be assessed at 12 months and secondary endpoints at 6 and 12 months.

Objectives:

Primary Objective:

To determine whether a fully-automated digital diabetes prevention program (dDPP) is at least as effective as human coach-based diabetes prevention programs (hDPP) in meeting the CDC benchmark for type 2 diabetes risk reduction.

Secondary Objectives:

To evaluate the cost-effectiveness of dDPP and hDPPs.

To compare the engagement and rates of program completion of dDPP vs. hDPPs and evaluate whether between-group differences in clinical outcomes are mediated by engagement.

To compare the acceptability and usability of a dDPP vs. hDPPs.

To explore the features of a smartphone-based dDPP program that are associated with attainment of type 2 diabetes risk reduction outcomes.

To explore predictors of success with dDPP and hDPPs.

To evaluate the feasibility of attaining the CDC's National Diabetes Prevention Recognition Program benchmark of 60% of program completers achieving the type 2 diabetes risk reduction outcome.

To validate self-reported physical activity (PA) outcomes among participants in DPP using Actigraphy as a gold standard.

Endpoints:

Primary Endpoint:

Achievement of CDC's benchmark for type 2 diabetes risk reduction, defined as *any* of the following:

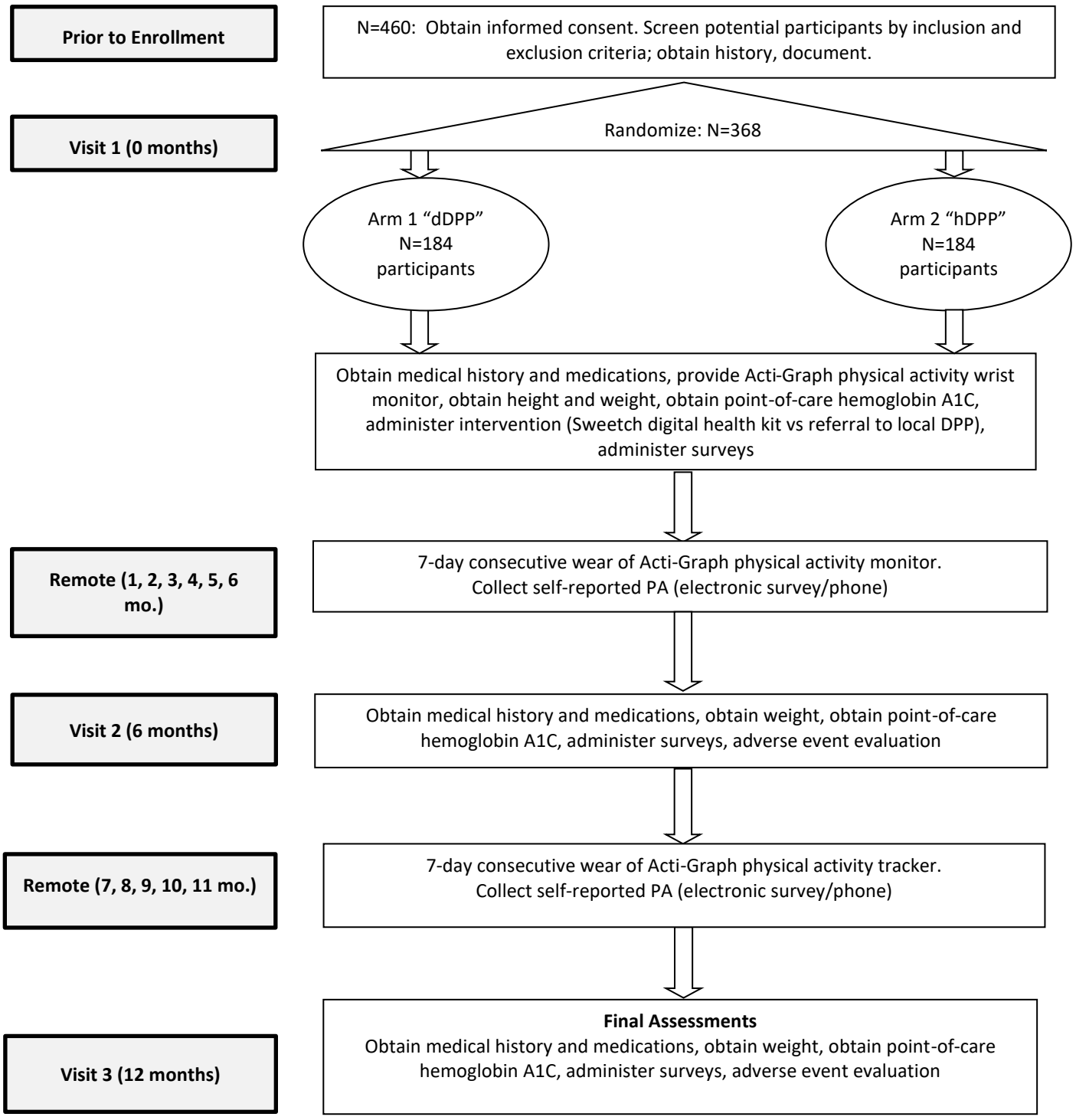
- At least 5% weight loss at 12 months
- At least 4% weight loss at 12 months and at least 150 minutes/week on average of PA (objectively measured using serial Actigraphy at one month intervals during months 1-11)
- At least 0.2% reduction in A1C at 12 months (for participants with baseline A1C of 5.7% to 6.4%)

Secondary Endpoints:

- Change in A1C from baseline to 6 months and 12 months
- Absolute and percentage weight change from baseline to 6 and 12 months
- Change in physical activity measures (average minutes/week of physical activity, MET-hours per week of physical activity, average number of steps per day) from baseline to 6 months and 12 months
- Individual endpoints of the composite primary endpoint assessed at 12 months
- Engagement and program completion rate
- Acceptability of digital and in-person DPPs
- Cost-effectiveness

Study Population:	Adults age 18-75 years with prediabetes (laboratory evidence of prediabetes on basis of fasting glucose, A1C and oral glucose tolerance test) with body mass index of $\geq$25 kg/m^2 (or $\geq$23 kg/m^2 for Asians), with proficiency reading English, and who use a smartphone (Android OS 9.0 or newer or iOS 13.3 or newer) enrolled from areas surrounding Baltimore, Maryland and Reading, Pennsylvania
Phase:	3
Description of Sites/Facilities Enrolling Participants:	2 enrolling sites: Johns Hopkins Health System, Baltimore, Maryland Reading Health System, Tower Health, Reading, Pennsylvania
Description of Study Intervention:	**Intervention Arm:** Participants randomized to the dDPP arm will receive the Sweetch digital health kit (Sweetch Health, Ltd.) consisting of a smartphone app and Bluetooth-enabled digital scale. The Sweetch dDPP uses self-tracking and multiple evidence-based persuasive eCoaching strategies to deliver just-in-time and/or adaptive support to promote evidence-based lifestyle changes for diabetes prevention. **Control Arm:** Participants randomized to the hDPP arm will be referred to a CDC recognized (preliminary or full recognition status) lifestyle change program located within 25 miles of one of the two enrolling sites.
Study Duration:	48 months
Participant Duration:	12 months for each individual subject to complete all visits

1.2 SCHEMA


Prior to Enrollment
N=460: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Visit 1 (0 months)
Randomize: N=368
Arm 1 "dDPP" N=184 participants
Arm 2 "hDPP" N=184 participants
Obtain medical history and medications, provide Acti-Graph physical activity wrist monitor, obtain height and weight, obtain point-of-care hemoglobin A1C, administer intervention (Sweetch digital health kit vs referral to local DPP), administer surveys
Remote (1, 2, 3, 4, 5, 6 mo.)
7-day consecutive wear of Acti-Graph physical activity monitor.
Collect self-reported PA (electronic survey/phone)
Visit 2 (6 months)
Obtain medical history and medications, obtain weight, obtain point-of-care hemoglobin A1C, administer surveys, adverse event evaluation
Remote (7, 8, 9, 10, 11 mo.)
7-day consecutive wear of Acti-Graph physical activity tracker.
Collect self-reported PA (electronic survey/phone)
Visit 3 (12 months)
Final Assessments
Obtain medical history and medications, obtain weight, obtain point-of-care hemoglobin A1C, administer surveys, adverse event evaluation

1.3 SCHEDULE OF ACTIVITIES (SOA)

		En.	Days from Enrollment													
Study Procedures	**-14 to 0**	**0**	**7**	**9**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**345**	**365**
Study Window (days)			+4	-1 to +5	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14
Baseline Study Visit*		x														
Follow-up Study Visits*										x						x
Consent		x														
Eligibility		x														
Review inclusion/exclusion criteria		x														
PAR-Q Screen (11.1)		x														
Medical Clearance Letter (11.2) if positive PAR-Q screen		x														
Survey Response Collection Method (text, email, in-person)		x														
Reminder phone call, text message, or email prior to visit										x						x
Physical Activity Measurement																
Actigraph device and instructions provided		x														
ActiGraph wear (consecutive 7-day periods with remote CentrePoint Sync app upload)		x			x	x	x	x	x	x	x	x	x	x	x	
*Reminder email/phone call/text message (Actigraph instructions)***					x	x	x	x	x	x	x	x	x	x	x	
Collect Actigraph device and charger from participant																x
Anthropomorphometric Measurements																
Height		x														
Weight		x								x						x
Laboratory Measurement																
Screening hemoglobin A1C (point-of-care sample)to -1	x									x						x
Repeat A1C (serum or alternative POC A1C device) if suspected erroneous A1CNow+ reading	x									x						x
Randomization																
Referral to hDPP		x														
Mail Sweetch digital health kit (research coordinator)			x													

		En.	Days from Enrollment													
Study Procedures	**-14 to 0**	**0**	**7**	**9**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**345**	**365**
Study Window (days)			+4	-1 to +5	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14
Download/register Sweetch app + sync scale (participant)				x												
Questionnaires/Surveys *(text, email, in-person)*																
Demographics (11.3)		x														
Medical history and medications (11.4)		x								x						x
Exercise stage of change questionnaire (11.5)		x								x						
*Self-reported PA information (11.6)***		x			x	x	x	x	x	x	x	x	x	x	x	
"Starting the Conversation" Brief Dietary Assessment *(11.7)*		x								x						x
Apps and Devices (11.8)		x														
NPART Survey (11.9)		x														
Acceptability (11.10)										x						x
Sweetch App Features (dDPP only) (11.11)										x						x
WHO-5 Well-Being Index (11.12)		x								x						x
Healthcare Utilization (11.14)		x								x						x
Monitoring of hDPP attendance and outcomes data entry (11.13)***										x						x
Local DPP reimbursement (window is ±60 days)										x						x
Adverse Event Evaluation (11.19)										x						x
Participant reimbursement		x								x						x
$40 for study visit (mailed after home visits; provided during on-site visits)		x								x						x
$60 or $70 for total Actigraph wear in months 1-6 ($10 per each wear period)										x						
$50 or $60 for total Actigraph wear in months 7-12 ($10 per each wear period)																x
Study End letter mailed to participant and primary care provider																x
Study End letter mailed/emailed to local DPP (hDPP arm)																x

En= enrollment;
* For JHU site, study visits conducted at home or at clinical research unit per participant preference; for Reading site, all study visits conducted at clinical research unit.
**Reminder 2 days prior to scheduled event and on day of event (or first business prior on or prior to event).

		En.	Days from Enrollment													
Study Procedures	**-14 to 0**	**0**	**7**	**9**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**345**	**365**
Study Window (days)			+4	-1 to +5	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14
*** Data from local DPPs will be entered into a RedCap database by the local DPP team. The research coordinator will validate the data entry and communicate with the local DPP as needed to correct any data entry errors or collect missing information.																

2 INTRODUCTION

2.1 STUDY RATIONALE

Millions of U.S. adults living with prediabetes, a high-risk state for future type 2 diabetes, do not receive appropriate lifestyle counseling to lower their risk of type 2 diabetes. Mobile health (mHealth) technologies represent a potential scalable solution to address this far-reaching problem. The objective of this study is to compare the real-world effectiveness of a digital diabetes prevention program (dDPP) to standard of care human coach-based diabetes prevention programs (hDPPs). This study will test a novel, fully-automated digital health platform (Sweetch Health, Ltd.) that uses artificial intelligence technology to provide just-in-time and adaptive lifestyle change coaching for prediabetic adults. Preliminary evidence from feasibility or observational studies suggests that just-in-time adaptive interventions (JITAIs), which are often delivered via smartphone apps by virtue of their ability to provide continuous self-monitoring and feedback, can be effective. However, it is currently not known whether dDPPs that deliver a JITAI are as effective as hDPPs in improving health outcomes in patients with prediabetes, a susceptible patient population that is positioned to benefit from such an intervention.

The overarching goal of this study, therefore, is to compare the effectiveness of the Sweetch digital diabetes prevention program (dDPP) to real-world human coach-based diabetes prevention programs (hDPPs) for promoting weight loss, increasing physical activity, and reducing hemoglobin A1C in prediabetic adults. The proposed study addresses an evidence gap in the science of chronic disease prevention and health behavior change and is supported by promising short-term results from a previous pilot trial conducted by our team. This study will advance chronic disease prevention and behavioral science research by elucidating the extent to which fully-automated digital interventions using artificial intelligence technology can deliver effective, scalable, sustainable, and cost-effective health-promoting behavioral change interventions in high-risk populations. The implications of this fully-automated approach for scalability in diabetes prevention are profound.

2.2 BACKGROUND

Prediabetes affects more than one-third of US adults.[1] It is projected that more than 470 million people worldwide will carry a diagnosis of prediabetes by 2030.[2] Considering that the microvascular and macrovascular complications associated with type 2 diabetes begin at the prediabetes stage[3-8] and that more than half of individuals with prediabetes will eventually develop diabetes[2], **efforts are urgently needed to intervene early on this large high-risk population.** Prediabetes has been linked to an approximately 20% increased risk of cardiovascular disease[9], with cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) showing surprisingly similar rates of myocardial infarction and stroke among people with prediabetes and overt diabetes.[8] Prediabetes has also been linked to a 15% increased risk of developing cancer and a 14% higher cancer mortality rate.[10] Studies have also found negative neurological sequelae in prediabetic patients, including slower processing speed, dementia, stroke, and depression.[11-13]

A recent systematic review and meta-analysis of 53 U.S. based studies found that **lifestyle programs modeled on the DPP are effective** across diverse settings and populations.[14] Real-world diet and exercise programs have been shown to reduce the incidence of diabetes by 41% and body weight by 2.2%.[15] These translational DPPs are recognized by the CDC, which maintains a national registry of DPPs[16]; however, there are only 1,530 recognized programs in the US, or 1 program per ~55,000 affected US adults with prediabetes,[1] which makes it highly unlikely that all patients who need these services can access them. The **rural/urban DPP access divide** is large, with 14.6% and 48.4% of rural and urban counties, respectively, having access to a national DPP site.[17,18]

Considering this **access barrier**, it is not surprising that only a miniscule proportion of the eligible population is ever referred to a DPP. A recent study found that only 4.2% of eligible Medicare beneficiaries with prediabetes report having ever been referred to a DPP, and only 2.4% report ever participating.[19] **Low referral rates** by healthcare professionals may be partly explained by their concerns about limited patient access to DPPs."[20-22] Insufficient reimbursement rates by Medicare to cover the costs of the DPP has created a **health disparity** for low income populations.[17,23]

Even among patients who are referred to DPPs, the unfortunate reality is that only about 35% actually attend the program.[20] Several factors have been postulated to explain the **low rates of engagement** in DPPs, including low insurance reimbursement[24] and patient competing priorities.[20] Patients face several barriers in participating in hDPPs: travel distance, inconvenient hours,

costs, competing work/family demands, and lack of motivation. These obstacles are concerning because **engagement is an important mediator of success** in hDPPs: the magnitude of weight loss and PA correlate with the number and frequency of overall sessions attended and duration in the program.[25-28] It appears that the main factors related to attrition are participants' perceptions of how likely they are to actually get diabetes, the effectiveness of behavioral change techniques, and program incentives. [25]

To improve patient access to diabetes prevention services, the format of the national DPP has evolved from individual human coach-based coaching to group sessions, and more recently to online (computer, tablet, smartphone) and distance learning (video conference) formats. Digital DPPs offer participants flexibility to complete lessons on their own schedule and have the ability to integrate with other technology (apps, devices, digital scales) for PA tracking and weight monitoring, which may encourage program engagement and adherence. Smartphone use is ubiquitous with 77% ownership in the US in 2018.[29] Despite the enormous potential of dDPPs, very few studies have evaluated their effectiveness on glycemic outcomes or diabetes incidence. Although there have been several RCTs using mHealth-based interventions for weight loss in overweight/obese[30-32] or physically inactive[33,34] populations, there have only been four RCTs of mHealth interventions conducted specifically in people with prediabetes.[35-38] Two RCTs evaluated static text message interventions: one found a 9% lower incidence of diabetes at 24 months[35] and the other a non-significant reduction in A1C 12 months.[39] Another RCT of a hybrid smartphone app and human coach-based DPP found no significant change in glycemic measures at 6 months.[36] Block et al. evaluated a fully digital DPP in an RCT using a delayed entry control design.[38] This digital intervention, which consisted of a web based program and mobile app with tailored goal setting, virtual phone coaching with interactive voice response, and electronic DPP curriculum, demonstrated 6-month changes in A1C of -0.26 and -0.18.[38] Notably, however, the comparator group was no intervention in that study. Observational studies of two hybrid digital/human coach-based DPPs found significant A1C reductions at 12 months (-0.14[40] and -0.4[41]). Taken together, these studies show that dDPPs are effective; however, a **direct comparison to hDPPs has never been formally investigated** to determine the relative effectiveness on clinical outcomes or participant engagement with the different modalities.

Unlike the other commercially available "second generation" digital DPPs (Omada[42], Noom[43], Livongo[44], Lark[45], Alive-PD/TurnAround Health[46]), which all offer both digital and human coach-based coaching, the Sweetch dDPP[47] could be considered a "third generation" DPP that is fully automated and, though highly personalized, requires no human coaches. Sweetch's AI algorithm uses reinforcement learning[48,49] to deliver a **just-in-time adaptive intervention (JITAI),** which has two fundamental components: 1) "just-in-time support" and 2) adaptation.

The term **"just-in-time"** refers to the provision of the right type or amount of support at the right time (i.e. during states of vulnerability or opportunity), and is rooted in several behavioral change and cognitive theories.[50] This approach is motivated by the idea that timing plays a critical role in one's ability to benefit from behavioral change support. Delivering support during various states of opportunity throughout the day can help reduce long-term goals into "short-term, specific, and achievable subgoals,"[50] and may provide teachable moments. In this way, 24/7 virtual support may offer an advantage over human coach-based coaching where changes in states of opportunity cannot be identified in real time.

Adaptation refers to the continuous modification of the "type, amount, and timing of support" based on the use of dynamic information collected about the user (i.e. response to previous recommendations).[50] For example, if notifications that are delivered at a specific time of day consistently fail to promote user action, then the system would adapt and attempt alternative times of day. Similarly, specific content of recommendations can be adjusted based on participant response, which helps to sustain engagement. By evaluating a fully automated dDPP, we hope to demonstrate that meaningful reductions in A1C, increases in PA, and weight loss (**Aim 1**) can be achieved without the need for personnel by using AI technology to replace human coaching with highly engaging and continuous virtual support.

Unlike other dDPPs that provide generic recommendations, static reminders, and pre-defined rigid goals at times when the user may not be able to respond (e.g. while driving), the Sweetch AI algorithm seamlessly collects data from the smartphone to characterize the user's behavior and context to generate personalized and timely notifications. Specifically, the platform considers the user's accelerometer data (to set PA goals), calendar (to know current availability), GPS (to know current location), current weather, weight data from the digital scale (to set weight goals), and past user response when recommending PA or sending a weigh-in reminder to maximize the probability that the participant can act on the recommendation at that time and place. For example, instead of offering a generic and non-engaging recommendation like "*It is recommended for you to walk 10,000 steps toda*y," Sweetch's recommendation would be: "*Good morning, Fred, you have 45 minutes before your next meeting. It's raining outside so take an umbrella and pick up a cappuccino from Gregory's Coffee, 327 Park Ave S. It's only 7 minutes away! You'll feel*

more vivid and achieve your 19 min activity goal." Sweetch continuously optimizes the user's goals and messages so they will be in the context, time, place, and tone-of-voice that will increase the probability of action by the individual.

Unlike hDPPs that provide general recommendations on a weekly basis, Sweetch's support is provided continuously and is adapted based on the user's response; therefore, this dDPP coaching may in fact prove to be superior to the human coaches in the hDPPs who give advice globally and not when the person can actually take action. We hypothesize that this approach will result in greater engagement with and acceptability of the dDPP.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The study poses minimal risk to subjects. Fingerstick A1C measurements may result in mild transient discomfort for participants. Although the study intervention aims to increase PA, the emphasis is on increase in light-to-moderate PA (i.e. walking) rather than strenuous exercise. Thus, exercise-related adverse events, such as cardiovascular events, would be considered unexpected or unanticipated in this study. Despite this theoretical concern, there is very little evidence that low to moderate intensity physical activity increases the risk of death or non-life-threatening adverse events. In fact, a large body of evidence supports beneficial effects of increasing doses of exercise over time on morbidity and mortality, particularly in at-risk groups such as pre-diabetic patients.

2.3.2 KNOWN POTENTIAL BENEFITS

The intervention has the potential to improve glycemic control, reduce weight, and increase adherence to recommended physical activity guidelines. Clinical studies have shown that these outcomes may delay or prevent the onset of type 2 diabetes in adults with prediabetes.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The minimal risks of this study are outweighed by the potential benefit to individual participants (given known health benefits of PA and maintenance of normal weight) and the importance of the knowledge to be gained from the results of this study, which could inform future interventions to help the very large number of patients living with prediabetes.

Any subject who reports shortness of breath or chest pain during periods of PA will be required to undergo additional medical clearance before continuing in the study. Furthermore, all participants will be screened with the "Physical Activity Readiness Questionnaire (PAR-Q)" (Section 11.1) at baseline visit and positive screening test will require a clearance letter from the participant's primary care physician. The study may pose minimal psychological risks (frustration, disappointment, etc.) or financial risks (travel expenses, etc.). Financial risks are mitigated by study compensation for all study procedures and participant reimbursement at study visits. Participants are free to withdraw from the trial at any time.

3 OBJECTIVES AND ENDPOINTS

3.1 OBJECTIVES

3.1.1 COMPARATIVE EFFECTIVENESS

The overall objective of this trial will be to compare the effectiveness of a fully automated digital diabetes prevention program (dDPP) to standard of care human coach-based diabetes prevention programs (hDPPs) in reducing the risk of type 2 diabetes in adults with prediabetes. A total of 368 prediabetic, overweight/obese adults ages 18-75 years will be randomly assigned 1:1 to receive the Sweetch digital health kit consisting of a smartphone app and digital scale (dDPP) or standard of care consisting of referral to a local CDC certified Lifestyle Change Program (hDPP) delivered via in-person or distance learning modality. We hypothesize that the dDPP will be at least as effective as the hDPP in attainment of the CDC's benchmark for type 2 diabetes risk reduction.

3.1.2 ENGAGEMENT AND PROGRAM COMPLETION

Secondary objectives of the trial will be a) to compare engagement with digital vs. human coach-based DPPs and evaluate whether between-group differences in clinical outcomes are mediated by engagement and b) to compare acceptability of digital vs. human coach-based DPPs. We will define an engagement score (out of 100%) for the hDPP based on the percentage of total number of sessions attended, using the most current CDC engagement definitions at the time of completion of the study. Percentage engagement will be defined out of a total of 8 sessions in month 1-6 and 3 sessions in month 7-12, for a total of 11 sessions across months 1-12. We will define an engagement score (out of 100%) for the dDPPs based on percentage of full weeks during which the app is installed and a) both push notifications and motion sensors are enabled or b) the participant accesses any component within the app for months 1-6 and months 7-12. We hypothesize that participant's level of engagement, regardless of treatment assignment, will be associated with the primary endpoint (attainment of CDC benchmark for diabetes risk reduction). We hypothesize that dDPPs will be considered more acceptable by participants owing to greater convenience, more timely support, and the provision of more effective tools for weight, diet, and activity monitoring.

3.1.3 ACCEPTABILITY AND USABILITY

This trial will also explore the features of a smartphone-based dDPP program that are associated with attainment of the primary endpoint in the dDDP arm. The Sweetch dDPP uses a variety of behavioral motivational tools to encourage engagement. We will collect objective (app log data) and subjective (participant questionnaire responses) data to identify the digital health kit components that are most strongly associated with favorable clinical outcomes and/or are perceived to be most useful to participants in promoting engagement (Section 11.11). We hypothesize that the push notifications, digital scale, weight and PA trackers will be perceived to be the most useful features of the digital DPP.

The study will also compare the acceptability of the two interventions with respect to perceived degree of engagement, usefulness, functionality/ease of use, aesthetics, information, and satisfaction (Section 11.10).

3.1.4 PREDICTORS OF SUCCESS

This intervention will randomize participants to two fundamentally different approaches for promotion of lifestyle change (fully-automated humanless intervention vs. human coach-based intervention) in adults with prediabetes. As different individuals may respond more favorably to one or the other type of intervention, an objective of this study will be to explore participant characteristics that are associated with successful attainment of the primary endpoint. We hypothesize that younger adults with higher digital skills would respond better to the dDPP, while older adults or those with lower digital skills would respond better to the hDPP given the greater social interaction and lower reliance on technology.

The NPART survey (Evaluation of Non-Participation in Digital Health Research) is a validated instrument that was originally designed to characterize non-participation in digital health research.[51] The survey covers five thematic areas: socioeconomic factors, self-rated health and subjective overall quality of life, social participation, time resources, and digital skills and use of technology. We will use this measure (Section 11.9) as a surrogate marker of need for social interaction (which might be associated with favorable response to the hDPP given human interaction with both lifestyle coach and other participants) and digital skills and technology use (which might be associated with favorable response to the dDPP). We will perform a subgroup analysis among participants in both groups who meet the primary endpoint to evaluate the association between baseline characteristics and NPART scores. Similarly, a subgroup analysis will be done among participants who do not meet the primary endpoint or who fail to engage with either program to identify characteristics associated with low likelihood of success with either intervention. Should this trial demonstrate non-inferiority of the intervention, a screening tool such as the NPART could be used to identifiy the optimal modality of the DPP for a given patient.

3.1.5 FEASIBILITY OF ATTAINING CDC BENCHMARK

The 2021 CDC National Diabetes Prevention Recognition Program benchmark for type 2 diabetes risk reduction, from which the primary endpoint is derived, has not been evaluated in a prospective trial. The CDC has set a benchmark of 60% of program completers meeting the primary endpoint. Few trials have evaluated the effect of the DPP on A1C reduction, which is a new outcome

in the composite primary endpoint. Therefore, a secondary objective of this trial will be to evaluate the feasibility of attaining the 60% benchmark for DPP program completers.

3.1.6 VALIDATION OF SELF-REPORTED PHYSICAL ACTIVITY DATA

The primary endpoint includes a PA measure of 150 minutes of PA per week. The CDC accepts self-reported PA data from local DPPs in benchmarking programs for full recognition. Studies have shown that self-reported PA data may be significantly over-estimated when compared to objectively measured PA data. A secondary objective of this trial will be to evaluate the correlation between self-reported PA data collected using different methods:

- Data collected and reported by hDPPs
- Self-reported PA data collected by study team obtained at 1 month intervals
- Objectively measured PA data (Actigraphy) obtained at 1 month intervals

3.1.7 COST-EFFECTIVENESS

This study seeks to evaluate the cost-effectiveness of a fully-automated intervention for diabetes prevention that does not require any human support outside of the maintenance and support of the app itself compared to a standard of care control group consisting of a human coach-based diabetes prevention program (hDPP) delivered via in-person or via distance learning modalities.

3.2 PRIMARY ENDPOINT

The trial is designed as a non-inferiority trial to evaluate whether the Sweetch dDPP is at least as effective as hDPPs on participant attainment of the CDC's benchmark for type 2 diabetes risk reduction, defined as one or more of the following:

- At least 5% weight loss by 12 months
- At least 4% weight loss at 12 months and at least 150 minutes/week of physical activity measured using monthly serial Actigraphy and averaged over months 1-11)
- At least a 0.2% reduction in hemoglobin A1C by 12 months (for participants whose A1C result obtained at baseline study visit is between 5.7% and 6.4%).

Thus, the prospectively defined primary endpoint will be a binary endpoint at 12 months, defined as 1 if at least one of the CDC "success" outcome measures is achieved and 0 if none are achieved. The primary endpoint was selected to align with the current CDC standards for full recognition of DPP programs (effective May, 2021). According to the CDC, participants may demonstrate type 2 diabetes risk reduction by fulfilling one or more of the above outcomes, and, given the broad range of eligibility criteria for the DPP (see Section 5.1), not all DPP participants are eligible to demonstrate success using each of three outcomes in our composite endpoint. Specifically, the A1C change measure can only be used for participants whose baseline measure is in the prediabetic range of 5.7% to 6.4%. These standards require that at least 60% of participants in a given DPP meet the endpoint for attainment of full recognition in order to become a Medicare DPP supplier. The CDC's Standards and Operating Procedures are subject to change during the course of the study. Should the benchmarks for type 2 diabetes risk reduction change prior to completion of the trial, to the extent possible (i.e. assuming we have collected required data during the trial), we will also analyze our outcomes to align with the updated benchmark.

3.3 SECONDARY ENDPOINTS

Secondary endpoints will include:

- Primary endpoint assessed using self-reported PA data in lieu of objectively measured PA data (Actigraphy).
    - In this trial, PA will be assessed using both participant self-reported data and Actigraphy. While the CDC relies on participant self-reported PA data for outcome assessment, in this trial, there is a potential bias introduced from using self-reported PA data alone since the dDPP arm will have access to objective PA data while the hDPP group may or may not (depending on their personal use of wearable devices or fitness tracking apps). Studies have shown over-estimation of PA by self-report.[52-54] Considering that the CDC accepts self-reported PA data, we

will also analyze results of the primary endpoint using self-reported PA data collected at same interval as serial Actigraphy.

- Change in A1C from baseline to 6 months and 12 months
- Absolute and percentage weight change from baseline to 6 and 12 months
- Changes in physical activity measures (average minutes/week of physical activity, MET-hours per week of physical activity, average number of steps per day) at 6 months and 12 months
- Incident type 2 diabetes (A1C $\geq$6.5%)
- Engagement level
    - The **dDPP engagement score** will be calculated as the percentage of full weeks during which the app was installed and a) both push notifications and motion sensors were enabled OR b) participant accessed any content within the app.
    - The **hDPP engagement score** will be calculated as a percentage of sessions attended. Per CDC definitions of engagement, the number of required hDPP sessions for months 1-6, 7-12, and 1-12 will be 8, 3, and 11, respectively. For participants who attend more than the required number of sessions across each of these intervals, the engagement score will be capped at 100%. A participant who attends 4 out of 8 sessions in months 1-6 and 1 out of 3 sessions in months 7-12 would receive an engagement score of 50% (4 out of 8 sessions in months 1-6), 33% (1 out 3 sessions in months 7-12), and 45% (5 out of 11 sessions in months 1-12).
    - Engagement will be analyzed across months 1-6, 7-12, and 1-12 months. For both arms, full weeks will be defined as the number of complete weeks between baseline visit and the 6 month or 12 month visit, respectively. For example, a participant who is followed for 25.4 weeks during months 1-6 and 26.2 weeks during months 7-12 would be considered to have 25 and 26 full weeks on study, respectively.
- Percentage of **program completers**
    - The CDC defines **completers** for the hDPP to be participants who attend at least 8 sessions in months 1-6 and whose time from first session held by the cohort to the last session attended by the participant is at least 9 months. For participants in the hDPP arm, we will evaluate the percentage of completers in the program according to the CDC's definition. Similarly, for the dDPP arm, completers will be defined as participants who meet the engagement definition for at least 8 weeks in months 1-6 AND whose time between app installation and last week of engagement is at least 9 months.
- Acceptability of digital and in-person DPPs
- Correlation of self-reported and objectively measured PA data
- Change in overall well-being scores
- Cost-effectiveness

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study will be a Phase 3, parallel group, 12-month non-inferiority RCT to evaluate whether the Sweetch digital diabetes prevention program (dDPP) is at least as effective as a standard of care control group. The control group participants will receive a referral to a local lifestyle change program with preliminary or full recognition status by the CDC for delivery of an in-person or distance learning (e.g. videoconference) based diabetes prevention program (hDPP).

We use the term effectiveness rather than efficacy as we wish to evaluate the real-world effect of both interventions without aggressive interference on the part of the study team. The primary endpoints across all the study aims will be assessed at 12 months, with secondary endpoints assessed at 6 and 12 months to evaluate the sustainability of the intervention.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

While there are previous RCTs evaluating DPPs in comparison to hDPPs, to our knowledge, there are no previous randomized controlled trials comparing a *fully automated* dDPP to hDPP. The landmark DPP study established that lifestyle modification is an effective strategy for preventing diabetes and the CDC's national DPP recognizes local DPP programs that are modeled after the DPP and have proven outcomes. Thus, in this study, the control arm will be referral to a local CDC-recognized hDPP. It would be

unethical to use a placebo arm in this trial since it is established that DPPs are effective at preventing diabetes. While there is rationale for selection of the individual endpoint measures used by the CDC in defining their DPRP standards, the CDC's rationale for selecting a target of 60% of completers meeting the endpoint is not clear. Therefore, in addition to comparing the effectiveness of the dDPP vs. hDPP in attaining the CDC standard success outcomes, a secondary objective of the study will be to assess the feasibility of attaining the 60% target defined by the CDC as a requirement for DPP full recognition.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female age 18-75 years
4. Laboratory evidence of prediabetes, defined as *any* of the following lab results, in the *past year**:
    a. Hemoglobin A1C 5.7% to 6.4%
    b. Fasting glucose 100-125 mg/dl
    c. Plasma glucose of 140-199 mg/dl measured 2 hours after a 75 gm glucose load
5. Body mass index (BMI) ≥25 kg/m^2 (or≥23 kg/m^2 for Asians)
6. Proficiency reading English
7. Smartphone user (Android OS 9.0 or iOS 13.3 or newer)
8. Plans to reside in recruitment area for the next 12 months (participant's zip code of residence is within ~45 miles of the study recruitment site)

*For each of these lab tests, the *most recent* clinically available result for each distinct lab test in the past year will be considered when ascertaining eligibility. These criteria are consistent with participant eligibility criteria for the DPP as defined by the CDC (May 2021 Standards and Operating Procedures).

5.2 EXCLUSION CRITERIA

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

1. Medical conditions that prevent adoption of moderate physical activity (per primary care clinician)*
2. Aortic stenosis
3. Unstable cardiac disease (myocardial infarction, heart failure, or stroke in previous 6 months, currently participating in cardiac rehabilitation).
4. Has a pacemaker, implantable cardioverter-defibrillator (ICD), or other implanted electronic device.
5. Use of any glucose-lowering medications, weight loss medications or any systemic glucocorticoids within the previous 3 months (section 6.5)
6. Active malignancy of any type or diagnosed with or treated for cancer within the past 2 years. Individuals with basal and squamous cell carcinoma of the skin that has been successfully treated will be allowed to participate.
7. Diagnosis of diabetes mellitus
8. Pregnancy or planned pregnancy in the next 12 months
9. Anemia
10. Receiving treatment for iron-deficiency anemia, vitamin B12 deficiency, or folate deficiency
11. Hemoglobinopathy (HbS or HbC disease).**
12. Blood transfusion in previous 4 months
13. On dialysis or active organ transplant list

14. Treated with erythropoietin
15. Major psychiatric disorder (schizophrenia) or use of antipsychotic medications within the past 1 year
16. Dementia or Alzheimer's disease
17. Diagnosed with an eating disorder (anorexia nervosa, avoidant/restrictive food intake disorder, binge eating disorder, bulimia nervosa, Pica, rumination disorder, other specified or unspecified feeding or eating disorder)
18. Diagnosed or self-reported alcohol or substance abuse
19. Known allergy to steel
20. Participation in another clinical trial related to lifestyle management or diabetes prevention
21. Currently attending or attended a diabetes prevention program in the previous 2 years
22. Unwilling to accept random assignment
23. Had bariatric surgery within the 12 months prior randomization or is planning to undergo bariatric surgery during the study.

*A modified PAR-Q (Section 11.1), focusing on screening for possible underlying cardiac disease, will be used to screen for participant's appropriateness to adopt moderate physical activity. A positive screen will trigger electronic communication/letter to primary care physician to obtain medical clearance prior to enrollment/randomization (Section 11.2)

**Carriers of sickle cell trait (HbAS) are eligible to participate, but would be required to have A1C measured using an A1C analyzer (either Afinion or Siemens) that is not susceptible to interference by hemoglobinopathy.

5.3 LIFESTYLE CONSIDERATIONS

This study will encourage participants to adopt moderate intensity physical activity and to follow a healthy diet for diabetes prevention. Otherwise, no restrictions will be imposed on participants with respect to their lifestyle. Participants in the hDPP will not be prevented from using other wearble devices or apps for weight management or PA tracking.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. The Clinical Research Management System (CRMS) will be used to track all screened individuals (screen fails and enrolled participants). A Research Electronic Data Capture (REDCap) screening database will be used to track reasons for screen fails in accordance with the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information will include demography, screen failure details, and eligibility criteria. Individuals who do not meet the criteria for participation in this trial (screen failure) will not be rescreened.

5.5 STRATEGIES FOR RECRUITMENT

5.5.1 ELIGIBLE PARTICIPANT POOL

EMR queries will be used to identify eligible participants in the Johns Hopkins Medicine and Reading Health systems. Those patients meeting eligibility criteria will be sent a secure research notification through the EMR patient portal (MyChart at Johns Hopkins; MyTowerHealth at Reading). Based on the majority of our eligibility criteria, we identified 21,410 eligible patients for this study in the Johns Hopkins Medicine health system from a query of the EMR. Of these participants, 13,910 (56%) are currently signed up on their patient portal to receive messages, including those related to research recruitment. The characteristics of this patient population are shown in **Table 1**. The age and gender distribution of eligible patients is similar at both sites, but **the racial distribution is significantly different**. Reading Health system is a predominantly rural, white population, while Johns Hopkins Medicine is comprised of an urban population with greater African American and Asian representation. There is also greater proportion of Latino patients in the Reading Health system.

Table 1. Characteristics of Eligible Patient Population.

	Johns Hopkins Medicine	**Reading Health System**
EMR	Epic	Epic
No. of Eligible Patients	21,346	8,751
Patients with Patient Portal Access (%)	13,910 (56)	4,892 (60)
Mean age (SD), yrs	54 (13)	57 (12)

Male, %	52	51
Race, %		
White	52	83
Black or African American	33	3
Unknown Race	9	4
Asian	6	1
American Indian	0	0
Native Hawaiian/Pacific Islander	0	0
Ethnicity, %		
Not Hispanic	91	80
Hispanic or Latino	6	10
Unknown Ethnicity	3	10

5.5.2 RECRUITMENT PROCEDURES

A comprehensive approach will be used to identify eligible participants. We will request a HIPAA waiver to screen the EMR with the thought being that the bigger the denominator, the easier it will be to reach recruitment milestones. We will use **multiple recruitment approaches** for this study, including MyChart (patient portal) recruitment, study recruitment website, social media (Facebook ads), flyers, letters or electronic communications (email, Microsoft Teams) to clinicians, in-hospital plasma tv ads, community engagement (health fairs), and registration of the trial on clinicaltrials.gov. Based on experiences from our pilot study, we anticipate that the majority of enrolled participants will be recruited using the electronic patient portal. Additional recruitment strategies will include direct physician referral, mailed recruitment materials (e.g. postcards, brochures) to residents within 25 mile radius of study sites, study business card, plasma tv ads, or clinicaltrials.gov. Flyers, brochures, and study business cards will be hung on bulletin boards as permitted and used for community-based advertisement. We will work closely with the recruitment consultation and coaching team of the Institute for Clinical and Translational research to identify best recruitment strategies, whether technology-based or through community engagement.

5.5.3 STUDY RECRUITMENT WEBSITE

A study recruitment website has been created within the existing website of the PI's research lab: *https://www.nestorasmathioudakislab.com/prediabetesclinicaltrial*

Individuals who express an interest in joining the trial will be directed to a link to provide basic information including name, email address, and cellphone number. Participants then will be contacted by a research coordinator for additional screening and eligibility.

Until approved by the IRB, this website will only be viewable to study team members and IRB members using the password provided in the eIRB application. Once approved by the IRB, the password login will be removed from the squarepace webpage and the site will be viewable by the general public and anyone who has access to the web link.

5.5.4 SOCIAL MEDIA

We will use targeted paid Facebook advertisements to recruit for this study. Facebook ads will be directed to users affiliated with the Facebook pages of the Johns Hopkins Medicine and Reading Hospital Tower Health who have expressed any interest related to diabetes, prediabetes, weight management, or physical activity. The Facebook ad will provide a link to a basic pre-screening survey including name, email address, cellphone number, zipcode, date of birth, and communication preference. Individuals who express an interest in joining the trial will be offered the option of either a) completing an electronic pre-screening survey to confirm eligibility or b) reviewing eligibility criteria with the study coordinator by phone. If the person expresses an interest to complete the prescreening electronically, we will either email or text the individual the link to the survey based on their

preference. Participants who pass the pre-screen will be contacted by a research coordinator for additional screening, and if eligible, to arrange a study visit. The landing page for the study website (Section 5.5.3) will be provided in the facebook ad.

We will also post Twitter messages with hyperlinks to the study recruitment website from the PI's twitter feed (@nesmathioudakis).

We will also use a social media recruitment service (BuildClinical) for recruitment. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. They utilize study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc. and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform. BuildClinical's Secure Socket Layer (SSL) software, which encrypts all inputted information, keeps information private and HIPAA compliant. The backend servers are stored in the USA at some of the most secure data centers in the world. They adhere to all IRBs guidelines and procedures.

5.5.5 MYCHART MESSAGES

MyChart (patient portal) messages is a relatively new strategy for recruitment at Johns Hopkins that has yielded successful results in several clinical trials. MyChart research notifications targeting eligible patients who live within a 25-mile radius of Johns Hopkins Hospital will be used as a recruitment strategy. The CCDA will identify participants who meet the study eligibility criteria outlined in Sections 5.1 and 5.2 from EMR. The MyChart recruitment service team will send an electronic message for the eligible patients and ask them to voluntary complete a basic pre-screening survey. Participants who pass the pre-screening and indicate interest to join the trial will be contacted by a research coordinator via phone call, text massage, or email for additional screening, and if eligible, to arrange a study visit. A given patient can only be contacted once every thirty days via MyChart. MyChart approval letter and template of the MyChart recruitment message are uploaded to section 20 question 2 and section 13 question 7 of the eIRB application, respectively.

Based on other clinical trials at Johns Hopkins medicine, response rates to MyChart recruitment range from 0.5% to 10%, with enrollment rates from 0.2% to 9.7%. Assuming a minimum response rate of 1% and enrollment rate of 1%, we anticipate recruiting a minimum of 140 participants via MyChart.

Reading Health System is currently implementing recruitment from MyTowerHealth (patient portal), which we anticipate will be available by the time enrollment begins for this trial. Assuming this capability is not available by the time this study begins, a query of the Reading EMR will be used to mail paper letters to potentially eligible patients. A similar proportion of patients are enrolled in the patient portal at Reading Health System and Johns Hopkins Medicine (60% and 56%, respectively).

5.5.6 DIRECT CLINICIAN REFERRALS

Emails or Microsoft Teams posts will be sent to all internal medicine physicians and advance practitioners (NPs, PAs) and endocrinologists within Johns Hopkins Medicine regarding the trial. We anticipate that approximately 20-30 participants will be recruited by clinician referral.

For JHM patients, the Epic query will be conducted by the CCDA based on inclusion/exclusion criteria. For patients who are in MyChart, a MyChart research notification will be sent directly. However, for patients who are not in MyChart, we will send an email (PCP in our health system) or letter (PCP outside our health system) informing the provider of eligible participants in our study. We will request that the CCDA provide us a list of patients, MRNs, patient address, PCP name, PCP address, and MyChart status, which will be stored on a folder in the SafeDesktop. For potentially eligible patients of physicians that are not on the study team, permission will be obtained from their personal providers to contact them about the study. A letter will be mailed to patients directly once permission has been obtained from the PCP. No contact will be initiated by the study team until permission is obtained from personal providers of potential study candidates. Further eligibility assessment will be conducted via a telephone screening script for participants who express interest.

We will also mention our trial during presentations (e.g. grand rounds) to relevant audiences.

5.5.7 MASS MAILING

We will mass mail postcards or brochures to homes with at least one resident age 40-75 years who live within an approximate 25-mile radius (by zip code) of study sites. We will only mail one method (postcard or brochure) with each batch and we will not send repeated mailings to the same recipient. We know that 1 in 3 adults has prediabetes, so we are casting a very wide net with the mass mailings hoping that we get a high response rate. A third-party company will be responsible for printing and mailing the postcards and will use a list of residents purchased from a partner mail house to identify homes with residents age 40-75 years. The study team will not have any PHI, names, or addresses of the recipients of the mailed recruitment materials. The study team members will be in contact with individuals who respond to the mailings indicating an interest in study participation using (i.e., this will be an opt-in approach, whereby only the recipients of mailed recruitment materials initiate contact with the study team by phone, email or the study website).

5.5.8 PUBLIC FACING COMMUNITY OUTREACH

We will recruit people at community-level sites and community health fairs. A qualified trained research coordinator will set a table on the site after receiving permission from the authorized person at the site. Individuals who will stop by the table will receive information about prediabetes and the importance of early diagnosis of prediabetes. The research coordinator then will ask individuals if they are voluntarily willing to take the prediabetes risk test (section 11.16) to check if they are at risk for prediabetes. If they score 5 or higher on the test, they will be asked if they are willing to voluntarily check their A1C level by using A1CNow+ (over-the-counter A1C kit). The research coordinator will explain the process of A1C testing for prediabetes including a clear explanation of the purpose of the A1C test, and the implications of the results. The research coordinator will conduct the A1C testing using appropriate equipment and following established protocol. If the A1C test result is within the prediabetes range, the research coordinator will then offer the potential participant the opportunity to come to the research unit for consenting and full screening. Participants who decline participation in our research study will also be provided information about local diabetes prevention programs. We will not retain any health fair prediabetes risk test and POC HbA1c data for individuals who either ineligible or decline to join the study if they are eligible. However, for eligible individuals who choose to join the study, their POC hemoglobin A1c data may be retained. Once the participant has provided their consent and been enrolled in the study, all screening data and any research data collected will be protected along with any research data collected or generated during the study. Confidentiality and privacy of participant's information will be maintained throughout the recruitment and screening process. If screening participants are found to have elevated A1C in the diabetes range (and they were unaware of the diagnosis), they will be advised to follow-up with their healthcare provider.

5.5.9 RADIO ADVERSTISEMENTS

We will use radio advertisements to recruit participants for this study. The advertisements will be broadcasted on local radio stations (e.g. traffic and weather networks) in the study recruitment areas. The content of the advertisements will include brief information about the study, eligibility criteria (prediabetes, residing within 45 miles of recruitment site), and will direct listeners to the study website (prediabetesstudy com).

5.5.10 TARGETED EMAIL ACQUISITION

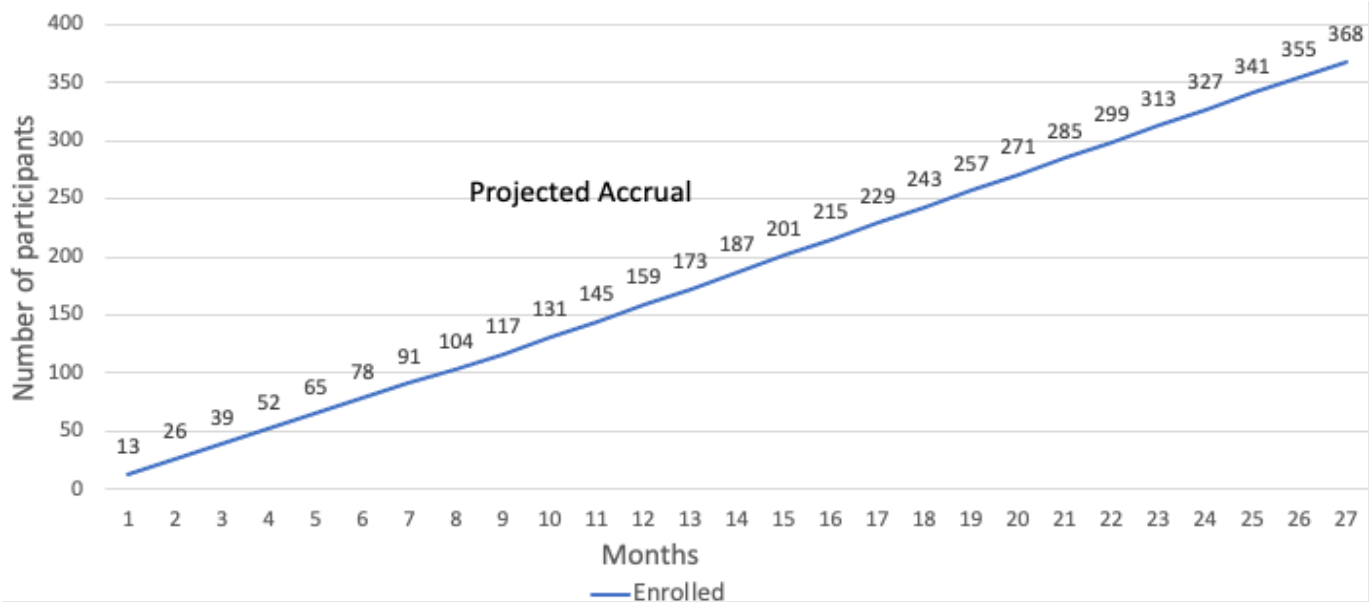
We will use a targeted email acquisition approach through iHeartDigitalSolutions to recruit highly responsive clinic trial participant prospects. The email will target prospects with a likely medical diagnosis of obesity residing within the target site areas. The targeting will be done using detailed behavior and qualitative data by matching 1st party data (IP addresses) with 3rd party browsing history, thus gleaning the target list.

The email will include brief information about the study, eligibility criteria (prediabetes, residing within 45 miles of recruitment site), and will direct listeners to the study website (prediabetesstudy.com). iHeartDigital Solutions will provide full service and permission-based Acquisition Email Marketing. The emails will appear to be coming from JHU, not iHEARTMEDIA, and all recipients are 100% OPTED-IN and compliant with the CAN-SPAM Act of 2003. iHeartDigital Solutions guarantees a 10% open rate for email recruitment.

5.5.11 PROJECTED ACCRUAL

Figure 1 shows the projected accrual of the study. Enrollment will occur over a 27-month period, with projected enrollment of 13 participants (from two sites combined) per month in the first 9 months, then 14 participants (from two sites combined) per month for the rest of the trial duration. We anticipate that 65% of participants will be recruited from Johns Hopkins Hospital and 35% from Reading Hospital.

Figure 1. Projected Accrual



5.6 RETENTION PROCEDURES

5.6.1 EFFICIENT STUDY DESIGN

To increase retention, we have minimized burdens on participants in the protocol design. For example, the screening and baseline visits are combined into a single visit (since point-of-care A1C measurements will be used to establish the diagnosis of diabetes, rather than fasting labs which require return visits). In addition, for the JHU site, we are offering the option of home study visits, which we believe will be perceived as an attractive option by interested candidates and will help to increase recruitment.

5.6.2 INCENTIVES

5.6.2.1 PARTICIPANTS

Participants will be compensated $40 for each completed study visit and $10 for each 7-day period of ActiGraph wear time (total of 12 measurement periods). If a participant is required to have separate screening and baseline visits (due to the need for repeat A1C testing, see Section 11.17), they will not be eligible for additional compensation; however, all parking expenses would be covered for each visit. Thus, the participant is eligible to receive $240 for the entire study. Participants will indicate whether they would like a phone call, email, or text message reminder regarding their follow-up visit at the baseline visit. The participant's preferred approach will be used by the research coordinator in sending the reminder prior to the upcoming visit per the study schedule. At the baseline visit, we will discuss potential or anticipated barriers to attending the follow-up appointments. To show appreciation to our enrolled participants, we will email virtual holiday and birthday cards.

5.6.2.2 LOCAL DPPS

Presently, some local DPPs participating in this trial seek reimbursement from insurance companies for the services they provide to their beneficiaries. **To encourage participation in the trial, we will cover all costs of the DPP for all study participants who are randomized to a local DPP**. We will implement contracts with each of the DPPs per participant enrolled in their program according to the current Medicare Diabetes Prevention Program Payment and Billing Guide at the time of completion of the participant's 6 and 12 month study visits. Reimbursements will be paid to the local DPPs at the 6 month and 12 month time points for each enrolled participant at their site. Since we will be collecting data from local DPPs as part of this study using an electronic data capture form (Section 11.13), we will compensate all local DPPs per participant referred to their program to cover the administrative expenses associated with data entry.

Local DPPs will receive payment once there data are marked "complete" for the participants record in an electronic data capture form and there are no validated data entry errors. The study coordinator will review data entry to identify any missing data or transcriptional errors and will contact the local DPP coordinator to resolve any data entry issues prior to dispensing payment. For participants who do not complete any local DPP visits, the DPP coordinator will simply mark the form "complete" and no data entry will imply that the participant did not engage in the program.

Contracts will be established with each of the participating DPPs in the study to define expectations with respect to referral process, data entry, and billing procedures. Local DPPs will be asked to upload an invoice into the RedCap database system at the 6 month and 12 month time points, which will be reviewed by our study coordinators for payment verification. Payment will be sent within 30 days of receipt of the invoice. Reimbursement to the local DPPs will be based on attendance and outcomes data shared by the local DPP with the study team. A RedCap database will be created and DPPs will be asked to enter attendance and outcomes information for study participants into this database (see Section 11.13). The research coordinators will review the attendance and outcomes data to determine eligibility for payment, which will be assessed at the 6-month and 12 month time points. If the participant is inadvertently charged for any study-related expenses, including invoicing of their insurance company for their participation, we will reimburse the participant directly.

A total of $75 will be paid for the 6-month data entry and $75 for the 12-month data entry. Since there may be a lag between time from randomization in this trial and enrollment in the DPP, we will base the 6 month and 12 month time points on the time from initial local DPP visit for those participants who engage in the program; for participants who do not engage in the DPP (i.e. do not attend a single session), reimbursement will be based on the 6-month and 12-month *study visit* time points. In other words, if a participant completes their 12-month visit at a local DPP at time point 13 months on study, the local DPP will be expected to enter the attendance data (Section 11.13) received at time point 13 on study (12 month DPP program time point).

Data use agreements will be established with each of the participating DPPs in the study to define expectations with respect to data sharing, data entry, referral process, and study reimbursement.

	Core Sessions (Months 0-6)	**Core Maintenance Sessions (Months 7-12)**	
		Interval 1 (3 sessions)	Interval 2 (3 sessions)
Attendance Only	1 session total: **$26 (G9873)** 4 sessions total: **$52 (G9874)** 9 sessions total: **$94 (G9875)**	Attend 2 sessions (without at least 5% weight loss): **$15 (G9876) OR**	Attend 2 sessions (without at least 5% weight loss): **$15 (G9877)**
Attendance and Weight Loss	5% weight loss is not required to receive payment	Attend 2 sessions (with at least 5% weight loss): **$63 (G9878)**	Attend 2 sessions (with at least 5% weight loss): **$63 (G9879)**
Additional Codes	5% weight loss achieved by 12 months: **$168 (G9880)**		
	9% weight loss achieved: **$26 (G9881)**		

5.6.3 MINIMIZING PARTICIPANT BURDEN

We have designed the study to minimize participant burden. The option of home study visits will be provided for participants enrolled at the JHU site, which we expect will increase recruitment yield by making the study more convenient for participants. We will initially conduct home study visits during weekdays and daylight hours, but may consider weekend visits if needed to

increase enrollment rate. If participants report challenges making it to the research clinic site for follow-up visits due to scheduling conflicts, we will consider adding non-business and weekend hours to accommodate participant's schedules as much as possible. After a participant is enrolled in the study, research staff will be expected to follow our Difficult to Reach Protocol (Section 5.6.5). All attempts to contact, including the failed attempts and the outcome of the attempts, will be documented in the electronic case report form. A copy of the letter(s) sent to the participants will be saved in the case report form.

5.6.4 STUDY PARTICIPANT INFORMATIONAL RESOURCES

5.6.4.1 STUDY PARTICIPANT WEBSITE

A study resource webpage will be provided to study participants at the following URL:

https://www.nestorasmathioudakislab.com/study-participants

Access to the study participant website will require a password , which will be provided to the study participant at the baseline visit by the study coordinator. This website is intended to provide reference materials regarding study schedule of activities and procedures to simplify the process for our study participants. No data will be collected from study participants through this website.

5.6.4.2 STUDY PARTICIPANT INSTRUCTION GUIDE

A study participant manual (replicating content from the study participant website) will also be provided to participants at the baseline visit. This is intended to provide important contact information and reference materials regarding study schedule of activities.

5.6.5 DIFFICULT TO REACH PROTOCOL

A total of 10 contact attempts are made to all the phone numbers provided by the participant at varying times of the day. The calls may be divided in the following manner: 2 calls before 11 AM, 2 calls between 11 AM and 3 PM, 2 calls between 3 PM and 6 PM, 2 calls after 6 PM, and 2 calls on the weekend.

a) At least 5 text messages are sent.
b) At least 5 emails are sent – if email provided.
c) One "unable to contact letter" is sent to the home address. The letter must contain name and address of the participant, visit, compensation amount, date, name and contact information of the study team member.
d) Attempt to contact 1-3 alternative contact(s); defined for the participant as 'someone who will know how to reach you.'

5.6.6 POTENTIAL PROBLEMS AND ALTERNATIVE STRATEGIES

If the pace of recruitment is below the target goal of 13-14 participants per month, we will pursue the following strategies to increase recruitment:

a) If accrual is limited by lack of resources for screening (i.e. insufficient research coordinator effort one or both recruitment sites), we will reallocate resources accordingly to ensure that there is sufficient resource coordinator time and effort available to screen and enroll interested participants.
b) If accrual is limited by lack of interested participants, we will consult experts in the ICTR for advice regarding alternative recruitment strategy methods. We could consider, for example, advertisements on buses, radio, or other online sites if appropriate based on the advice of our local recruitment experts. We could consider addition of another recruitment site if allowable per study budget, or if accrual is significantly below target, we could request a budget supplement to include an additional site.

c) If accrual is limited by eligibility criteria, we will consider modifying the eligibility criteria to be less restrictive without compromising the validity of the study findings.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION DESCRIPTION

Participants randomized to the dDPP will receive the Sweetch digital health kit (app log in instructions and Bluetooth-enabled digital scale) within 8-12 days via mail. The rationale for mailing the digital health kit is to allow participants to obtain baseline PA measurements prior to starting the intervention, and also to replicate the real-world experience in which there would likely be some delay between prescriber ordering of the dDPP and patient receipt of the product.

The referral process to the Sweetch dDPP will be generated in a RedCap database, with an automated email sent to Sweetch Health, Ltd. The RedCap referral will include the following participant identifiers at the time of the referral:

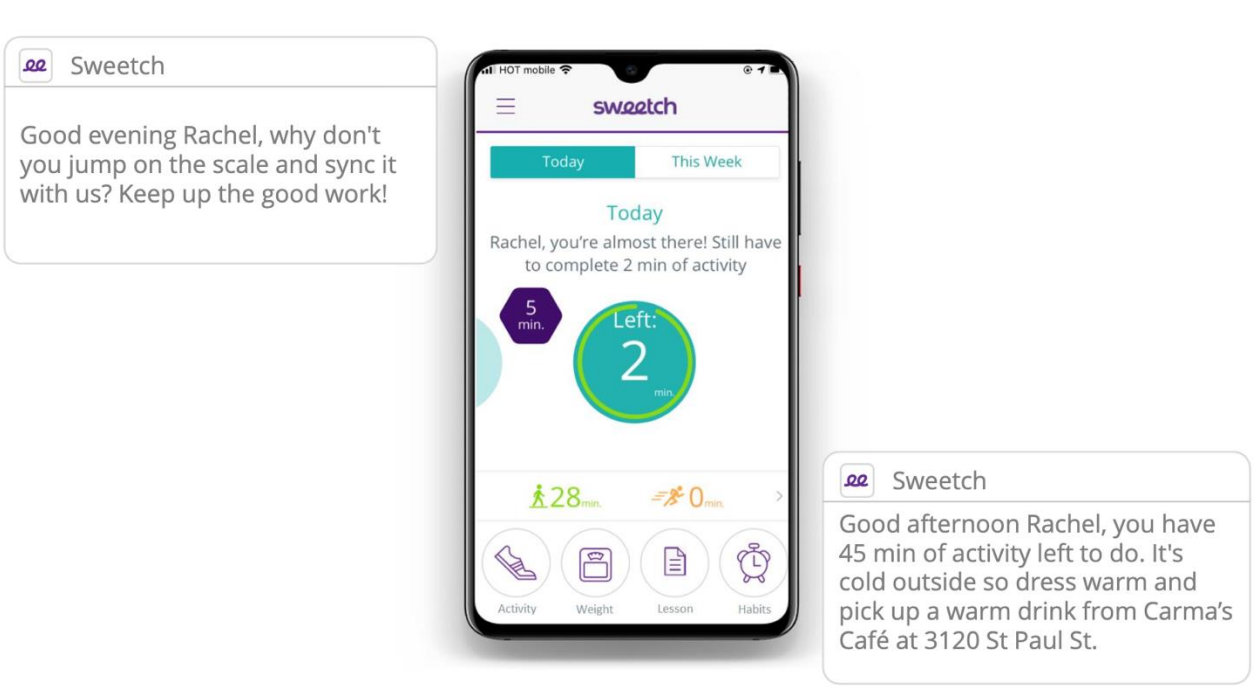
- First Name
- Last Name
- Email Address
- Phone Number
- Baseline Weight
- Baseline BMI
- Laboratory measure(s) that rendered the participant eligible for the DPP (A1C, fasting glucose, plasma glucose after 75 gram OGTT) and date of the relevant lab result(s)

This will allow the Sweetch support team to contact the participant directly in the event that the user has any technical difficulties installing the app and/or syncing the Bluetooth enable digital body weight scale. A maximum of 5 communication attempts will be made directly by Sweetch to register the participant in the app. Baseline weight, BMI, and A1C data are provided to the dDPP arm as this information is also required for referral to the hDPP arm.

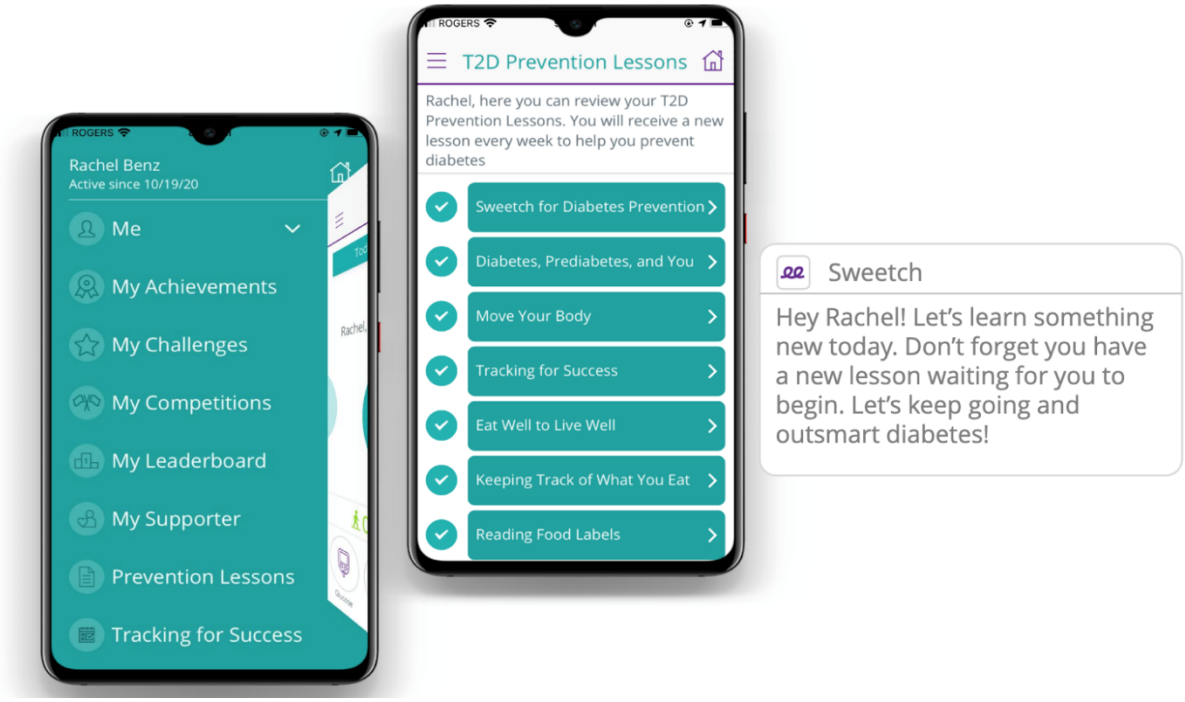
The Sweetch app uses self-tracking and multiple evidence-based persuasive eCoaching strategies, which have been described in detail in a recent review of automated technologies seeking to promote behavioral change. Notably, not only does the app itself employ multiple persuasive systems design elements, but the adaptive push notifications do as well: reduction (breaking down goals into smaller goals), tunneling (guiding user step by step), tailoring, personalization (continuously tuning goals and messages based on past real-world compliance and capabilities), simulation, praise, reminders, suggestion, competition, recognition, education and goal-setting.

The Sweetch AI algorithm is used in several app components to deliver just-in-time support and/or adapt recommendations or goals in real-time based on the user's response. For example, push notifications will be sent when the algorithm detects that the user is potentially available and able to act upon the recommendation, based on various parameters including location, previous response, calendar availability, and weather, etc. These tailored pushed notifications motivate participants to meet the PA goal of 150 minutes per week, lose 5% of body weight, monitor meals and drinks, and complete the 19 CDC in-app diabetes prevention lessons for the core phase (months 1-6) and 6 in-app lessons for the core maintenance phase (months 7-12). A maximum of 10 push notifications will be sent per day; however, participants who are meeting their goals may not receive any notifications on a given day. In some instances, notifications/reminders will be sent via email mainly for educational content and technical support. For example, an email will be sent to participants upon referral to the dDPP providing the user a link to download the Sweetch app and instructions on how to complete the registration process. Also, for some participants, emails may be sent to supplement the education provided via the in-app lessons. Participants will be able to turn off/on push notifications at any time within the Sweetch app, but will not be able to make modifications to the frequency or timing of the notifications as these are generated using AI technology and are continuously adapted based on the participant's behavioral patterns and progress in the program.

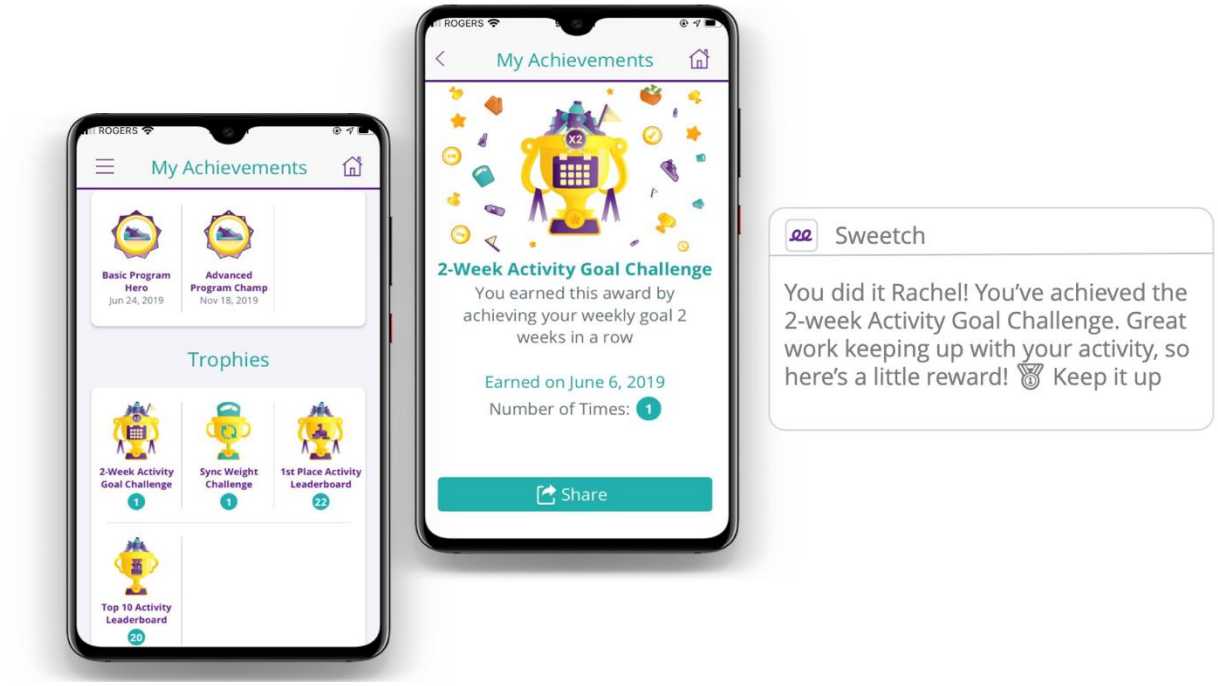
This screenshot shows an example of the Sweetch personalized push notification, and home screen with goal tracking (PA, weight, in-app lessons, and habits):


Sweetch
Good evening Rachel, why don't you jump on the scale and sync it with us? Keep up the good work!
HOT mobile
sweetch
Today
This Week
Today
Rachel, you're almost there! Still have to complete 2 min of activity
5 min.
Left:
2
min
28 min.
0 min.
Activity
Weight
Lesson
Habits
Sweetch
Good afternoon Rachel, you have 45 min of activity left to do. It's cold outside so dress warm and pick up a warm drink from Carma's Café at 3120 St Paul St.

This screenshot shows the main page of the app and the T2D Prevention Lessons based on the CDC curriculum. Participants are reminded to take the in-app lessons:



This screenshot shows the participant achievements, a form of social support:



6.2 CONTROL ARM DESCRIPTION

Participants randomized to the hDPP arm will be provided a list of participating CDC recognized lifestyle change programs within a 25 mile radius of the main study site. Eligible programs will be identified using the CDC's Recognized Lifestyle Change Program Website[55], which maintains a registry of recognized programs.

For this trial, eligible local programs must meet the following criteria:

- Have preliminary or full recognition status by the CDC (i.e. identifiable on the CDC's online registry)
- Provide in-person or *synchronous* distance learning (video conferencing) modalities
- Expressed interest in participating in the clinical trial
- Agree to share outcomes and attendance data (per CDC reporting requirements) using study team's electronic data capture form.

To achieve preliminary or full recognition, local DPPs must adhere to the CDC's Diabetes Prevention Recognition Program Standards and Operating Procedures.[56] Sessions are delivered by trained lifestyle coaches and each site offers at least 16 sessions during the first 6 months (core phase) and 6 sessions during the last 6 months (core maintenance phase). Each program follows a CDC approved curriculum, using either the 2012 National DPP curriculum or the more recent CDC-developed PreventT2 curriculum (majority).[57] Core sessions are held weekly for months 0-6, then typically bi-monthly for the core maintenance sessions in months 7-12, which is divided into two intervals (months 7-9 and months 10-12). Programs are required to offer at least 6 sessions during the last 6 months (3 per interval).

The CDC recognizes several modalities for DPP, including in-person, distance learning, and online. Distance learning refers to both synchronous and asynchronous delivery using video and phone conferencing. In **synchronous** delivery, instruction is conducted in real time. That is, all participants are present at the same time. Synchronous delivery most closely resembles a traditional classroom, despite the participants being located remotely. It requires an organized timetable and an instructor to be present. Participants can typically interact with the instructor and they may even interact with each other. In **asynchronous** delivery, instruction is self-paced. Participants access course materials on their own schedules and are not required to be together at the same time. Delivery technology includes video and audio recordings, discussion board forums, e-mail, and self-directed print materials. Hybrid, or blended, learning is when synchronous and asynchronous technologies are combined.

Among these CDC-reognized delivery modalities, for participants randomized to receive the hDPP, local DPPs will only be permitted to use in-person, **synchronous** distance learning, or combined modality to avoid contamination with the dDPP intervention. The online only modality will not be permitted. Online platforms often use wireless weight tracking, PA trackers, and social support and engagement tools that would introduce contamination with the study intervention. In addition, *asynchronous* distance learning will not be permitted as it will be practically challenging to track participant engagement in these programs. However, a combination of asynchronous and synchronous distance learning will be permitted if we are able to capture all the "attendance" data.

Eligible programs have been identified from a search of the CDC National Diabetes Program website and the state department of health websites for Maryland[58] and Pennsylvania.[59] The in-person delivery of these local DPPs occurs in various settings (hospital outpatient, primary care, community, church). Programs may use any video conferencing platform (e.g. Zoom, WebEx, Google Meet) to deliver synchronous distance learning. If additional DPP programs meeting our eligibility criteria are identified after study initiation, they will be approached by the study team for inclusion in the trial.

COVID-19 has introduced significant challenges in the delivery of in-person DPP, and the majority of local DPPs have transitioned nearly entirely to distance learning through the use of video conferences. Since programs enroll cohorts at different frequencies on a rolling basis, participants will be informed that once they initiate in a program, they will need to continue in that program at least through the duration of the core phase (months 1-6), after which they may switch to an alternative hDPP. However, participants will be encouraged to complete the full program at the same hDPP.

For participants expressing interest in a distance learning DPP, the study team will refer the participant to the program with the earliest availability. For participants expressing interest in in-person DPP, the study team will refer the participant to the closest program that is closest to their home and has the earliest availability. The referral process will be generated in RedCap, with an

automated email sent to the local DPP coordinator. The RedCap referral will include the following participant identifiers at the time of the referral:

- First Name
- Last Name
- Email Address
- Phone Number
- Baseline Weight
- Baseline BMI
- Laboratory measure(s) that rendered the participant eligible for the DPP (A1C, fasting glucose, plasma glucose after 75 gram OGTT) and date of the relevant lab result(s)

Local DPPs will then initiate outreach as part of their normal protocols. We will advise local DPPs that a maximum of 5 attempts should be made to reach our study participants for enrollment in their programs.

6.3 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.3.1 ACQUISITION AND ACCOUNTABILITY

Sweetch Health, Ltd. will provide the Sweetch app, digital scales, instructional materials, technical support for participants, hosting of the app, and sharing of all app system usage data with the study team.

6.3.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The Sweetch digital health kit will consist of the Sweetch app and Bluetooth enabled digital scale. The scale will be packaged in a branded white box with the Sweetch logo. A user manual will be provided with the scale.

6.3.3 PRODUCT STORAGE AND STABILITY

The Sweetch health kit will be stored in a locked office at room temperature. With the exception of informational materials, there are no products to be provided to control participants.

This study will be using various A1C testing devices, all of which are FDA approved and certified according to NGSP (National Glycohemoglobin Standardization Program) standards. The A1C testing devices include the Afinion™ 2 Analyzer, Siemens DCA Vantage, and A1CNow®+ test kits (Professional Multi-test HbA1C System; Polymer Technology System, Inc., Indianapolis, IN). All test kits and control solutions will be stored according to manufacturer's instructions. A log will be maintained to ensrue that kits are used prior to expiration date. Any expired test kits will be discarded.

6.4 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Block stratified randomization by baseline A1C level (5.7% to 6.0% vs. 6.1% to 6.4%) and recruitment site (JHU vs. Reading) will be done to ensure that the groups are balanced with respect to this variable, since higher A1C level at baseline is the strongest risk factor for progression to incident diabetes and potential need for glucose-lowering medications.

For several pragmatic reasons, this will be an open-label trial (i.e. treatment allocation will be unblinded to both participants and the study team). For efficiency, research coordinators conducting the home study visit will also be responsible for randomization and measurement of height and weight. Since the study team members will also need to interact with local DPPs, it would be practically challenging to blind the study team members to treatment assignment. The biostatistician will also be unmasked to treatment assignment and will provide required reports to the DSMB. The study team will have real-time access to all systems log data collected by Sweetch in the form of a dashboard.

Considering that hDPPs enroll participants to their programs on a rolling basis depending on the number of interested participants available to join a new cohort and availability of lifestyle coaches, it is possible that there will be times during the enrollment period where there may be an absence of available hDPPs to accept participants randomized to that arm in a timely fashion. Since the outcomes of this trial are based on time from randomization (and not time from first visit in the hDPP), all efforts will be made to minimize the lag time between randomization and the time to first available hDPP session for a given participant. It is likely that hDPPs will reduce the frequency of new cohort starts during periods of holidays. **To ensure that there is no more than a 4 week lag time from date of randomization to the date of the first available visit for ANY of the hDPPs across the study, randomization will be temporarily suspended until at least one program that offers both in-person and synchronous distance learning has an available start date to accept a hDPP participant within 4 weeks.** While participants will be offered the option of selecting a hDPP (based on distance from home, offerings, and other factors), in the event that the program that they are interested in does not have an available cohort starting until after 4 weeks, participants will be referred to the hDPP with the soonest available start date.

To operationalize referrals to hDPPs, hDPPs will be required to provide the study team an updated schedule of their class sessions and frequency of new cohort enrollment at least quarterly and whenever there is a change in their schedule. Participants will be encouraged to find a program that has an available start date no longer than 8 weeks from the time of enrollment.

6.5 PROHIBITED MEDICATIONS

Treatment with any of the medications below will not be permitted, whether taken alone or as a component of a combination drug within previous 3 months. These medications can influence glycemic control directly or indirectly.

Glucose Lowering Medications		**Weight-Loss Medications**	**Systemic steroids**
Insulin or Insulin Secretagogues	Other		
Insulin • Insulin glargine (Lantus; Toujeo; Semglee) • Insulin basaglar or biosimilar • Insulin detemir (Levemir) • Insulin degludec (Tresiba) • Insulin NPH (Novolin N; Humulin N) • Insulin aspart (Novolog, FlexPen, Fiasp) • Insulin Fiasp • Insulin lispro (Humalog; Admelog) • Insulin glulisine (Apidra) • Insulin regular (Novolin R, Humulin R)	Metformin (Glucophage, Glucophage XR, Glumetza, Riomet, Fortamet) Thiazolidenediones • Pioglitazone (Actos) • Rosiglitazone (Avandia) DPP-4 Inhibitors • Sitagliptin (Januvia) • Saxagliptin (Onglyza) • Linagliptin (Tradjenta) • Alogliptin (Nesina) • Vildagliptin (Galvus) Alpha Glucosidase Inhibitors • Acarbose (Precose) • Miglitol (Glyset)	Orlistat (Xenical) Lorcaserin (Belviq) Phentermine-Topiramate (Qsymia) Liraglutide (Saxenda) Buproprion-Naltrexone (Contrave) Benzphetamine (Didrex; Regimex) Diethylpropion Phentermine (Adipex; Lomaira; Suprenza) Phendimetrazine (Bontril) Bromocriptine (Parlodel, Cycloset) Colesevelam (Welchol)	Oral formulations • Hydrocortisone • Cortisone • Prednisone • Prednisolone • Dexamethasone Intra-articular injections* • Triamcinolone • Methylprednisolone • Hydrocortisone

<table>
<tr><th colspan="2">Glucose Lowering Medications</th><th>Weight-Loss Medications</th><th>Systemic steroids</th></tr>
<tr><td>Insulin or Insulin Secretagogues</td><td>Other</td><td></td><td></td></tr>
<tr><td>• Novolog Mix 70-30 (insulin aspart protamine-insulin aspart)
• Humalog Mix 75-25 (insulin lispro protamine-insulin lispro)
• Humalog Mix 50-50 (insulin lispro protamine-insulin lispro)
• Humulin 70/30 (human insulin NPH-human insulin regular)
• Novolin 70/30 (human insulin NPH-human insulin regular)
• Ryzodeg (insulin degludec-insulin aspart)
Sulfonylureas
• Glimepiride (Amaryl)
• Glipizide (Glucotrol)
• Glyburide (Micronase, Diabeta)
• Tolbutamide (Orinase)
Meglitinides
• Nateglinide (Starlix)
• Repaglinide (Prandin)</td><td>SGLT-2 Inhibitors
• Canagliflozin (Invokana)
• Dapagliflozin (Farxiga)
• Empagliflozin (Jardiance)
• Ertugliflozin (Steglatro)
GLP-1 agonists / dual GLP-1/GIP agonists
• Exenatide (Byetta; Bydureon)
• Liraglutide (Victoza)
• Dulaglutide (Trulicity)
• Albiglutide (Tanzeum)
• Pramlintide (Amylin)
• Semaglutide (Ozempic, Rybelsus)
• Tirzepatide (Mounjaro)
Combination Oral Pills
• Alogliptin/Metformin (Kazano)
• Alogliptin/Pioglitazone(Oseni)
• Empagliflozin/Linagliptin (Glyxambi)
• Empagliflozin/Metformin (Synjardy)
• Canagliflozin/Metformin (Invokamet)
• Dapagliflozin/Metformin XR (Xigduo XR)
• Glyburide/Metformin (Glucovance)
• Glipizide/Metformin (Metaglip)
• Linagliptin/Metformin (Jentadueto)
• Rosiglitazone/Metformin (Avandamet)
• Pioglitazone/Metformin (ActoPlus Met)
• Pioglitazone/Glimepiride (Duetact)
• Rosiglitazone/Glimepiride (Avandryl)
• Sitagliptin/Metformin (Janumet)
• Sitagliptin/Metformin (Janumet XR)
• Repaglinide/Metformin (PrandiMet)
• Pioglitazone/Metformin XR (ActoPlus Met XR)
• Saxagliptin/Metformin XR (Kombiglyze XR)</td><td></td><td></td></tr>
</table>

Glucose Lowering Medications		**Weight-Loss Medications**	**Systemic steroids**
Insulin or Insulin Secretagogues	Other		
* Since intraarticular joint injections can have prolonged systemic effects, a single joint injection of any of the following medications will result in subject withdrawal. Note: Otic, ophthalmic, and inhaled glucocorticoids WILL be permitted			

6.6 RESCUE MEDICINE

Not applicable. If a participant has an A1C measurement of 6.5% or greater during the course of the trial (consistent with possible type 2 diabetes), a letter will be sent to their primary care physician for consideration of further evaluation Section 11.19). The decision to use antihyperglycemic medications for participants diagnosed with type 2 diabetes will be at the discretion of their treating clinician.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Given the focus of this study on increasing PA and promoting healthy diet and weight loss, we do not anticipate any serious adverse events that we require discontinuation of the study intervention. For participants who do not engage with the study intervention, whether randomized to the dDPP or hDPP, all efforts will be undertaken by the research coordinator to keep the participant in the study for assessment of efficacy and adverse events.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

The study team will only withdraw a participant if any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation would not be in the best interest of the participant. Participants who develop diabetes mellitus during the course of the study **will be eligible** to continue, and all new medications that are initiated for glycemic control will be reported. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the 12 month study visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 30 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study record.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4 PARTICIPANT STUDY END DEFINITION

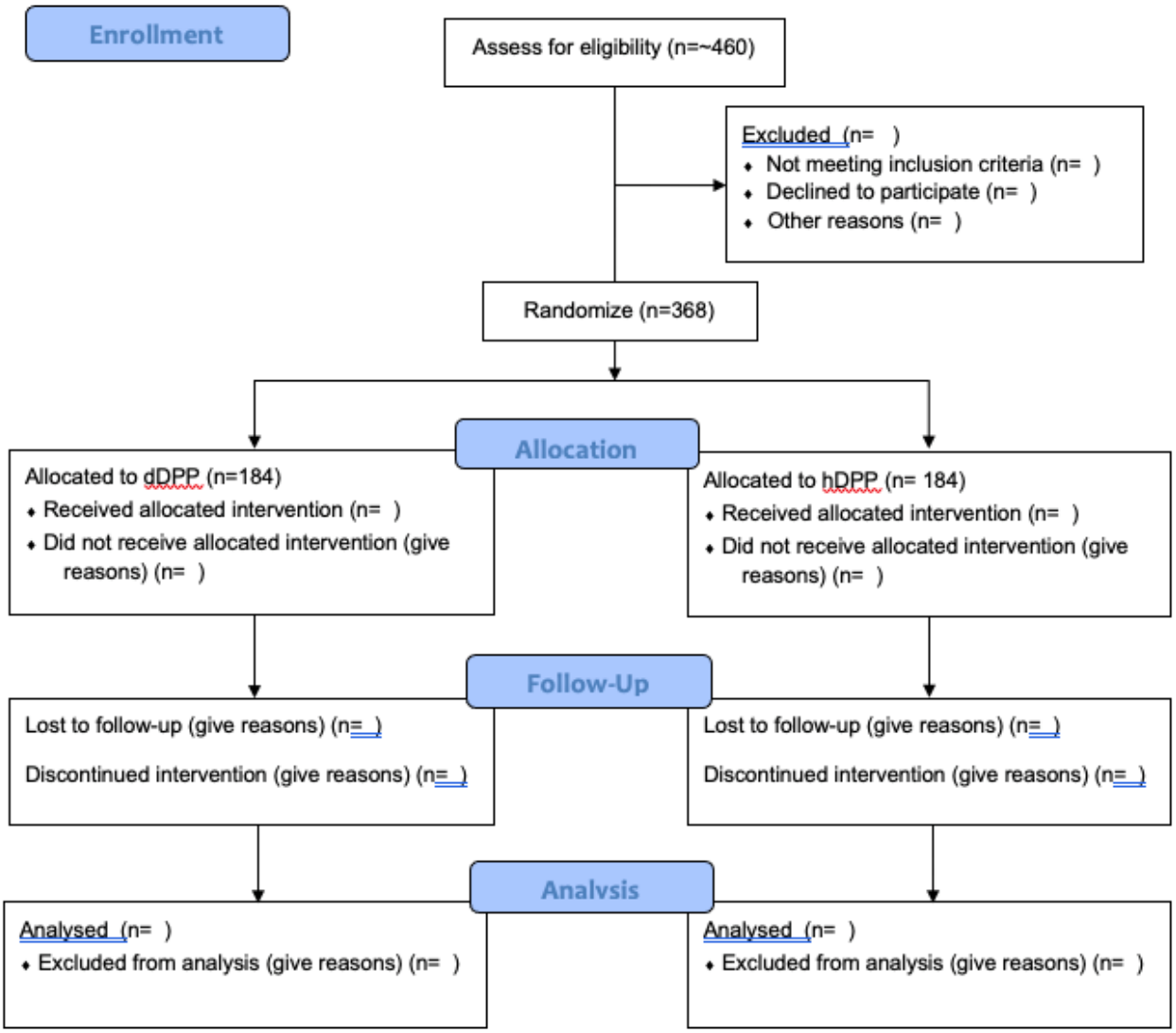
A participant will be considered "off-study" (i.e. completer) when all of the following criteria are satisfied:

- Completion of the 12 month study visit
- *For hDPP arm only*: 12 months have elapsed from the date of the first visit in the hDPP. If participant never attends a hDPP, this criterion is not applicable.

8 STUDY ASSESSMENTS AND PROCEDURES

For the JHU site, participants who express interest in the study will be offered the option of home study visits or on-site study visits. Home study visits will be conducted during daylight hours in accordance with a defined safety protocol (Section 11.19).

8.1 STUDY CONSORT DIAGRAM



8.2 EFFECTIVENESS ASSESSMENTS

At the study visits, the following procedures and evaluations will be performed by a trained research coordinator according to the Schedule of Activities (Section 1.3):

8.2.1 PHYSICAL EXAMINATION

Height will be recorded to nearest 0.1 cm using a portable stadiometer. Weight will be recorded to the nearest 0.1 kg using a portable digital scale. The same scale will be used for all participants for each measurement. Participants will be asked to wear light clothing, remove shoes, and void prior to weight measurements.

8.2.2 LABORATORY EVALUATIONS

In this study, we will be using A1C testing for two purposes: a) safety (ruling out diabetes at screening visit) and b) measuring change in A1C (one of the composite endpoints of the study). Considering that some participants could have progressed from prediabetes to diabetes since their last A1C test, a repeat A1C test will be obtained at the screening visit for safety reasons to exclude patients with possible type 2 diabetes (A1C of 6.5% or greater). Such participants will be ineligible to join and will be advised to contact their primary care provider for confirmatory diagnostic testing.

For participants who have not had a laboratory test to confirm the diagnosis of prediabetes as specified in our inclusion criteria (Section 5.1), the POC A1C measurement will be used for screening purposes to ascertain eligibility, and a result between 5.7% and 6.4% would render the participant eligible. For example, if a participant had an A1C result two years ago of 6.2% but has not had a repeated A1C test or fasting glucose in the past year, the screening test would be done to determine prediabetes status.

The second reason for the A1C test will be to determine change in A1C at 6 months and 12 months from the baseline study visit, which is one of the composite endpoints of our study. Of note, the CDC has defined reduction in A1C of 0.2 or more at 1 year to be an indicator of success in the DPP. This outcome measure (a component of our composite endpoint) will be limited to participants whose baseline A1C (obtained by our study team) is between 5.7% and 6.4%.

A1C will be obtained using FDA cleared, CLIA-waived, and NGSP-certified devices (Afinion^{TM} 2 Analyzer, Siemens DCA Vantage, or A1CNow+ test kit). These point-of-care tests require a fingerstick blood sample and an A1C result is obtained in 5 minutes. All A1C testing will be performed by a trained research coordinator.

The A1CNow+ test is a portable testing device that can be used for home study visits. While this device is FDA approved and NGSP certified, it has larger mean bias from laboratory-obtained gold standard compared to the Afinion Analyzer and Siemens DCA vantage machines; in addition, this testing device is more susceptible to interference from hemoglobinopathies (e.g. sickle cell trait or disease) and the presence of rheumatoid factor. For study participants who request a home study visit, a screening protocol will be followed to exclude conditions that could lead to interference with the A1CNow+ test (Section 11.18). If the participant has an underlying condition that could interfere with the accuracy of the A1CNow+, they will be offered a study visit at the clinical research unit, where testing can be performed using more accurate devices that are not prone to interference from these conditions (Afinion^{TM} 2 Analyzer or DCA Vantage). If a quality control error message is received using any of the point-of-care testing devices, the test will be repeated with a second sample. A1CNow+ failure will be defined as two quality control or error messages during a study visit. In addition, an A1CNow+ reading that differs from an A1C obtained in the past 3 months by less than or equal to -0.9 points or greater than or equal to 0.8 points (outside the 95% confidence interval of A1CNow+ test compared to venous sample A1C[60]), could suggest possible unrecognized interfering condition (hemoglobinopathy or rheumatoid factor) resulting in a spurious result. In this case, the participant will be offered repeat screening with an alternative A1C testing method, either point-of-care test conducted in the clinical research unit or serum A1C measurement obtained at a Labcorp facility.

Section 11.17 summarizes the interpretation of A1C results during the screening visit for this study using the different A1C testing devices.

8.2.3 PHYSICAL ACTIVITY MONITORING

Participants will be provided an ActiGraph (either GT9X-BT link or CPIW) wrist monitor and asked to wear the device for 7-days of consecutive wear time at enrollment and once approximately every 1 month thereafter for the duration of the study. A reminder email, phone call, or text message one day prior to the scheduled event and on the day of event will be sent by our team. Participants will return the ActiGraph device at the 12-month visit. If the actigraphy wrist monitor or accessories are damaged during a scheduled wear period, replacement device or accessories will be mailed to the participant.

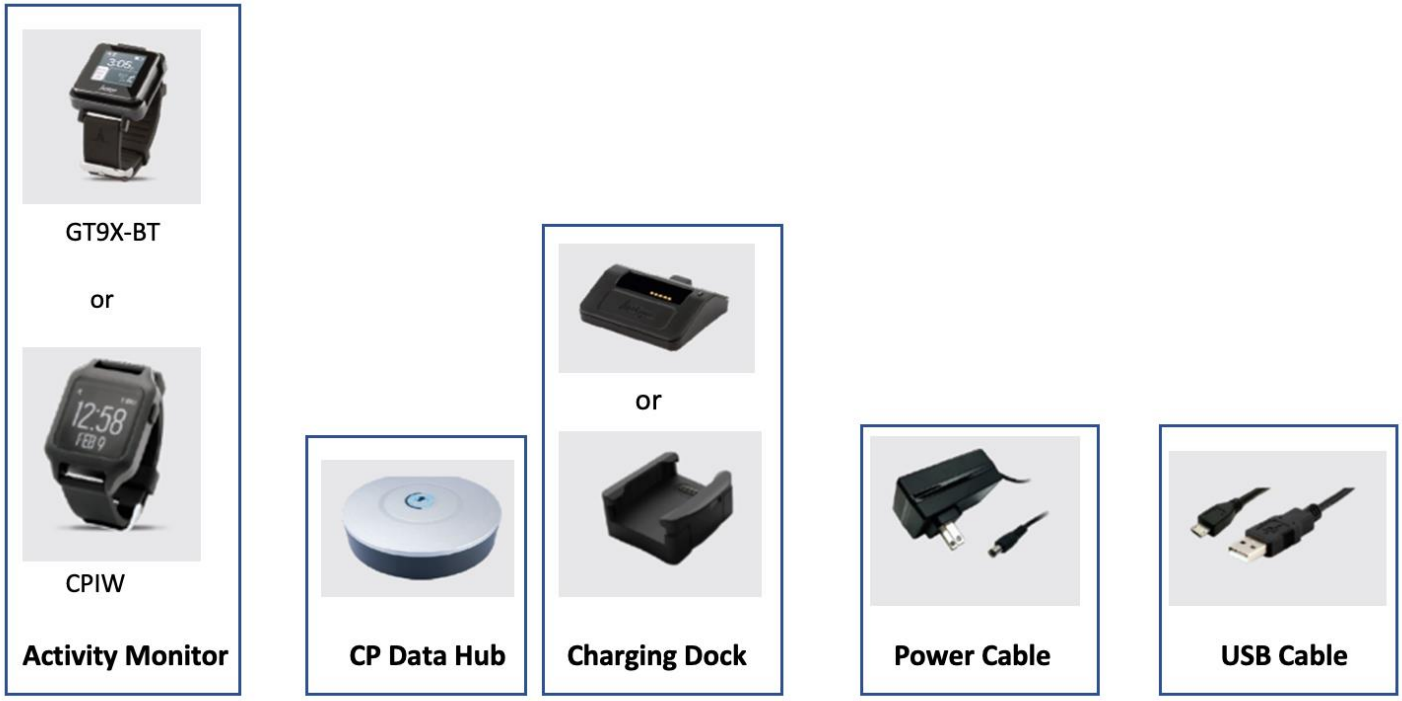
The ActiGraph GT9X-BT Link and CPIW are FDA-cleared devices, which have the ability to distinguish non-wear time from physical inactivity. Both devices capture and record high resolution raw acceleration data, which are converted into a variety of objective activity measures. The CPIW, which is the newer model of the ActiGraph wrist monitor, has an extended 30-day battery life allowing

for continuous wear time during the scheduled wear period, which minimizes participant burden and the potential for missing data associated with frequent device charging. ActiGraph provides a cloud based service platform, CenterPoint, which allows automated capture of actigraphy data from the ActiGraph monitor. The participant will be blinded to the Actigraph data.

At the baseline visit, participants will be provided 1) the ActiGraph activity monitor, 2) Centrepoint (CP) data hub, 3) charging dock, 4) power cable and 5) USB Cable (see screenshot below), and a participant guide will be provided with clear insturctions on how to use these devices. The CentrePoint data hub uses 3G cellular network (paid for by study team) to transmit data collected from the ActiGraph activity monitor to the study team via the CentrePoint cloud-based software. The participant's home WiFi will not be utilized for the remote data capture. The CentrePoint datahub uses Bluetooth technology to automatically capture data from the ActiGraph device when the participant is in close proximity to the datahub. Participants will also be asked to upload the raw data collected from the ActiGraph activity monitor to the CenterPoint data hub after each wear period by connecting the physical activity monitor to the data hub using a provided USB cable/charging dock (see screenshot below). This physical connection will provide the raw data required by the study team. The study team will track study participant compliance remotely using the CentrePoint software, which will indicate Bluetooth captured data as well as manual data upload to the data hub.

If the study team does not see that the participant is wearing their physical activity monitor, we will contact the participant by text message, email, or phone call to remind them to wear the device, ensure that the data hub is plugged in, and/or encourage the participant to upload data from their activity monitor to the datahub. If data show that fewer than 75% of the 7-day period comprised actual wear time, participants will be asked to repeat the consecutive 7-day period as soon as this is noted, and the previously collected incomplete/invalid data will be disregarded. Once the participant has been deemed compliant, a message or email will be sent to communicate that they have satisfactorily completed their 7-day wear period.

This screenshot shows the accessories that will be provided to study participants at the baseline visit for physical activity tracking.



This screenshot shows the connection between the activity monitor/charging dock to the CP Data hub, which will occur after every 7-day wear period to upload raw data to the Centerpoint cloud software, which is accessible by the study team.

The approach outlined above would allow the study participant to keep the activity monitor and accessories in their possession for the full duration of the trial (Section 8.2.3.1). If, for some reason, this approach is technically challenging for some participants or we find poor adherence with this strategy, we may elect to have study participants mail back their activity monitor each month as an alternative workflow (see Section 8.2.3.2.).

8.2.3.1 PARTICIPANT KEEPS ACTIVITY MONITOR IN POSSESSION

Participant is provided an actigraph monitor at baseline visit together with charging device and accessories. Participant keeps the actigraph monitor in their possession between the baseline visit and 6 month visit, and charges the device as instructed between each wear period. A new or same device is provided at the 6 month visit and the participant again keeps the actigraph monitor in the possession between the 6 month visit and the 12 month visit.

8.2.3.2 PARTICIPANT RETURNS ACTIVITY MONITOR VIA MAIL EACH MONTH

Participants are provided only a charged activity monitor prior to each wear period and asked to return the device via mail after each successful wear period. Participants will be provided a return postage paid mailer and asked to mail back the activity monitor after they receive confirmation from our study team that they have successfully completed the 7 day wear period. Once the device is received by the study team, the raw data will be downloaded and the device will be charged. The activity monitor will then be mailed back to the study participant at the time of their next wear period together with a postage paid return mailer for them to return the device after confirmation by our study team that they have successfully completed the 7-day wear period. The main barrier to Option #2 is the burden of participant mailing the monitor. We will make this process as simple as possible for study participants by providing postage paid mailers and clear instructions on how to return the device.

8.2.3.3 DETERMINING WHICH ACTIGRAPH MONITORING APPROACH TO USE

The decision to use either of the above options will be based on several factors. There are several potential barriers to participant compliance with keeping the actigraph monitor in their possession (Section 8.2.3.1), including higher probability of device damage due to longer term use (e.g. wrist band breaks, charger fails, etc.), and higher probability that the device will go into Halt mode due to complete loss of battery life. If a device goes into Halt mode, the activity monitor would need to be physically collected back from the participant and the data downloaded, with a new device initialized and provided back to the participant. If we find that an individual study participant is struggling to comply with this approach, we may recommend shifting to the serial mailing approach (Section 8.2.3.2) for a given participant. We will continuously monitor compliance with both approaches and may need to shift our strategy to favor the approach that yields the higher compliance with the study procedures.

8.2.4 SELF-REPORTED PHYSICAL ACTIVITY DATA

For participants who agree to complete surveys electronically, a Redcap electronic survey will be emailed to participants 7 days after each scheduled Actigraph assessments to collect the number of minutes of moderate or brisk physical activity completed during the preceding week. If a participant reports doing no activity during the preceding week, then zero (0) minutes will be recorded. If participants do not respond to the email survey, the research coordinator will contact the participant by phone to collect this information. There is a potential that a participant who has not been compliant with the scheduled wear period will be asked to self-report PA in a week that they were not also wearing the actigraph device, which will limit our ability to correlate self-report to objectively measured PA in all instances; however, we suspect that averaged on the 12 month period of the trial, self-reported PA in a close window of time relative to the actigraph wear period will correlate with objectively measured PA within an approximate window of time.

8.2.5 ADMINISTRATION OF QUESTIONNAIRES

Several questionnaires will be administered in this study at the baseline and follow-up assessment (see Section 11). For on-site visits, participant responses will be entered into an electronic data capture form. For home-visits, a paper form will be used to record responses and transcribed into the electronic data system after the visit by the research coordinator. All participants will be offered the ability to complete questionnaires for the follow-up assessments via an electronic survey (RedCap). Incomplete responses will be follow-up by phone or collected at the study visits.

8.2.6 DPP SESSION ATTENDANCE AND CONTENT TRACKING

Upon referral to a participating DPP, the research coordinator will create a record in a RedCap database linking the study participant to a specific DPP. This will serve as the mechanism of communicating a referral to the local DPP. Local DPP program coordinators will be asked to report attendance and outcome measures as outlined in Section 11.13. The local DPP programs will be asked to provide data they are already collecting from their participants as required by the CDC. Complete and validated data entry will be used to determine compensation to local DPPs as described in Section 5.6.2.2. Local DPPs will **not** have access to the JHU research databases.

8.3 SAFETY AND OTHER ASSESSMENTS

Since this study is focused on lifestyle modification (physical activity, healthy nutrition, and weight management) for diabetes prevention, it is considered to be a low-risk study with no obvious safety concerns. Participants will be informed of their laboratory results, height, and weight measurements at the study visit.

Participants' individual electronic medical records will be reviewed during screening and assessment of adverse events. Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements should be followed, as applicable.

A brief AE evaluation will be conducted (Section 11.20) at the 6 month and 12 month study visits.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

An AE is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects or other persons whether or not related to the investigational medical device.

- This includes events related to the investigational device.
- This includes events related to the procedures involved (any procedure in the clinical investigation plan).
- For users or other persons this is restricted to events related to the investigational device, i.e., HCPs.

The study team will record all of the adverse events documented in CRF. During the study all adverse events that occurred should be recorded in the CRF tables. Only clinically significant abnormal lab test results as determined by researchers will be reported as adverse event.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An Adverse Event that led to death; significant deterioration in health, that either resulted in life-threatening illness or injury, permanent impairment of a body function or permanent damage to a body structure, or required in-patient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent any one of the outcomes listed above.

- This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken, or b) intervention had not been made, or c) if circumstances had been less fortunate.
- A planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without a serious deterioration in health, in not considered to be a serious adverse event.

A serious adverse event may be an unanticipated adverse device effect. An unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

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

- Grade 1: Mild, asympomatic, or mild symptoms; clinical or diagnostic observations only; no intervention indicated
- Grade 2: Moderate, minimal, local, or noninvasive intervention indicated
- Grade 3: Severe or medical insignificant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatning consequences; urgent intervention indicated
- Grade 5: Death related to adverse event

8.4.3.2 RELATIONSHIP TO STUDY INTERVENTION

For all collected AE's, the clinician who examines and evaluates the subject will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Definitely related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the intervention (dechallenge) should be clinically plausible.
- Probably related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possibly related - There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g. the subject's

clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

- Not Related - The AE is completely independent of the study intervention, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.3.3 EXPECTEDNESS

Based on the experience from our pilot study, we do not anticipate any intervention-related AEs. Although the study intervention aims to increase PA, the emphasis is on increase in leisure time PA (i.e. walking) or light-moderate PA rather than moderate or strenuous exercise. Thus, exercise-related AEs, such as cardiovascular events, would be considered unexpected (unanticipated) in this study. On the other hand, muscle soreness, fatigue, or musculoskeletal injuries that relate directly to PA, would be considered expected (anticipated) AEs. Any participant who reports shortness of breath or chest pain during periods of PA will be required to undergo additional medical clearance before continuing in the study. The PI, Nestoras Mathioudakis, MD MHS, will be responsible for determining whether an AE is anticipated or unanticipated. An AE will be considered unanticipated if the nature, severity, or frequency of the event is not consistent with the risk information previously described for mHealth-based interventions targeting weight loss or physical activity.

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

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed by clinician), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

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

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

8.4.5 ADVERSE EVENT REPORTING

AEs will likely be reported first to research coordinators during scheduled study visits or during follow-up communications and will be documented in the participant's electronic case report form.

Research Coordinators are expected to enter adverse event information immediately into REDCap. The Research Coordinator will report the date of onset and resolution of the AE, description of the problem, adverse event preferred term using the MedDRA medical terminology, and the perceived grade of the AE. The Research Coordinator will contact the PI and Project Manager immediately by phone or text message for any perceived Grade 4 or higher AE (life-threatening consequences; urgent intervention indicated, or death related to adverse event). For all AEs entered into REDCap, the PI and project manager will immediately receive an email notification indicating that an adverse event has been reported, prompting further AE assessment. The PI will review the event and determine the grade, relatedness, and adverse event preferred term using the MedDRA medical terminology. If the lead PI (Dr. Nestoras Mathioudakis) is not available, the research coordinator will contact the co-investigator (Dr. Adrian Dobs) who will serve as a back-up.

The PI will record all reportable events with start dates occurring at any time after informed consent is obtained until 7 days (Grades 1-2) or 30 days (Grades 3-5) after the last day of study participation. At each study visit, the research coordinator will inquire about the occurrence of AEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The PI will inform the IRB, DSMB, and NIH program officer immediately when five grade 3 AEs are determined to be "probably related" to the study intervention. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible.

The DSMB will provide recommendations to the study team and sponsor (NIH). If the NIH determines that an unanticipated intervention effect presents an unreasonable risk to subjects, investigations, or parts of investigations presenting that risk will be terminated as soon as possible.

8.4.6 SERIOUS ADVERSE EVENT REPORTING

We will follow the Johns Hopkins Organizational Policy on Prompt Reporting of Reportable Events to the IRB.

- Any **unexpected death** that is/may be related to the study intervention will be reported to the IRB within 72 hours after discovery.
- **Unanticipated problems involving risks to subjects or others (UPIRSO)** will be reported promptly to the IRB (i.e. as soon as possible after the event is discovered but in all cases within 10 working days after discovery of the event). UPIRSO meet all the following criteria:
  - It is unexpected (in terms of nature, severity, or frequency) given the research procedures described in this study and the characteristics of the study population
  - It is related or possibly related to participation in the research
  - It places subjects or others at greater risk of harm than was previously known or recognized.
- Other SAEs, regardless of relationship, will be submitted to the study sponsor and the reviewing IRB during the annual report.
- All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and will be reported as soon as possible.

8.4.7 REPORTING OF PREGNANCY

Women who are pregnant at the time of screening or who are planning pregnancy during the study period will be excluded from participation in the study. Since pregnancy can result in spurious changes in A1C and would be expected to result in weight increases and possible higher BG due to insulin resistance, pregnancy during the study would be considered a protocol violation. Women who report becoming pregnant during the study will be withdrawn from the study.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

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

To satisfy the requirement for prompt reporting, UPs will be reported according to the Johns Hopkins University School of Medicine's Organizational policy on prompt reporting of reportable events.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This non-inferiority trial is designed to demonstrate that the Sweetch fully automated dDPP is no worse than the standard of care hDPP with respect to participant attainment of the CDC's benchmark for type 2 diabetes risk reduction. We will assume a percentage of "success" (i.e. attainment of the binary composite endpoint) in both the dDPP and hDPP of 50% and an equivalence limit, d, of 15%.

The percentage of participants that meet the primary endpoint will be compared between the two randomized groups. The null hypothesis is that the percentage for those in the standard treatment hDPP (π_s) is better than the percentage on the experimental fully automated treatment dDPP (π_e) by 15 or more percentage points, versus the alternative that the percentage for those on the new treatment is $\pi_s - 15$ or better, i.e.

H_0: $\pi_s \geq \pi_e + 15$

H_a: $\pi_s - 15 < \pi_e$

In selecting the equivalence margin for this non-inferiority trial, we considered the guidance provided by the U.S. FDA.[61] As we seek to evaluate a composite endpoint that has not previously been evaluated in a RCT, our assumptions are based mainly on the primary endpoint of the 5% weight loss outcome at 12 months (one of the three endpoints in our composite endpoint). Weight loss has been shown to be the most significant driver of type 2 diabetes risk reduction.[62] In the landmark DPP trial, the risk difference in attainment of 5% weight loss at 12 months among participants randomized to the intensive lifestyle intervention (active control in the present trial) vs. placebo was 46.7% (95% CI 43.1% - 50.2%).[63] Thus, the fraction of our equivalence margin to the entire effect of the active control is ~32%, which is significantly less than the recommended 50% threshold suggested by the FDA.

Considering the low rates of referral[19] and retention[64] in the hDPP, a 15% difference in the primary endpoint would be considered acceptable in our clinical judgment in order to gain the advantages of a cheaper and scalable alternative to the current available intervention. In addition, there is significant variability in outcomes attained in real-world DPPs to justify this equivalence margin. Among a subset of hDPPs participating in our study (N=5), the proportion of completers achieving the 5% weight loss outcome was 50% (range 47% to 60%) and the 4% weight loss and 150 minutes of PA outcome was 50% (range 29% to 80%) (unpublished data). Of note, however, the outcomes reported by hDPP are calculated based on program completers (per protocol analysis). In our trial, we plan on conducting an intent-to-treat analysis. Thus, we expect that the observed π_s will be closer to the 30-40% range based on participant-level data across the U.S. from the CDC's national DPP.

9.2 SAMPLE SIZE DETERMINATION

Under a 1:1 randomization design, with a significance level (alpha) of 5% and 80% power, and assuming 50% of the participants achieve the primary outcome in both arms, 138 participants are required to enroll in each of the two arms, for a total study sample size of n =276. Assuming a conservative attrition rate of 25% at 12 months, the adjusted sample size is set to 184 per group (368 total) to ensure the minimal necessary analyzable sample of 276 is retained. If there is truly no difference between the hDPP and dDPP, then 276 participants are required to be 80% sure that the upper limit of a one-sided 95% confidence interval will exclude a difference in favor of the hDPP of more than 15%. While it was previously noted that π_s will be closer to the 30-40% range, we used 50% in the non-inferiority sample size calculations as this choice yields the largest necessary sample size among all choices for π_s , and thus makes the study robust, in terms of statistical power, to other values for π_s.

9.3 POPULATIONS FOR ANALYSES

Consistent with the **intention-to-treat (ITT)** principle, results of all study participants will be evaluated according to initial randomization regardless of whether they adhered to their assigned treatment and regardless of protocol violations or deviations. Analyses of effectiveness endpoints, however, will exclude participants who withdraw from the study or withdraw consent. Effectiveness analyses will be performed for the ITT population. All primary statistical analyses of effectiveness measures will be unadjusted and two-sided tests of significance will be used. [65] A per-protocol analysis will also be conducted using the population of program completers in each group, as defined in Section 3.3, to benchmark outcomes against CDC standards.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

This clinical trial will be conducted under a common protocol with analyses conducted on pooled data from both sites. Data analyses will be conducted by a biostatistician. Exploratory data analysis will be performed to examine outliers, characterize the distributions of continuous and categorical measures, and track missing data. Mean, median, and frequency counts will be used to summarize baseline characteristics measured on a continuum, and proportions and frequency counts will be used for categorical measures. Baseline statistical differences in continuous measures between groups will be assessed using unpaired t-tests or Wilcoxon signed rank test, and statistical differences in categorical measures will be assessed using chi-square test or Fisher's Exact test as appropriate.

Between-group differences in primary and secondary outcomes will be evaluated in intention-to-treat analyses using mixed effects logistic regression models to account for potential within-program site clustering. For continuous measures in our secondary analyses, linear regression will be used to analyze the outcomes and for binary measures, logistic regression analyses will be used. Interaction terms will be used in regression models to evaluate effect modification.

9.4.2 MISSING OUTCOMES DATA

We anticipate that there will be a very low amount of missing data for the outcomes of A1C and weight for study completers, since both measures are collected by the technician at the study visits. However, since the outcome of PA measurement relies on participants to wear the ActiGraph devices at 1-month intervals, there may be more missing data for this outcome variable. If more than 5% of data for this outcome variable is missing, the primary analysis will be based on multiple imputation. A sensitivity analysis will also be done using a complete case analysis (i.e. participants with 100% of PA data) and if results differ significantly, the primary analysis will be interpreted in light of results from the sensitivity analysis.

9.4.3 BASELINE DESCRIPTIVE STATISTICS

Comparison of baseline characteristics between the intervention group and control groups will be conducted to assess the degree to which randomization was adequately achieved. Demographics (age, race, and gender), socioeconomic status (employment, education), comorbid conditions associated with metabolic syndrome (hypertriglyceridemia, hypertension, etc.) and factors relevant to the primary and secondary outcomes (baseline A1C, weight) will be reported. For normally distributed data, means and SDs will be shown. For non-normally distributed data, median and Interquartile range will be shown.

9.4.4 COMPARISONS BY STUDY SITE

This trial will enroll participants from Johns Hopkins Hospital (JHH) and Reading Hospital. These two sites differ substantially with respect to the sociodemographics of the patient populations they serve. In addition, access to in-person DPPs (i.e. number of available programs) differs by site. For all of the outcome measures, sensitivity analyses will be conducted to account for study site to evaluate whether there may be differences in the treatment or response to treatment by the study site (JHH vs. Reading).

9.4.5 COVARIATE ADJUSTMENT

We anticipate that randomization will minimize differences in participant characteristics that may be associated with the primary or secondary endpoints between the two groups. All primary statistical analyses will be unadjusted. However, if we identify differences in participant baseline characteristics, or exposure to potential confounders during the course of the study (e.g. steroid use, antihyperglycemic use), sensitivity analyses will be conducted to include these variables as covariates in multivariable logistic or linear regression models, as appropriate. These adjusted analyses will be viewed as supportive in interpreting the findings of the unadjusted analyses.

9.4.6 WITHIN-GROUP ANALYSES

Several exploratory analyses will be undertaken within the hDPP and DPP arms only to evaluate factors associated with success in either group. In addition, though not a primary focus of this trial, we will conduct a single arm analysis of the hDPP arm only to explore differences in outcomes by study site (JHH vs. Reading), hDPP program site and/or hDPP program type (hospital based, primary care clinic, church, community).

9.4.7 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary effectiveness endpoint will be analyzed using an intention to treat approach (ITT) using logistic regression models, where attainment of the CDC's benchmark for type 2 diabetes risk reduction will be the dependent variable and treatment group the

primary exposure variable. Covariate-adjusted models will include any variables that are identified to be statistically significantly different on univariate analysis between the two treatment groups at baseline or over the study period, including use of medications that could influence blood glucose (antihyperglycemics, steroids) and incident diabetes.

9.4.8 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will also be analyzed according to the ITT principle. Each of the individual outcomes in the CDC's benchmark for type 2 diabetes risk reduction (a composite endpoint) will be analyzed as a secondary endpoint at both the 6- and 12-month time points. As with the primary effectiveness endpoint, each outcome will be analyzed using logistic regression models. In addition, we will analyze change in A1C, absolute weight change and percentage weight change as continuous measures using linear regression models. Various physical activity measures will be analyzed as continuous measures, including average minutes/week of PA (light, moderate, intense), MET-hours per week of PA, and average number of steps per day. For responses from acceptability questionnaire (Likert-scale questions), non-parametric tests such as Spearman's correlation or chi-square test for independence will be used. For overall Likert scale scores, parametric tests such as Pearson's correlation or t-test will be used.

We anticipate that there will be a very low amount of missing data for the outcomes of A1C and weight for study completers, since both measures are collected by the research coordinator at the study visits. However, since the outcome of PA measurement relies on participants to wear the ActiGraph devices at 1-month intervals, there may be more missing data for this outcome variable. If more than 5% of data for this outcome variable is missing, the primary analysis will be based on multiple imputation. A sensitivity analysis will also be done using a complete case analysis (i.e. participants with 100% of valid PA data) and if results differ significantly, the primary analysis will be interpreted in light of results from the sensitivity analysis.

9.4.9 COST-EFFECTIVENESS ANALYSIS

We will analyze the cost-effectiveness of the dDPP and hDPP for a 12-month and lifetime horizon. For the 12-month horizon, we will evaluate the differences in costs and effects for participants in the dDPP and hDPP study arms. We do not anticipate substantial differences in healthcare utilization during the 12 months of the trial between the two arms, as participants have prediabetes rather than overt diabetes, and most relevant healthcare expenditures are expected to occur at the diabetes stage. For the lifetime horizon, we will construct a Markov model with model parameters populated from the trial results as well as other published literature. For example, we will estimate the cost savings associated with intermediate endpoints, such as percentage weight loss reduction, A1C reduction, or increased physical activity levels. Both analyses will be conducted from a health system perspective. Future costs and effects will be discounted at 3%.

Markov Model

For the lifetime horizon analysis, we will construct a Markov model to simulate hypothetical patients exposed to either a dDPP or hDPP. The model will consist of health states reflective of prediabetes and diabetes such as normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance, type 2 diabetes mellitus, and death. The transition probabilities between these health states will be calculated using data from the trial and published literature as needed. Again, given the relatively short duration of this trial, we do not expect a significant number of participants to convert from prediabetes to overt diabetes. Rather, we will estimate future diabetes incidence based on change in A1C as a proxy based on previously published studies. Life table estimates from the Centers for Disease Control and Prevention will be used to determine probabilities of death in all health states.

Costs

Costs will be estimated using a health system perspective and consist of formal healthcare costs and informal healthcare costs in accordance with best practices. Healthcare costs will be estimated using healthcare resources utilized multiplied by prices for resources. We anticipate that healthcare utilization costs during the trial will be similar between arms. Future healthcare utilization costs will be projected based on previously published literature in relation to our metabolic endpoints. We will use patient reported medical history and medication (Section 11.4) and healthcare utilization (Section 11.14) collected baseline, 6 months, and 12 months during the study to quantify healthcare resources utilized. Unit prices will be derived from public database and Medicare fee schedules. We will use published data to supplement cost data including cost estimates for each health state in the Markov model. Intervention costs will be estimated from data provided to us by the company developing the app, Sweetch Health, Ltd. Costs for the human coach intervention in the hDPP arm will be estimated using the Medicare Diabetes Prevention Program (MDPP) billing and fee schedule.

Effects

The effects for the cost-effectiveness analysis will be Quality-adjusted life years (QALYs). QALYs were selected because of their ability to capture both morbidity and mortality domains of health and they are used across existing literature. The calculation of QALYs will be based on a patient's time spent in a specific health state multiplied by the utility wait for that respective of the state. Utility weights will be derived from publish literature. For the 12-month analysis horizon, the time spent in each health state will be estimated using trial data. For the lifetime analysis horizon, a utility weight will be assigned to each health state and the running of the Markov model will provide the time spent for a hypothetical patient in each health state over their lifetime.

Analysis

The model will estimate incremental cost-effectiveness ratios (ICER) between the dDPP and hDPP interventions. The results will be compared to standard willingness-to-pay thresholds for similarly-scaled public health programs in the US. Cost-effectiveness will be determined if the incremental cost-effectiveness ratio (ICER) is below the willingness-to-pay threshold. Both univariate and probabilistic sensitivity analyses will be performed varying key transition, utility, and cost parameters. The results from a probabilistic sensitivity analysis will be used to construct a cost effectiveness acceptability curve.

9.4.10 SAFETY ANALYSES

Safety analyses will be performed on the ITT population. Summary tables (frequency tables) will be provided for safety variables.

9.4.11 PLANNED INTERIM ANALYSES

There is no planned interim analysis for this trial.

9.4.12 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual subject data will not be listed by measure and time point. Rather, summary measures will be reported for primary and secondary endpoints.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56 and/or the ICH E6.

10.1.2 INSTITUTIONAL REVIEW BOARD

Each participating institution will provide for the review and approval of this protocol and the associated informed consent documents and recruitment materials by an appropriate IRB registered with the OHRP. 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 changes are implemented to the study. All changes to consent form will be IRB approved; a determination will be made regarding whether previously consented subjects need to be re-consented.

10.1.3 INFORMED CONSENT PROCESS

10.1.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study procedures and risks are given to the subject and written documentation of informed consent is required prior to start intervention.

10.1.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator or study team member will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. An electronic consent form will be send to participants prior

to the baseline visit if requested so that they have time to review the consent form carefully. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or to think about it prior to agreeing to participate. Participants will have the opportunity to sign the consent form electronically through DocuSign or in-person at the baseline visit.

The paritcipant will sign the informed consent document prior to any procedures being done specially for the study. Participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

10.1.4 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agency, and Sweetch Health, Ltd. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

10.1.5 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

The study monitor, other authorized representatives of the sponsor, and representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to, the REDCap case report forms and electronic medical records of participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Johns Hopkins University School of Medicine. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Johns Hopkins University School of Medicine research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Johns Hopkins University School of Medicine.

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who

have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.6 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Johns Hopkins University School of Medicine. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Johns Hopkins University Data Archive (archive.data.jh.edu) for use by other researchers including those outside of the study. Permission to transmit data to the Johns Hopkins University Data Archive will be included in the informed consent.

10.1.7 KEY ROLES AND STUDY GOVERNANCE

Lead Principal Investigator (PI):

Nestoras Mathioudakis, MD MHS, Associate Professor of Medicine

Johns Hopkins University School of Medicine

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Baltimore, MD 21287

Email: nmathio1@jhmi.edu

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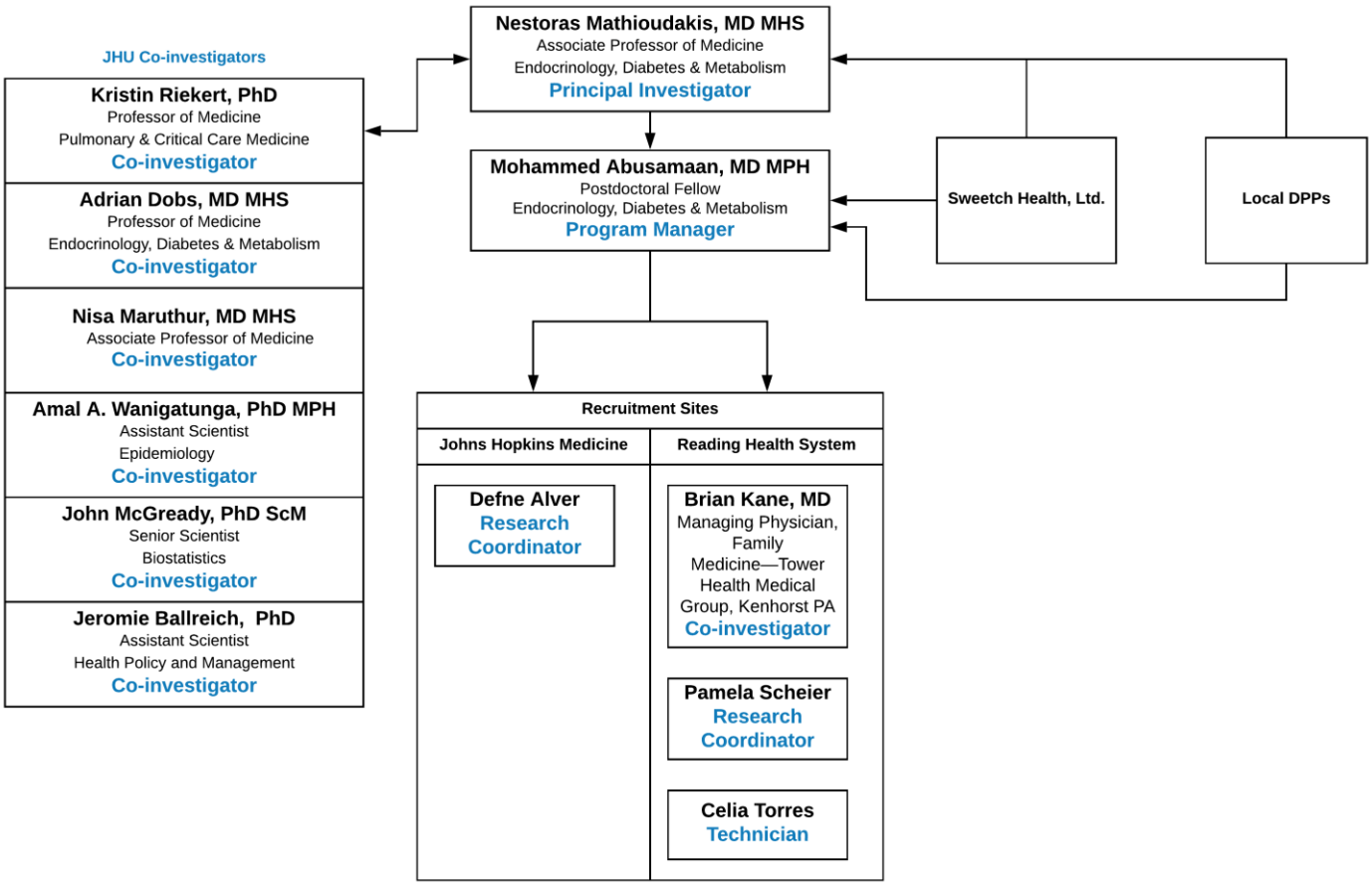


10.1.8 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including:

- Dr. Sara Benjamin-Neelon, Associate Professor in Public Health Promotion
- Dr. Seth Martin, Associate Professor of Cardiology
- Dr. Nae-Yuh Wang, Associate Professor, Biostatistician

Members of the DSMB are independent from the study conduct and free of conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study PI.

10.1.9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Audits will be conducted by the PI and Program Manager at a minimum of 3-month intervals to ensure monitoring practices are performed consistently across all participating sites.

Each clinical site will perform internal quality management of study conduct, data collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

10.1.10 QUALITY ASSURANCE AND QUALITY CONTROL

Since the primary endpoint of this study relies on a POC laboratory result, quality assurance and quality control regarding the POC A1C procedure are paramount. Study personnel performing the A1C testing will be required to undergo training overseen by the Johns Hopkins POCT office. QC will be assessed annually and a self-study written test will be conducted once per year. Staff personnel will be required to participate in proficiency testing (rotation among trained operators) at least once annually.

10.1.11 DATA HANDLING AND RECORD KEEPING

10.1.11.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

A central, electronic system will be used and data will be processed in an ongoing fashion. Study staff are expected to enter data in real-time using eCRFs in REDCap. Copies of the eCRF will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the subject's official electronic study record.

All screened and enrolled participants will be entered into CRMS, which will be used to generate the continuing enrollment reports for the IRB.

Clinical data (including AE's, concomitant medications) and laboratory data will be entered into REDCap (Research Electronic Data Capture), a 21 CFR Part 11-compliant data capture system provided by the Johns Hopkins University. The data system includes password protection and internal quality checks, such as missing data and automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

For dDPP arm, real-time data will be transmitted from the participant's smartphone to a secure server. All communication of data between participant devices and the server will be encrypted using secure sockets layer (SSL) certificates before storage. With the exception of data supplied by the participant using in-app questionnaires (first name or nickname, age, gender, satisfaction, etc.), no personal identifiers will be transmitted through the Sweetch app to the server. Data transfers between the Smartphones and the server will be encrypted and only accessible using SSL with a 128-bit encryption across all channels for the Smartphone to server and server to database. All data will be encrypted according to the latest encryption standards, authenticated, and checked for integrity. All clinical variables (e.g. weight, physical activity minutes/week) will be transmitted as numbers without any accompanying PHI, and will be linked to participant data on the protected server. Both the Sweetch Health, Ltd and the university investigators will have access to smartphone data in real-time, with access limited by valid user identification and passwords. All data access will be tracked by requiring unique usernames and password to log into the database to view information. Participants will create user accounts with a unique username and password. If a Smartphone is lost or replaced, the participant can use the same account credentials to continue using the Sweetch app on a new smartphone.

ActiGraph Centrepoint system will be used for the PA data colleted by ActiGraph GT9X-BT. The CentrePoint system provides a mechanism to automatically capture actigraphy data from the deployed activity monitors. The source data records are protected to enable their accurate and ready retrieval throughout the records. Authentication is required to access the system web portal for viewing or retrieving data. Each end-user will have a unique username (email address) and password. Data access is controlled to ensure that subject data can only be accessed by authorized users. The CentrePoint system and data storage are implemented within the infrastructure of Amazon Web Services (AWS) and Microsoft Azure. These vendors provide Actigraph an infrastructure as a service including security, data backups, and other datacenter essentials. Source data captured from activity monitors is stored in both Amazon's Simple Storage Service (S3) and Relational Data Storage (RDS) systems which are distributed throughout the United States. Web services and application interfaces are deployed within the Microsoft Azure cloud platform to provide a secure framework for our public facing cloud services.

The CentrePoint Study Admin System does not collect or store Personally Identifiable Information as defined by the U.S. Department of Commerce's National Institute of Standards and Technology (NIST). Each subject record is only required to have the following attributes: Subject Identifier (a unique identifier or code for linking to external systems) and Wear location of the monitor.

10.1.11.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 3 years have elapsed since the formal discontinuation of clinical development of this investigational product. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable.

10.1.12 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

- Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the DCC. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.13 PUBLICATION AND DATA SHARING POLICY

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

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. The PI, Dr. Nestoras Mathioudakis, who wrote this study protocol, will be the first or senior author on any manuscripts arising from the results of this study. The order of remaining authors will be determined according to the principles outlined by the Council of Science Editors.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.14 CONFLICT OF INTEREST POLICY

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

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
DPP	Diabetes prevention program
dDPP	Digital diabetes prevention program
hDPP	Human coach-based diabetes prevention program
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
JITAI	Just-in-time adaptive intervention
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NGSP	National Glycohemoglobin Standardization Program
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
WHO	World Health Organization

11 APPENDIX

11.1 PHYSICAL ACTIVITY READINESS QUESTIONNAIRE (PAR-Q)

PAR-Q Screening Tool (7-item)

Please read the questions below carefully and answer each one honestly. Please check YES or NO.

1. Has your healthcare provider ever said that you have a heart condition and that you should only do physical activity recommended by a healthcare provider?	☐ Yes
	☐ No
2. Do you feel pain in your chest when you do physical activity?	☐ Yes
	☐ No
3. In the past month, have you had chest pain when you were not doing physical activity?	☐ Yes
	☐ No

If participant answers **Yes** to one or more of the above questions, the study team will contact the primary care physician via electronic message or letter to obtain medical clearance prior to enrollment/randomization (See 11.3)

11.2 MEDICAL CLEARANCE LETTER

Dear [Provider Name]:

Your patient, _____, [date of birth], has expressed interest in participating in our clinical trial to evaluate the effectiveness of a digital diabetes prevention program versus in-person diabetes prevention programs in adults with prediabetes. This 12-month study will randomize participants to receive a lifestyle change intervention delivered by a local CDC recognized lifestyle change program or a digital diabetes prevention program consisting of an app and digital body weight scale. Both programs will encourage participants to follow the evidence-based recommendations for diabetes prevention, which include:

- 5% weight loss
- adherence to a healthy diet
- 150 minutes per week of moderate intensity physical activity

During the screening process for our study, your patient responded yes to one of more of the following screening questions on the Physical Activity Readiness Questionnaire, a tool designed to assess the safety/appropriateness of a patient before beginning a moderate intensity physical activity regimen (all questions above will be shown with positive responses indicated).

As you know, the Diabetes Prevention Program encourages gradual attainment of the moderate intensity physical activity goal, and your patient may still be an appropriate candidate for our study. Please note that the DPP is NOT an exercise program and aims for gradually attainment of moderate intensity exercise.

We are seeking your medical advice and clearance before enrolling your patient in our trial. Based on your review of the patient's health status, which of the following do you recommend for your patient:

___ Patient is appropriate for the study and can engage in moderate or brisk physical activity, starting slowly and building up gradually.

___Patient is not appropriate for the study.

___I require additional information about your study before making an assessment. Please contact me at the following phone number: _____.

Provider Name: _____

Provider Signature: _____ Date: _____

Sincerely,

Nestoras Mathioudakis, MD MHS

Principal Investigator

11.3 DEMOGRAPHICS

Demographics Questionnaire (15-item)

Enrollment ID	Unique Record ID for each participant
Screening ID	Will be used to automatically pull information from screening database for participants who pass screening and are randomized and enrolled
First Name	
Middle Initial	
Last Name	
Medical Record Number (if patient in health system)	
Date of birth	
Sex	☐ Female
	☐ Male
Marital Status	☐ Single
	☐ Married
	☐ Significant Other
	☐ Divorced
	☐ Legally Separated
	☐ Widowed
	☐ Declined to Answer
	☐ Other
Race	☐ American Indian or Alaskan Native
	☐ Asian
	☐ Black of African American
	☐ White or Caucasian
	☐ More than One Race
	☐ Native Hawaiian or Other Pacific Islander
	☐ Declined to Answer
	☐ Other. Specify: _____
	☐ Unknown
Ethnicity	☐ Not Hispanic or Latino
	☐ Hispanic or Latino
	☐ Declined to Answer
	☐ Unknown
Street Address	
Zip Code	
	☐ Elementary School

Educational Attainment	☐ Middle School
	☐ High School Graduate
	☐ Some College or More
	☐ Associate's Degree or equivalent level
	☐ Bachelor's Degree or equivalent level
	☐ Master's Degree or equivalent level
	☐ Doctoral Degree or equivalent level

11.4 MEDICAL HISTORY AND MEDICATIONS

	Past Medical History (resolved)	**Active diagnosis or problem**
Hypertension (high blood pressure)	☐	☐
Hypertriglyceridemia (high triglycerides)	☐	☐
Hyperlipidemia (high cholesterol)	☐	☐
Coronary artery disease (heart disease)	☐	☐
Polycystic Ovarian Syndrome (PCOS)	☐	☐
Smoking	☐	☐
Depression	☐	☐
Anxiety	☐	☐
Bipolar disorder	☐	☐
Stroke	☐	☐
Transient ischemic attack (TIA or mini stroke)	☐	☐
Peripheral vascular disease	☐	☐
Back pain	☐	☐
Osteoarthritis	☐	☐
Hypothyroidism	☐	☐
Asthma	☐	☐
Chronic Obstructive Pulmonary Disease (COPD)	☐	☐
Hepatitis B	☐	☐
Hepatitis C	☐	☐
Malignancy	☐	☐
Insomnia or sleep disorder	☐	☐
List any other past medical history of active diagnosis/problem not listed above.		

List the generic names of each medication you are currently taking.	

11.5 EXERCISE STAGE OF CHANGE QUESTIONNAIRE

Exercise Stage of Change Questionnaire (4-item)

For each of the following questions, please select Yes or No.

Physical activity or exercise includes activities such as walking briskly, jogging, bicycling, swimming, or any other activity in which exertion is at least as intense as these activities.

1. I am currently physically active (at least 30 minutes per week).	☐ Yes ☐ No
2. I intend to become more physically active in the next 6 months.	☐ Yes ☐ No

For activity to be regular, it must add up to a total of 30 minutes per day and be done at least 5 days per week. For example, you could take on 30-minute walk or take three 10-minute walks for a total of 30 minutes.

3. I currently engage in **regular** physical activity.	☐ Yes ☐ No
4. I have been **regularly** physically active for the past 6 months.	☐ Yes ☐ No

Scoring Key:

- *No* to 1, 2, 3, and 4 = Pre-contemplation stage
- *No* to 1,3,and 4, Yes to 2= Contemplation stage
- *Yes* to 1 and 2, No to 3 and 4= Preparation stage
- *Yes* to 1 and 3, Yes or No to 2, No to 4= Action stage
- *Yes* to 1,3,and 4, Yes or No to 2= Maintenance stage

11.6 SELF-REPORTED PHSICAL ACTIVITY

Administered via electronic survey or phone call in the week preceding Actigraph measurement.

How many minutes of moderate or brisk physical activity did you complete in the preceding week? Examples of moderate or vigorous activity can be found here.	(Be sure to report your activity in total minutes per week, NOT hours. For example, if you exercised for 30 minutes on 5 days in the past week, enter 150.)
Please provide any comments about your physical activity in the past week (optional).	

11.7 "STARTING THE CONVERSATION" BRIEF DIETARY ASSESSMENT

"Starting the Conversation" Brief Dietary Assessment (8-item)

Over the past few months:			
1. How many times a week did you eat fast food meals or snacks?	☐ Less than 1 time	☐ 1-3 times	☐ 4 or more times
2. How many servings of fruit did you eat each day?	☐ 5 or more	☐ 3-4	☐ 2 or less
3. How many servings of vegetable did you eat each day?	☐ 5 or more	☐ 3-4	☐ 2 or less
4. How many regular sodas or glasses of sweet tea did you drink each day?	☐ Less than 1	☐ 1-2	☐ 3 or more
5. How many times a week did you eat beans (like pinto or black beans), chicken, or fish?	☐ 3 or more times	☐ 1-2 times	☐ Less than 1 time
6. How many times a week did you eat regular snack chips or crackers (not low-fat)?	☐ 1 time or less	☐ 2-3 times	☐ 4 or more times
7. How many times a week did you eat desserts and other sweets (not the low-fat kind)?	☐ 1 time or less	☐ 2-3 times	☐ 4 or more times
8. How much margarine, butter, or meat fat do you use to season vegetables or put on potatoes, bread, or corn?	☐ Very little	☐ Some	☐ A lot

Scoring Key: The left column indicates the most healthful dietary practices (scored 0); the center column indicates less healthful practices (scored 1); and the right column indicates the least healthful practices (Scored 2). Item scores are added to create a summary score (range 0-16), with lower scores reflecting more healthful diet.

11.8 APPS AND DEVICES QUESTIONNAIRE

Apps and Devices Questionnaire (7-item)

Are you currently using any **apps to help monitor your weight**?	☐ Yes. If yes, please specify which one(s).
	☐ No
Do you currently have a **body weight scale at home**?	☐ Yes
	☐ No
Do you currently have a **digital body weight scale** (Wi-fi or Bluetooth enabled) that automatically connects with your smartphone?	☐ Yes
	☐ No
Are you currently using any apps to help you monitor your **nutrition or diet**?	☐ Yes. If yes, please specify which one(s).
	☐ No
Are you currently using any apps to help you monitor your **physical activity or exercise**?	☐ Yes. If yes, please specify which one(s).
	☐ No
Are you currently using any apps to **track your health data**, such as labs or imaging results?	☐ Yes. If yes, please specify which one(s).
	☐ No
Are you currently using any **wearable fitness trackers**?	☐ Yes. If yes, please specify which one(s).
	☐ No

11.9 NPART SURVEY

NPART Survey (Adapted) (28-item*)

The NPART (Evaluation of Non-Participation in Digital Health Research) survey is a validated instrument to characterize non-participation in digital health research.[51] The survey was developed and evaluated in an European population. We have adapted the questions for the U.S. setting. For the purposes of this trial, the results of this survey will not be used to exclude eligible participants. Rather, responses will be analyzed as predictors of responsive to digital vs. in-person DPPs.

What is your current employment status?	☐ 1 Employed. _____ hours per week
	☐ 0 Not employed, looking for work
	☐ 0 Not employed, NOT looking for work
	☐ 0 Retired
	☐ 0 Disabled, not able to work
What is/was your primary **job**?*	
Which of the following categories best describes your primary **area of employment**?	☐ 1 Manager
	☐ 2 Professionals
	☐ 3 Technicians and Associate Professionals
	☐ 4 Clerical Support Workers
	☐ 5 Services and Sales Workers
	☐ 6 Skilled Agricultural, Forestry, and Fishery Workers
	☐ 7 Craft and Related Trade Workers
	☐ 8 Plants and Machine Operators, and Assemblers
	☐ 9 Elementary Occupations
	☐ 10 Armed Forces Occupations
	☐ 11 I have never worked
*Do you have a **partner**?**	☐ 1 Yes
	☐ 0 No
*Do you live **alone**?**	☐ 1 Yes
	☐ 0 No
How often in the past 12 months did you **care for a sick or disabled person**?	☐ 4 Almost daily
	☐ 3 Almost every week
	☐ 2 Almost every month
	☐ 1 Less often
During the past 12 months, how often have you participated in **social activities** such as volunteer or charity work, attended a training course visited a sports club, social club or	☐ 4 Almost daily

other kind of club, participated in the activities of a religious organization, or participated in the activities of a political or community-related organization?	☐ 3 Almost every week ☐ 2 Almost every month ☐ 1 Less often
During the past 12 months, how often did you **have contact with your children**, either in-person, by phone, by mail, by e-mail or by other electronic means?	☐ 5 Almost daily ☐ 4 Almost every week ☐ 3 Almost every month ☐ 2 Less often ☐ 1 I do not have any children
During the past 12 months, how often did you have contact with or meet with your **friend and/or neighbors**?	☐ 4 Almost daily ☐ 3 Almost every week ☐ 2 Almost every month ☐ 1 Less often
In the past 12 months, would you like to have had more **contact with** or met more frequently your children, relative, and/or friends?	☐ 4 Much more ☐ 3 Little more ☐ 2 Not more ☐ 1 Less
How would you rate **your memory** at the present time? Would you say it is..	☐ 5 Very good ☐ 4 Good ☐ 3 Fair ☐ 2 Bad ☐ 1 Very bad
How is your **health** in general? It is …	☐ 5 Very good ☐ 4 Good ☐ 3 Fair ☐ 2 Bad ☐ 1 Very bad
During the last 6 months, to what extent have you been **limited because of your health** in activities people usually do? Would you say you have been….	☐ 3 Severely limited ☐ 2 Limited but not severely ☐ 1 Not limited at all
Do you **require any help** taking care of your health, such as taking medications or attending/booking appointments?	☐ 4 Almost daily ☐ 3 Almost every week ☐ 2 Almost every month ☐ 1 Less often

How would you rate your **quality of life**?	☐ 5 Very good
	☐ 4 Good
	☐ 3 Neither poor nor good
	☐ 2 Poor
	☐ 1 Very poor
*NPART is 36 item questionnaire, but 8 questions appear on our demographics survey and will not be repeated.	

Now there are some questions regarding the use of the internet and technology.

How well do you think you master the following activities?	Excellent	Good	Fair	Poor	Very Poor
Sending/receiving e-mails	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Buying goods or services over the Internet	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Reading or downloading online news, newspaper or magazines	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Internet banking	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Accessing institutions	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Playing or downloading games, images, films, or music	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Listening to web radio or watching web television	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Telephoning or making video calls over the Internet	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Social networking, for example Facebook or Twitter	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Posting messages to chat sites, blogs or forums, or instant messaging	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Do you think using a mobile phone, smartphone, tablet or the Internet might…	Yes	Maybe	No
Support you in performing everyday activities (e.g. remembering medications and appointments, calling for emergency)	☐ 3	☐ 2	☐ 1
Be useful in **monitoring** your health (e.g. sleeping, diet, blood pressure, general symptoms)	☐ 3	☐ 2	☐ 1
Be useful for contacting **nurses, physicians, and other healthcare professionals**	☐ 3	☐ 2	☐ 1

Finally, we would like to ask you how often you use:	Daily	At least once per week	At least once per month	Less than once per month	Never
Computer	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Mobile phone	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Smartphone and/or tablet	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Smart television and/or games console	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

11.10 ACCEPTABILITY QUESTIONNAIRE

Acceptability Questionnaire (32-item)

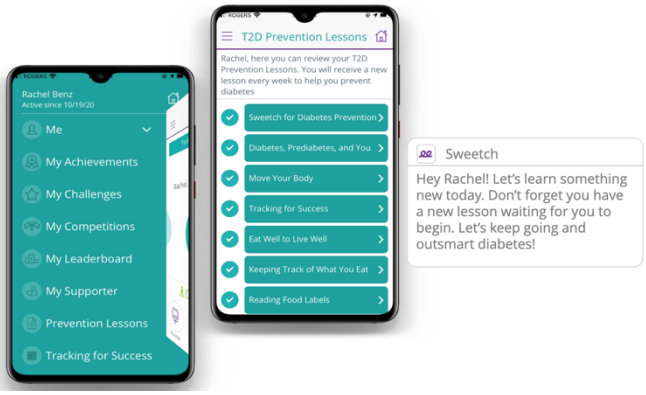
Please rate your diabetes prevention program from strongly disagree to strongly agree to strongly agree:	**Strongly disagree**	**Disagree**	**Neutral**	**Agree**	**Strongly agree**
1. The [Sweetch DPP/ In-person DPP] gave me information and advice in an **interesting** way.	☐1	☐2	☐3	☐4	☐5
2. I **had fun** using the [Sweetch DPP/ In-person DPP]	☐1	☐2	☐3	☐4	☐5
3. The [Sweetch DPP / In-person DPP] **motivated me** to make lifestyle changes to prevent diabetes.	☐1	☐2	☐3	☐4	☐5
4. The [Sweetch DPP/ In-person DPP] **is appropriate** for patients like me with pre-diabetes.	☐1	☐2	☐3	☐4	☐5
5. I **felt capable** of meeting the expectations of the [Sweetch DPP/ In-person DPP]	☐1	☐2	☐3	☐4	☐5
6. The [Sweetch DPP/ In-person DPP] **helped me to become or stay active**.	☐1	☐2	☐3	☐4	☐5
7. The [Sweetch DPP/ In-person DPP] **helped me to adhere to a healthy diet**.	☐1	☐2	☐3	☐4	☐5
8. The [Sweetch DPP/ In-person DPP] **helped me to achieve or maintain a healthy body weight.**	☐1	☐2	☐3	☐4	☐5
9. The **information** collected by the [Sweetch DPP/ In-person DPP] **would be useful for my doctor to see.**	☐1	☐2	☐3	☐4	☐5
10. The [Sweetch DPP/ In-person DPP] **helped me to lower my risk of developing diabetes.**	☐1	☐2	☐3	☐4	☐5
11. The [Sweetch DPP/In-person DPP] **provided me useful tools** to succeed in preventing diabetes.	☐1	☐2	☐3	☐4	☐5
12. The [Sweetch DPP/ In-person DPP] was **easy to use** with my daily routine.	☐1	☐2	☐3	☐4	☐5
13. The **instructions** for the [Sweetch DPP/ In-person DPP] **were helpful**.	☐1	☐2	☐3	☐4	☐5
14. **Information** from the [Sweetch DPP/ In-person DPP] was **provided in a way I could understand**.	☐1	☐2	☐3	☐4	☐5
15. The [Sweetch DPP/In-person DPP] was **frustrating**.	☐5	☐4	☐3	☐2	☐1
16. It was **easy to move between the** [Sweetch app screens / In-person DPP course materials or sessions].	☐1	☐2	☐3	☐4	☐5

17. The [Sweetch DPP/ In-person DPP] **did not have** [functions/information] I thought it would.	☐5	☐4	☐3	☐2	☐1
18. The [Sweetch DPP/In-person DPP] **was convenient** for me.	☐1	☐2	☐3	☐4	☐5
19. The [Sweetch app/ In-person DPP course materials or sessions] were **logically ordered**.	☐1	☐2	☐3	☐4	☐5
20. The [graphics and icons/ visual materials] were consistently **high quality.**	☐1	☐2	☐3	☐4	☐5
21. I **liked the way** the [Sweetch app/ In-person DPP course materials] **looked**.	☐1	☐2	☐3	☐4	☐5
22. The layout and appearance made the [Sweetch app/ In-person DPP course materials] **easy to [navigate/follow].**	☐1	☐2	☐3	☐4	☐5
23. I **trusted** the information from the [Sweetch app/In-person DPP] was accurate.	☐1	☐2	☐3	☐4	☐5
24. The information provided by the [Sweetch app/ In-person DPP] was **relevant** to me.	☐1	☐2	☐3	☐4	☐5
25. The [graphs and dashboards/ graphs and charts] made it **easier to understand the information**.	☐1	☐2	☐3	☐4	☐5
26. I **learned new things** about prediabetes from the [Sweetch app/In-person DPP].	☐1	☐2	☐3	☐4	☐5
27. I **would like to keep using** the [Sweetch DPP/ In-person DPP].	☐1	☐2	☐3	☐4	☐5
28. I **would recommend** the [Sweetch DPP/In-person DPP] to people with prediabetes.	☐1	☐2	☐3	☐4	☐5
29. I **am satisfied** with the [Sweetch DPP/In-person DPP].	☐1	☐2	☐3	☐4	☐5
30. The good things about the [Sweetch DPP/In-person DPP] **weren't worth how much effort I had to put in**.	☐5	☐4	☐3	☐2	☐1
31A. For dDPP arm only: I think I **would have preferred an in-person diabetes prevention program** over the digital version.	☐5	☐4	☐3	☐2	☐1
31B. For hDPP arm only: I think I **would have preferred a digital diabetes prevention program** over the in-person version.	☐5	☐4	☐3	☐2	☐1
32. Please provide any comments regarding your overall experiences with the [dDPP or in-person DPP]					

Scoring: Sum up all responses to questions 1-31, divide by 155 and multiply by 100 to calculate percentage score out of 100%. Range of possible scores is 20% (lowest acceptability) to 100% (highest possible acceptability).

11.11 SWEETCH APP FEATURES QUESTIONNAIRE

Sweetch App Features Questionnaire (23-item)



Please respond to each question from strongly disagree to strongly agree.	**Strongly Disagree**	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**
1. The Sweetch App **push notifications (messages)** helped me to achieve my goals in the program	☐1	☐2	☐3	☐4	☐5
2. The Sweetch App **"My Achievements"** feature helped me to achieve my goals in the program.	☐1	☐2	☐3	☐4	☐5
3. The Sweetch App **"My Challenges"** feature helped me to achieve my goals in the program.	☐1	☐2	☐3	☐4	☐5
4. The Sweetch app **"My Competitions"** feature helped me to achieve my goals in the program.	☐1	☐2	☐3	☐4	☐5
5. The Sweetch app **"My Leaderboard"** feature helped me to achieve my goals in the program.	☐1	☐2	☐3	☐4	☐5
6. The Sweetch app **"My Supporter"** feature helped me to achieve my goals in the program.	☐1	☐2	☐3	☐4	☐5
7. The Sweetch app **"T2D Prevention Lessons"** helped me to achieve my goals in the program.	☐1	☐2	☐3	☐4	☐5
8. The Sweetch app **"Activity Tracking**" helped me to achieve my goals in the program.	☐1	☐2	☐3	☐4	☐5
9. The Sweetch app **"Weight Tracking"** helped me to achieve my goals in the program.	☐1	☐2	☐3	☐4	☐5
10. The Sweetch app **"Habits"** feature helped me to achieve my goals in the program.	☐1	☐2	☐3	☐4	☐5
11. The **Digital Body Weight scale** helped me to achieve my goals in the program.	☐1	☐2	☐3	☐4	☐5
12. The Sweetch app **accurately measured my physical activity** overall.	☐1	☐2	☐3	☐4	☐5

13. The Sweetch app **did not capture certain types of physical activity** that I performed.	☐5	☐4	☐3	☐2	☐1
14. I **would have liked to be able use a wearable fitness tracker** with the Sweetch app.	☐5	☐4	☐3	☐2	☐1
15. The push notifications I received felt **personalized** (i.e. tailored to me).	☐1	☐2	☐3	☐4	☐5
16. The push notifications came to me at the **right time** in the day.	☐1	☐2	☐3	☐4	☐5
17. The push notifications usually came to me when I was in the **right place** to be able to respond.	☐1	☐2	☐3	☐4	☐5
18. The push notifications came at the right **frequency/amount.**	☐1	☐2	☐3	☐4	☐5
19. It felt like the recommendations that I received in the push notifications were **coming from a human coach**.	☐1	☐2	☐3	☐4	☐5
20. I usually **ignored** the push notifications.	☐5	☐4	☐3	☐2	☐1
21. I found the push notifications **annoying or bothersome**.	☐5	☐4	☐3	☐2	☐1
22. Please provide any comments/feedback regarding the Sweetch app overall or its individual features.					

	Not at all likely										**Extremely likely**
23. How likely is it that you would **recommend** the Sweetch Digital Diabetes Prevention Program to a friend or colleague?	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10

Scoring: Sum up responses to items 1 to 21, divide by 105 and multiply by 100 to calculate score out of 100%. Range of scores 20% (lowest usability/acceptability) to 100% (highest usability/acceptability)

Net Promoter Score (Q. 23) Scoring:

The Net Promoter Score is calculated based on responses to a single question: *How likely is it that you would recommend the Sweetch digital diabetes prevention program to a friend or colleague?* The scoring for this answer is most often based on a 0 to 10 scale. A score of 0-6 is considered a detractor, 7-8 passive, and 9-10 a promoter. The Net Promoter Score is calculated by subtracting the % promoters - % detractors = NPS.

11.12 WHO-5 WELL-BEING INDEX

The 5-item WHO-5 index[66] is a widely used questionnaire to assess subjective psychological well-being.

Please indicate for each of the 5 statements which is closest to how you have been feeling over the past 2 weeks.

Over the past 2 weeks…	All of the time	Most of the time	More than half the time	Less than half the time	Some of the time	At no time
… I have felt cheerful and in good spirits	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
… I have felt calm and relaxed	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
….I have felt active and vigorous	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
…I woke up feeling fresh and rested	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
… my daily life has been filled with things that interest me	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

Scoring: The raw score ranging from 0 to 25 is multiplied by 4 to give the final score from 0 representing the worse imaginable well-being to 100 representing the best imaginable well-being.

11.13 LOCAL DPP DATA COLLECTION

Participating DPPs will be asked to enter the following data for participants referred to their program using a RedCap electronic data capture form:

Organization Code (assigned by CDC)	
Delivery Mode	☐ 1= In-person
	☐ 2= On-line (*Not permitted for trial)
	☐ 3= Distance learning (**Only synchronous video/phone conference will be permitted)
Session Type	☐ C= Core Session
	☐ CM= Core maintenance session
	☐ MU-C= make-up sessions in the core phase
	☐ MU-CM= make up session in the core maintenance phase
Session Date	MM/DD/YY
Participant's weight (recorded to nearest lb.)	
Participant's physical activity (in minutes).	Number of self-reported minutes of moderate or brisk PA participant completed in the preceding week. If a participant reports doing no activity during the preceding week, then zero (0) minutes should be recorded.
Curriculum Used:	☐ 2021 National DPP
	☐ Prevent T2

Curriculum Topic(s) covered: select all that apply.	
2012 National DPP Curriculum	PreventT2 Curriculum
Core Phase (Months 1-6)	
☐ Welcome to the National Diabetes Prevention Program	☐ Program Overview & Introduction to the Program
☐ Being Active- A Way of Life	☐ Get Active to Prevent T2
☐ Move Those Muscles	☐ Track Your Activity
☐ Be a Fat and Calorie Detective	☐ Track Your Food
☐ Three Ways to Eat Less Fat and Fewer Calories	☐ Eat Well to Prevent T2
☐ Jump Start Your Activity Plan	☐ Get More Active
☐ Tip the Calorie Balance	☐ Burn More Calories Than You Take In

☐ Healthy Eating	☐ Shop and Cook to Prevent T2
☐ You Can Manage Stress	☐ Manage Stress
☐ The Slippery Slope of Lifestyle Change	☐ Find Time for Fitness
☐ Make Social Cues Work for You & Talk Back to Negative Thoughts	☐ Cope with Triggers
☐ Heart Health from months 7-12	☐ Keep Your Heart Healthy
☐ Problem Solving	☐ Take Charge of Your Thoughts
☐ Taking Charge of What's Around You	☐ Get Support
☐ Four Keys to Healthy Eating Out	☐ Eat Well Away from Home
☐ Ways to Stay Motivated	☐ Stay Motivated to Prevent T2
Core Maintenance Phase (Months 7-12)	
☐ Welcome to Sessions 7-12	☐ N/A
☐ Balance Your Thoughts for Long-Term Maintenance	☐ When Weight Loss Stalls
☐ Staying on Top of Physical Activity	☐ Take a Fitness Break
☐ Stepping up to Physical Activity	☐ Stay Active Away from Home
☐ A Closer Look at Type 2 Diabetes	☐ More About T2
☐ More Volume, Fewer Calories	☐ More About Carbs
☐ Fats- Saturated, Unsaturated, and Trans Fat	☐ Eat Well to Prevent T2 from Months 1-6
☐ Healthy Eating – Taking it One Meal at a Time & Food Preparation and Recipe Modification	☐ Have Healthy Food You Enjoy
☐ Stress and Time Management	☐ Get Enough Sleep
☐ Preventing Relapse	☐ Get Back on Track
☐ Handling Holidays, Vacations, and Special Events	☐ Eat Well Away from Home from months 1-6
☐ Heart Health	☐ Stay Active to Prevent T2
☐ Healthy Eating with Variety and Balance	☐ Shop and Cook to Prevent T2 from months 1-6
☐ Looking Back and Looking Forward	☐ Prevent T2- for Life!

11.14 HEALTHCARE UTILIZATION

How many times did you visit your primary care provider in the past 6 months?	
How many times did you visit a non-primary care specialist in the past 6 months?	
Why did you see a non-primary care specialist?	
How many times were you hospitalized in the last 6 months?	
Why were you hospitalized?	
How many times did you go to the emergency department in the past 6 months?	
Why did you visit the emergency department?	
What is the name of your primary care provider?	
What is your primary care provider's address?	

11.15 HOME STUDY VISIT SAFETY PROCEDURES (JHU SITE ONLY)

For participants recruited from the JHU site, the option of study visits conducted in the participant's home will be provided to increase recruitment and retention. Community-based research is generally safe but there are risks. The following procedures will be followed to ensure that the privacy/confidentiality of the participant and that the safety and security of all staff are protected in the rare event of urgent or emergency situations.

Participant Privacy/Confidentiality

All home visits will only be conducted by Johns Hopkins study team members. No non-study team members will be present for the home visit aside from the study participants (and residents of the home) themselves.

Prior to the home study visit, the research coordinator will inform the participant that informed consent will be obtained during the home visit and that ensuring privacy and confidentiality in the home will be the participant's responsibility.

COVID-19 Safety Plan

See Section 11.19

Reportable Situations

The informed consent form will specify the research team will be required to i) report any information regarding potential child abuse or neglect reported by the participant or observed at the home during the research visit and ii) report if there is a reasonable suspicion, based on information provided by the participant or observed during the research visit at the home, that the participant may present a danger or home to others or that they participant may harm themselves unless protective measures are taken. It will be communicated that the study team is not directly seeking this information as part of the study.

Daylight Hours

Study visits will be conducted so that the entire visit can be completed during daylight hours.

Emergencies and Urgent Matters

If an emergency or urgent matter occurs, the staff member must call the PI, Dr. Nestoras Mathioudakis. If unable to reach one of the PIs, the staff member will call the Study Program Manager, followed by Co-PIs. The staff member should continue to call until s/he reaches a study team member. If an important but non-urgent matter arises, staff members will call a supervisor or PI.

Study Cell Phones

All staff members working in the community, clinic, or with patients after-hours are required to program the office and cell phone numbers for the Study PIs, research coordinator(s), and supervisor(s) into their study provided cell phones. It is recommended that they also program the contact information of their co-workers assigned to the same study or studies as they are. All staff members must ensure that their study-provided cell phone is charged and functioning before going into the community. Staff driving for work must follow state driving laws in regards to the use of a mobile phone.

Staff Safety Concerns

All staff members are encouraged to raise safety concerns during weekly meetings. Discussing concerns, experiences, situations, and possible solutions will benefit the entire staff. If a staff member has an urgent concern or prefers to speak in private, s/he may call the PIs or supervisor with any safety concern.

Perceived Unsafe Situation

Upon arriving at a participant appointment or an off-campus meeting, if a staff member deems the situation unsafe, s/he may leave the location. As soon as s/he is safely able to do so, s/he must contact the PIs or supervisor to inform them of the situation.

No Tablets or Computers

Survey forms will be printed out in advance of the visit and data will be recorded on paper. An electronic survey will also be sent out in advance of the visit for participants who are willing and able to complete the survey electronically. This will minimize the amount of time spent in the participant's home. If data are collected on paper, results will be transcribed after the visit into the electronic data capture form. This will minimize the potential for theft of tablets and computers. In addition, Wi-Fi access cannot be guaranteed in the participant's home.

11.16 PREDIABETES RISK TEST

Prediabetes Risk Test

NATIONAL DIABETES PREVENTION PROGRAM

1. How old are you?

Write your score in the boxes below

Younger than 40 years (0 points)
40–49 years (1 point)
50–59 years (2 points)
60 years or older (3 points)

2. Are you a man or a woman?

Man (1 point) Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?

Yes (1 point) No (0 points)

4. Do you have a mother, father, sister, or brother with diabetes?

Yes (1 point) No (0 points)

5. Have you ever been diagnosed with high blood pressure?

Yes (1 point) No (0 points)

6. Are you physically active?

Yes (0 points) No (1 point)

7. What is your weight category?

(See chart at right)

Total score:

Height	Weight (lbs.)		
4'10"	119-142	143-190	191+
4'11"	124-147	148-197	198+
5'0"	128-152	153-203	204+
5'1"	132-157	158-210	211+
5'2"	136-163	164-217	218+
5'3"	141-168	169-224	225+
5'4"	145-173	174-231	232+
5'5"	150-179	180-239	240+
5'6"	155-185	186-246	247+
5'7"	159-190	191-254	255+
5'8"	164-196	197-261	262+
5'9"	169-202	203-269	270+
5'10"	174-208	209-277	278+
5'11"	179-214	215-285	286+
6'0"	184-220	221-293	294+
6'1"	189-226	227-301	302+
6'2"	194-232	233-310	311+
6'3"	200-239	240-318	319+
6'4"	205-245	246-327	328+
	1 Point	2 Points	3 Points
	You weigh less than the 1 Point column (0 points)		

Adapted from Bang et al., Ann Intern Med 151:775-783, 2009. Original algorithm was validated without gestational diabetes as part of the model.

If you scored 5 or higher

You are at increased risk for having prediabetes and are at high risk for type 2 diabetes. However, only your doctor can tell for sure if you have type 2 diabetes or prediabetes, a condition in which blood sugar levels are higher than normal but not high enough yet to be diagnosed as type 2 diabetes. **Talk to your doctor to see if additional testing is needed.**

If you are African American, Hispanic/Latino American, American Indian/Alaska Native, Asian American, or Pacific Islander, you are at higher risk for prediabetes and type 2 diabetes. Also, if you are Asian American, you are at increased risk for type 2 diabetes at a lower weight (about 15 pounds lower than weights in the 1 Point column). Talk to your doctor to see if you should have your blood sugar tested.

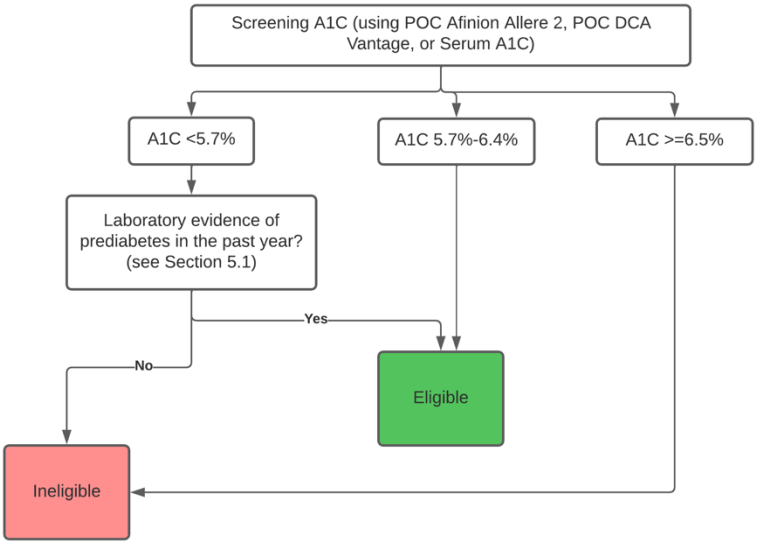
You can reduce your risk for type 2 diabetes

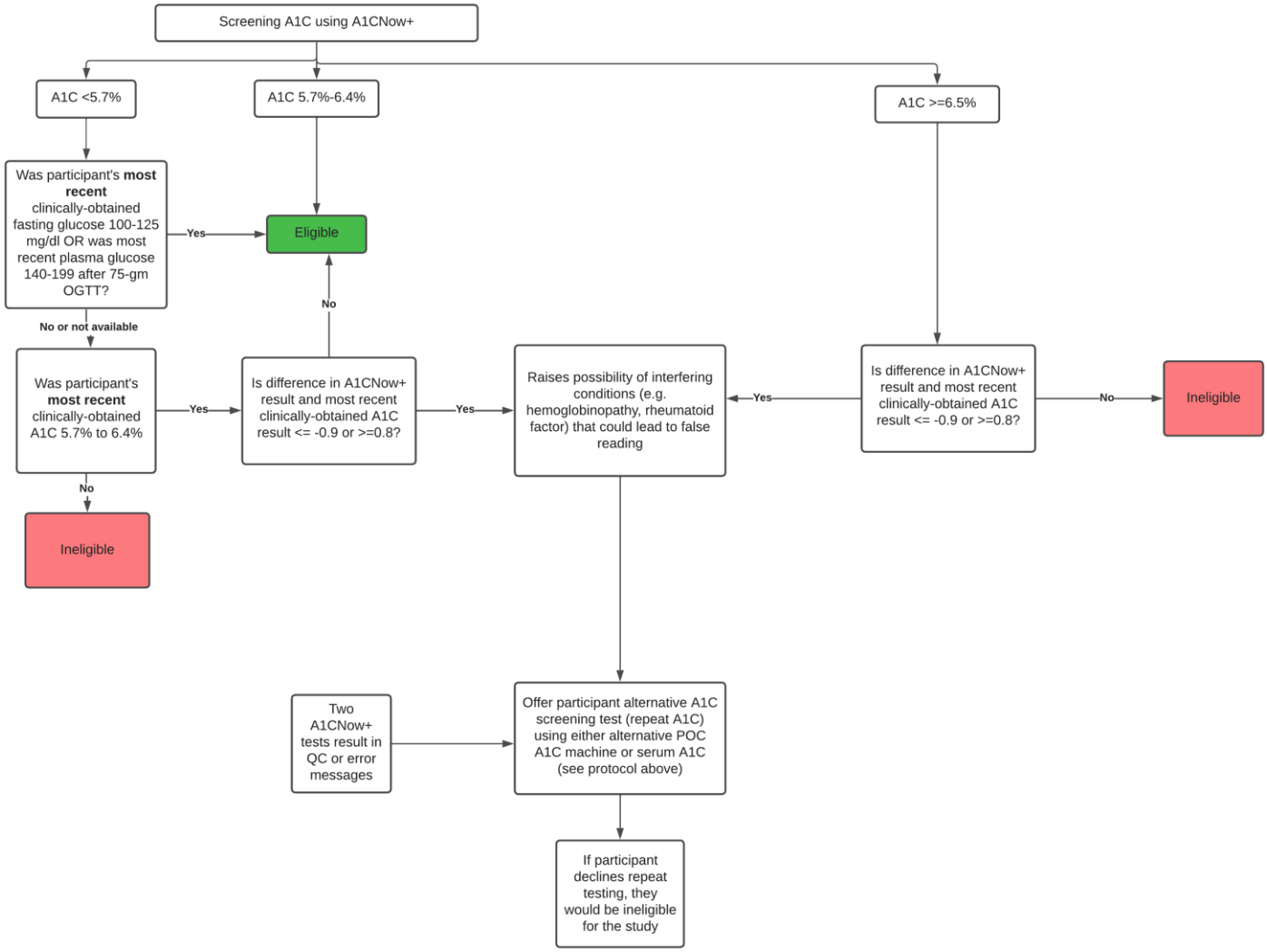
Find out how you can reverse prediabetes and prevent or delay type 2 diabetes through a **CDC-recognized lifestyle change program** at https://www.cdc.gov/diabetes/prevention/lifestyle-program.

Risk Test provided by the American Diabetes Association and the Centers for Disease Control and Prevention.

American Diabetes Association. CDC

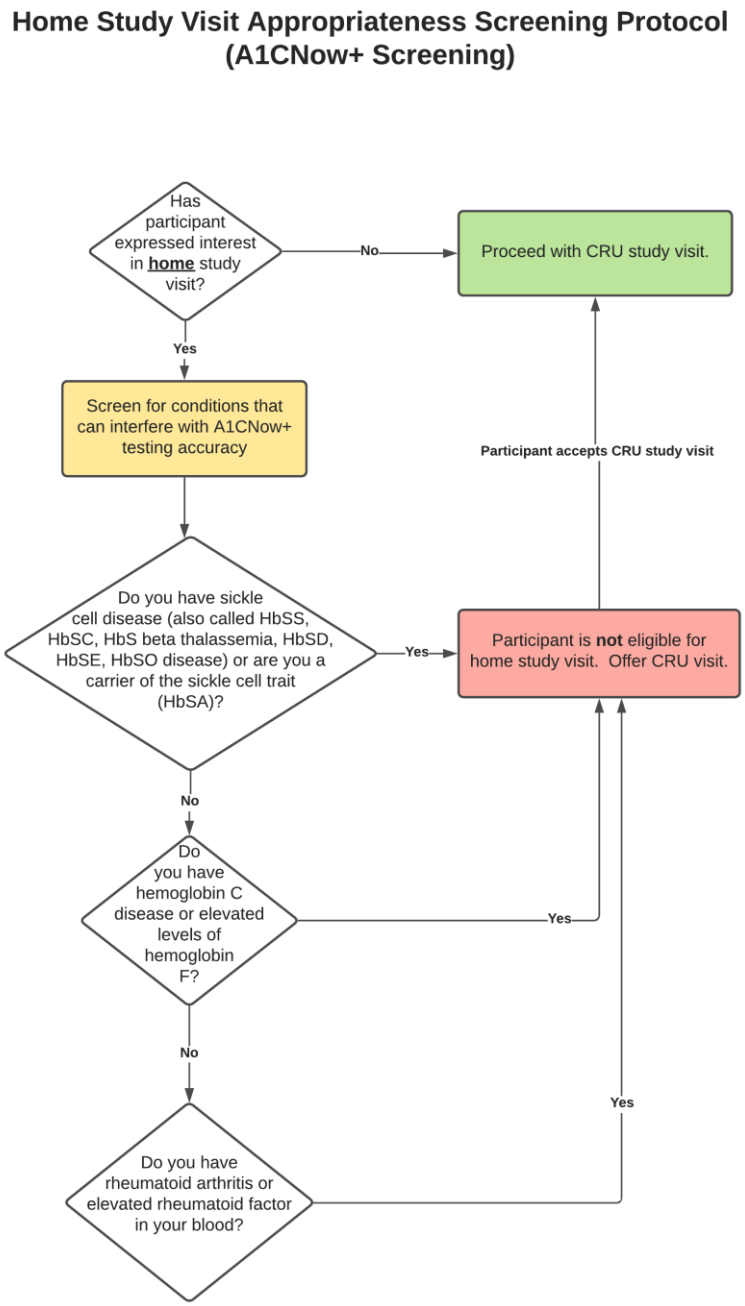
11.17 HEMOGLOBIN A1C SCREENING PROTOCOL




Screening A1C using A1CNow+
A1C <5.7%
A1C 5.7%-6.4%
A1C >=6.5%
Was participant's **most recent** clinically-obtained fasting glucose 100-125 mg/dl OR was most recent plasma glucose 140-199 after 75-gm OGTT?
Yes
Eligible
No
No or not available
Was participant's **most recent** clinically-obtained A1C 5.7% to 6.4%
Yes
Is difference in A1CNow+ result and most recent clinically-obtained A1C result <= -0.9 or >=0.8?
Yes
Raises possibility of interfering conditions (e.g. hemoglobinopathy, rheumatoid factor) that could lead to false reading
Yes
Is difference in A1CNow+ result and most recent clinically-obtained A1C result <= -0.9 or >=0.8?
No
Ineligible
No
Ineligible
Two A1CNow+ tests result in QC or error messages
Offer participant alternative A1C screening test (repeat A1C) using either alternative POC A1C machine or serum A1C (see protocol above)
If participant declines repeat testing, they would be ineligible for the study

11.18 HOME STUDY VISIT APPROPRIATENESS SCREENING PROTOCOL (A1CNOW+ SCREENING)

For home study visits, the portable A1CNow+ test kit will be used for measuring A1C. This device is susceptible to interference/inaccuracy from certain underlying conditions. Therefore, the following screening algorithm will be followed to determine whether the participant is appropriate for a home study visit. If not, the participant will be offered the option of a study visit at the clinical research unit.



11.19 INCIDENT DIABETES LETTER

Date

Dear [Name of Clinician],

Your patient [Participant's Name/ DOB] has been a participant in our clinical trial entitled "Effectiveness and Cost-Effectiveness of Fully-Automated Digital vs. Human Coach-Based Diabetes Prevention Programs" since [date of enrollment]. Our trial is comparing two different methods of diabetes prevention (a digital approach vs. standard of care human coach-based DPPs) in overweight adults with prediabetes. This trial lasts 12 months for each participant.

During this study, your patient….

(choose one)

Option #1:

was found to have a point-of-care hemoglobin A1C measurement of _____[list result] on _____ [date]. This result was obtained using an over-the-counter test kit (A1CNow+, PTS Diagnostics). We advised your patient to follow-up with you to determine whether additional testing is needed to confirm the diagnosis of diabetes mellitus. Since our study was using an over-the-counter test, we would suggest repeating the A1C test using a serum A1C sample together with a fasting glucose sample for further diagnostic evaluation. However, we would defer to your clinical judgment in determining the need for additional testing.

Option#2: informed our study team that they have been diagnosed with diabetes mellitus.

Please note that your patient will remain eligible to participate in this study even if confirmed to have diabetes or started on any antihyperglycemic medications.

Please feel free to contact our team at [phone] or email the PI, Dr. Nestoras Mathioudakis, at *nmathio1@jh.edu* if you have any additional questions or concerns.

Sincerely,

Nestoras Mathioudakis, MD MHS

Principal Investigator

Associate Professor of Medicine
Division of Endocrinology, Diabetes & Metabolism
Johns Hopkins University School of Medicine

Phone: 667-306-8085

Fax: 410-367-2042

Email: *nmathio1@jh.edu*

11.20 COVID-19 SAFETY PLAN

11.20.1 PRIOR TO STUDY VISIT

- All participants will be asked about COVID-19 symptoms and potential exposures to COVID-19 via phone call by the study coordinator one day before each study visit.
- All participants will be advised to put on a face covering, regardless of symptoms, during the in-person visit.
- Participants will be instructed to notify the study coordinator prior to the visit if they have fever (T > 100.4°F) or symptoms of COVID-19. If they have symptoms, we will cancel the visit and participants will be advised to contact their healthcare provider. The study visit will be postponed until they are symptom-free for 14 days.
- All study personnel who will have direct contact with study participants are required to take a daily health screening survey before reporting to work. This is mandatory to protect our research personnel and participants. Any study personnel with symptoms should not report to work.
- We will clean and disinfect all study devices and equipment before use.
- We will follow Johns Hopkins Medicine general guidance and policies related to COVID-19.

11.20.2 DURING STUDY VISIT

- Research staff and participants must wear a face covering or mask over the nose and mouth. If the study participant is not already wearing a cloth face covering, we will provide a face mask.
- All study participants will be screened on arrival. They will be asked whether they have a fever (T > 100.4°F) or symptoms of COVID-19, including cough or shortness of breath, sore throat, fever, muscle aches, headache, the new loss of taste or smell, repeated or shaking chills. If they have symptoms, we will cancel the visit and participants will be advised to contact their a healthcare provider. The study visit will be postponed until they are symptom-free for 14 days.
- We will maintain social distancing (staying 6 feet or more away from others) between staff and participants whenever possible.
- All study team members will be advised to wash and sanitize hands often.
- We will clean and disinfect all study devices and equipment before use.
- We will follow Johns Hopkins Medicine general guidance and policies related to COVID-19.

11.21 ADVERSE EVENT EVALUATION

Have you had any new medical problems since the last visit?	☐ Yes. Please describe the new medical problem(s).
	☐ No
Do you think the medical problem(s) was related to your [use of the Sweetch digital diabetes prevention program/ participation in the DPP]	☐ Yes. If Yes, Why do you believe the medical problem(s) was related to the [Sweetch DPP/ DPP]?
	☐ No

12 REFERENCES

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