Manual of
Operations and Procedures

The SODAS Trial

Study **O**f **D**rinks with **A**rtificial **S**weeteners in people with type 2 Diabetes

5/30/2019

Funded by:

NIH-NIDDK

ClinicalTrials.gov ID NCT03944616

Principal Investigator: Andrew Odegaard, PhD, MPH

University of California, Irvine

Co-Investigators: Mark Pereira, PhD, MPH, MS – University of Minnesota

Andrew Reikes, MD - University of California, Irvine

Elizabeth Seaquist, MD - University of Minnesota

Anne Bantle, MD - University of Minnesota

Study Coordinators: Syma Rashid, MBBS - University of California, Irvine

Sarah Rydell, MPH - University of Minnesota

1. Study Background and Overview

Diet beverages are the single largest contributor to artificial sweetener intake in the U.S. diet, and consumption of diet beverages has significantly increased over the past 30 plus years in concert with the twin epidemics of obesity and type 2 diabetes. The dietetic and scientific organizations have approved the use of diet beverages, and these beverages are marketed as healthy, suitable for weight loss, and thus advantageous for diabetes control. The underlying public health concern is that there are few data to support or disprove the benefit or harm of habitual diet beverage consumption by people with diabetes.

The SODAS (Study Of Drinks with Artificial Sweeteners in People with Type 2 Diabetes) Study is being done to test the effect of diet beverage intake on diabetes control parameters in free-living adults with type 2 diabetes.

The trial is a collaboration between the University of California, Irvine (UCI) and the University of Minnesota (UMN), and is federally funded by the National Institutes of Health/NIDDK.

The trial will recruit up to 240 patients with type 2 diabetes who are usual consumers of commercial diet beverages and randomize them to receive and consume either:

1) A commercial diet beverage of choice (3 servings or 24 fl. oz. daily); or,
2) Unflavored bottled water of choice (sparkling or plain) (3 servings or 24 fl. oz. daily)

Of note, if randomized to consume diet beverages, participants will be able to choose their beverage(s) of choice. If randomized to consume water and avoid artificially sweetened beverages, participants will have the choice of plain or plain sparkling bottled water

2. Study Population

Participants will include adults, 35 years and older in Orange County California and the Twin Cities Metro in Minnesota with type 2 diabetes who are usual consumers of diet beverages. Participants will include both men and women; all participants must be able to speak and understand English or Spanish.

3. Participating Centers

University of California, Irvine: Institute of Clinical and Translational Science (ICTS) - UCIMC and Hewitt Hall

University of Minnesota: Epidemiological Clinical Research Center (ECRC)

All Minnesota study visits will take place at the ECRC.

University of Minnesota: Nutrition Coordinating Center (NCC)

NCC will collect all dietary recall data for the study by phone.

4. Study Timeline (2018-2023)

The study is funded for 5 years. Rolling recruitment will occur over a 2.5 year period, from years 1 - 3. The duration of participation for each participant will last 26 weeks (6 months), which includes a 2-week run-in period and a 24-week intervention period.

5. Recruitment

The trial will be advertised widely to spur recruitment. All study correspondences and advertisements will utilize the IRB approved recruitment materials.

5.1. Recruitment Methods

A variety of recruitment methodologies will be employed. Each method is detailed below.

5.1.1. Medical Records

Active recruitment will occur at UCI through an established private and secure recruitment database, via access of electronic medical records (EMR) using ICD codes as a general screener for major inclusion/exclusion criteria (e.g. having type 2 diabetes, no recent major chronic disease events). Potential subjects identified via EMR will have an informational letter sent to them regarding details of the study, explaining how we obtained their information, and how to contact the study with questions or to express interest in participating. All people who receive a letter from the study will receive a follow-up contact via phone/email to actively survey their interest. A similar process of recruitment via medical records will occur at the UMN, although the UMN does not allow for any follow-up contact via phone/email.

5.1.2. Physician Referral

UCI and UMN physicians will be encouraged to share study information with their patients who may be eligible.

5.1.3. Social Media

Recruitment text about the study will be posted on NextDoor and various Facebook pages. Cross-posting of materials by individuals viewing the recruitment posts will be encouraged to facilitate snowball sampling.

5.1.4. Websites & Listservs

The study will be advertised on the UCI Medical Center Clinical Trials web page and via UCI email and list serves, including the consent-to-contact listserv at UCI which identifies people who have agreed to be contacted about study participation, as well as targeted community outreach. A smaller, but similar, consent-to-contact listserv (kept by the UMN study coordinator) will be used at UMN.

5.1.5. Fliers

Fliers will be posted in high traffic public spaces at both UCI and UMN, such as the ICTS, campus and community billboards, and local medical care facilities. Fliers will also be posted on virtual billboards (e.g. CraigsList)

5.2. Recruitment Log

Study staff will maintain a recruitment log; all respondent contact information will be kept in the recruitment log in REDCap.

All potentially eligible participants will be reviewed by study investigators on an ad hoc basis with the study team for eligibility.

5.3. Screening of Potential Participants

All screening will follow best practices guidelines for clinical trials and the procedures approved by the UCI IRB.

5.3.1. Primary Screening

Initial screening will be carried out via the REDCap online screener. This will be accessible via a url link for the participant to complete; alternatively, it can be filled out by the study team via conversation with the subject over the phone. The online screener will assess all aspects of the study's inclusion/exclusion criteria (see section 5.4). A secondary screening will serve to review all online responses (see section 5.5).

5.3.2. Inclusion/Exclusion Criteria

The Inclusion and Exclusion Criteria are detailed below.

Inclusion criteria:

- Adult M/F ≥ 35 years old with physician diagnosed type 2 diabetes ≥ 6 months prior to screening
- HbA1c 6.5-8.5% within the last 2 months or at participant screening
- Current treatment with lifestyle or stable diabetes-related medication levels for the past 3 months
- Willingness to provide consent to contact treating physician and physician agreement to refrain from changing diabetes-related medications during the trial (change defined as > 2 fold change in dose of any 1 hyperglycemic agent or addition or subtraction of an agent)
- No physician-directed medication change for 3 months if prescribed medication for lipids or blood pressure
- Usual consumers of diet beverages (≥ 3 servings/ week (24 oz.) and the willingness to maintain fidelity of the intervention, and participate in all aspects of the intervention
- Not actively looking to make major lifestyle alterations during the study period with stable weight for 2 months (within 3%)

Exclusion Criteria:

- Type 1 diabetes or suspected type 1 diabetes (lean with polyuria, polydipsia, and weight loss with little response to metformin)
- "Secondary" diabetes due to specific causes (e.g. monogenic syndromes, pancreatic surgery, and pancreatitis)
- Diabetic Ketoacidosis hospitalization within last 6 months
- Severe/major hypoglycemia in the last 3 months (severe/major hypoglycemia is defined as a hypoglycemic event in which patient requires assistance of another person to manage the episode)
- Glucocorticoid use (prednisone 2.5 mg/d or more or its equivalent)
- History of intolerance or allergy to diet beverages or AS or phenylketonuria
- Any condition that is known to affect the validity of the glycemic measures (HbA1c)

- Major cardiovascular disease event or surgery within the past 6 months
- Gastrointestinal, Renal or liver disease
- Current treatment for cancer
- Those with major surgery planned or history of bariatric surgery
- Antibiotic treatment (> 6 days) within past 6 months
- Currently pregnant, planning to become pregnant during the study period, or if recently pregnant with < 1 year postpartum and breastfeeding
- Current participation in another interventional clinical trial
- Previous randomization in this study
- Heavy alcohol consumption (on average >1 drinks/day for women & >2 drinks/day for men)
- Habitual consumer of SSB ≥ 1 serving / day (8 oz.)
- Does not drink diet beverages
- Non-smoker* *(*aiming to only recruit non-smokers, if possible)*
- BMI < 20.0 kg/m^2

5.3.3. Secondary Screening

Participants who appear to meet eligibility criteria will be contacted to complete a secondary screener over the telephone with study staff. The questions on this secondary screener are nearly identical to the questions asked on the online survey, but allow for staff to probe more deeply into questions that impact study eligibility. If the eligibility of someone is questionable after the completion of this phone call, study staff will bring questions to the study team to make a final determination of whether this individual should be invited to attend the Consent & Screening visit.

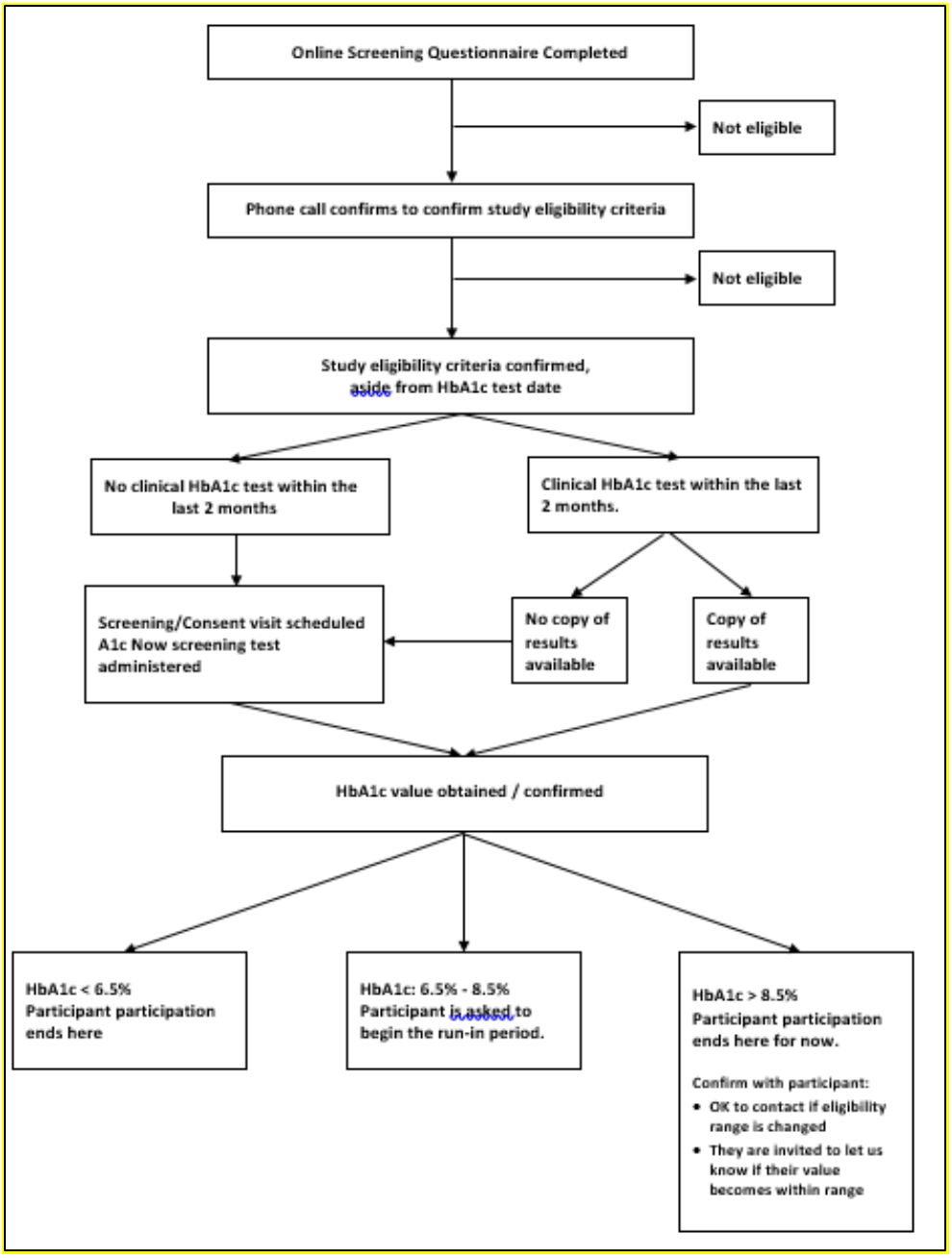
5.3.4. Confirmation of Eligibility

Participants who appear to meet eligibility criteria after completing the online and secondary screening will be invited to attend an in-person Consent & Screening visit (see section 8.4) As study eligibility requires HbA1c to be within a desired range (6.5% - 8.5%), recent HbA1c results are queried during the Primary and Secondary screening process. Those who report having had a recent test within the past two months will be asked to bring valid documentation (e.g. via EMR, lab printout from provider, screenshot of data, etc.) of these results with them to this confirmatory visit. Those who do not have valid documentation or are unsure of their recent results will be invited to attend this visit but be asked to complete a rapid HbA1c test (i.e. A1cNow+) to determine whether their HbA1c value falls within range. A confirmatory venipuncture will be done for those with A1cNow+ values of: 6.2%-6.7%, & 8.0%-8.7%.

It should be noted that all participants who are invited to confirm their eligibility will have had the informed consent form sent to them via USPS mail or email prior to this visit.

6. Enrollment

Subjects who are determined to be eligible and consent to participate will be invited to enroll in the study. See the summary flow chart below.



7. Randomization

All subjects who successfully complete the Run-In Period and Baseline visit will be formally randomized to the intervention. The study coordinators will email the UCI statistician who will enter the participant into the randomization program; the statistician will email back the results of randomization (i.e. the diet beverage condition, or water condition). Participants will be notified of their assigned study arm no later than one day after completion of their baseline visit, and drink delivery will commence no more than three days following the baseline visit.

8. Study Visits

Each study visit has a corresponding Visit Assessment Form that details at the study activities and measures to be completed at that time. Study staff should greet participants upon arrival *(e.g.* ***Hi! Are you here today for the SODAs Study visit? Your name please _____? Hi, _____, I'm _____. Nice to meet you. Thanks for coming today****)*, provide participants with an overview of what to expect at the start of each visit, and complete the activities in the order as listed on the form.
Please reference the Assessment Forms in Appendix XXX.
Summaries of all visits are detailed below.
More information on study measures can be found in Section 9.

8.1. Scheduling

Study visits will be scheduled with the aim of being as accommodating as possible. All UCI visits will occur during the ICTS hours (8am-5pm M-F), and all UMN visits will occur during ECRC hours (7a-4:30/6:00p, depending upon day of the week). With notice, it is possible to schedule participant visits for Saturday mornings, but this is dependent upon ICTS/ECRC staffing availability.

UCI scheduling occurs through the ICTS website (http://www.icts.uci.edu/index.php). The portal is under the clinical research services tab. For all scheduled visits, the Study Coordinator and PI contact information and IRB # (HS# 2018-4756) need to be noted. A reply email confirming the visit will be received.

UMN scheduling occurs through the CTSI scheduling portal (https://ctsi.ahc.umn.edu/portal/). Reference the CTR Portal Scheduling System Manual for more information on the scheduling process.

8.2. Visit Reminders

Reminder phone call or text message for all study visits should be made 24 hours before the visit will occur. The outcome of reminder calls/texts must be documented in the patient contact database. A message will be left if the subject does not answer.

8.3. Visit Locations

All study visits at UCI will occur at the ICTS in Hewitt Hall on the main UCI campus, or at the ICTS branch at the UCI medical center in Orange. All study visits at the UMN will occur at the ECRC.

8.4. In-Person Screening Visit

As mentioned earlier in Section 5.3.4, presumed eligible participants will be invited to the clinical research center for the informed consent process and confirmation of eligibility. A copy of the consent form, HIPAA form, and study timeline will be mailed or emailed to all participants prior to this visit.

Prior to commencing any confirmation activities, participants will be consented in a private setting. Time will be given for the participant to read through the consent form in its entirety, if they have not already done so.

The following steps should be followed prior to obtaining participant consent:

- ❑ Review the entire consent form, HIPAA form, and study timeline with the participant.
- ❑ Answer any questions raised by the participant.
- ❑ Confirm understanding of the randomization process and their willingness to be randomized.
- ❑ Remind them:
    - All study data is confidential
    - All activities today and in the future are voluntary

After the above steps are complete, the participant and study staff will sign the informed consent form. A copy of this signed form should be offered to the participant.

Once consent is obtained, study staff should complete the rest of the screening visit. This will include verifying BMI ≥ 20 kg/m^2 and their current HbA1c value (i.e. within 6.5% - 8.5% via recent test results or via the A1cNow+ rapid test). Once eligibility is confirmed, the participant can continue with, or be scheduled for, the Run-In visit.

8.5. Run-In Visit

This visit can be scheduled at the same time as visit 8.4, or separately. It will occur roughly 2-weeks prior to the start of the intervention, such that the 2-week run-in period can serve to collect data on participant usual habits and clinical glycemic variability status (CGM). Participants will visit the clinical research center where they will be:

- outfitted with the activity monitor (activPAL) to be worn on their leg which will collect objective data on the participants' physical activity levels over a 7-day period
- outfitted with a continuous glucose monitor (CGM) on their upper arm to collect usual variations in blood glucose levels over 14 days
- Provided a gut microbiome kit with instructions to collect a fecal sample to understand the composition of their gut microbiome.

- Asked to provide their availability to complete two, unannounced 24-hr dietary recalls over the next 2 weeks (an orientation to the Food Amounts Booklet used for these recalls will also be provided).

See Section 9 for more information on all of these measures.

Preparation of participant materials for this visit:
Book an examination room ahead of time for this visit. The Project Coordinator will have a participant materials packet, double checked for completeness, for each participant that day. Each packet will contain:

- ❑ Waterproofed activPAL and related materials
- ❑ FreeStyle Libre Pro sensor and reader
- ❑ Gut Microbiome kit with pre-addressed mailing label and plastic disposable cup
- ❑ Printed patient care instruction sheet
- ❑ Alcohol wipes
- ❑ Gloves
- ❑ a gown (optional if arm & thigh aren't accessible)

8.6. Baseline visit - FASTING

The baseline visit will correspond to the end of the run-in period when participants return to the clinical research center to return data collection devices from the past 14 days. The visit requires a fasting (≥ 10 hours) blood draw, so will likely occur in the morning. Participants will also be reminded to avoid any dietary supplements, OTC pain meds (e.g. Tylenol, Aspirin, Ibuprofen etc.), or any alcoholic beverages the day before. Participants will be instructed to avoid heavy exercise on the morning of the visit. They also should be told that they can drink water (and are encouraged to do so).

Measures completed at this visit include:

- Blood Pressure
- Weight
- Venipuncture
- Urine collection
- Availability for recalls (Period 1 & 2)
- Study Survey
- CONFIRM LIST IS COMPLETE

The Project Coordinator will have a participant materials packet, double checked for completeness, for each participant that day. Materials include:

- ❑ Baseline Assessment Form
- ❑ Biospecimen Collection Kit (i.e. Labeled storage vials and assembled lab kits)
- ❑ Laptop for participants to take surveys
- ❑ Snacks

- ❑ Compensation ($75 cash)
- ❑ Gown

8.7. Week 6 visit - FASTING

The visit requires a fasting (≥ 10 hours) blood draw, so will likely occur in the morning. Participants will also be reminded to avoid any dietary supplements, OTC pain meds (e.g. Tylenol, Aspirin, Ibuprofen etc.), or any alcoholic beverages the day before. Participants will be instructed to avoid heavy exercise on the morning of the visit. They also should be told that they can drink water (and are encouraged to do so).

Measures completed at this visit include:

- Blood Pressure
- Weight
- Venipuncture
- Availability for recalls (Period 2)
- Study Survey
- CONFIRM LIST IS COMPLETE

The Project Coordinator will have a participant materials packet, double checked for completeness, for each participant that day. Materials include:

- ❑ Week 6 Assessment Form
- ❑ Biospecimen Collection Kit (i.e. Labeled storage vials and assembled lab kits)
- ❑ Laptop for participants to take surveys
- ❑ Snacks
- ❑ Gown
- ❑ Compensation ($40 cash)

8.8. Week 10 visit

At this non-fasting visit, participants will:

- have an activPAL placed on their right thigh
- have a CGM device placed on their non-dominant upper arm
- be given a gut microbiome kit for fecal collection
- provide availability for recalls (Period 3)

Preparation of participant materials for this visit:

Book an examination room ahead of time for this visit. The Project Coordinator will have a participant materials packet, double checked for completeness, for each participant that day. Each packet will contain:

- ❑ Week 10 Visit Form
- ❑ Waterproofed activPAL and related materials
- ❑ FreeStyle Libre Pro sensor and reader

- ❑ Gut Microbiome kit with pre-addressed mailing label and plastic disposable cup
- ❑ Printed patient care instruction sheet
- ❑ Alcohol wipes
- ❑ Gloves
- ❑ Gown (optional if arm & thigh aren't accessible)
- ❑ Compensation ($10)

8.9. Week 12 visit - FASTING

The visit requires a fasting (≥ 10 hours) blood draw, so will likely occur in the morning. Participants will also be reminded to avoid any dietary supplements, OTC pain meds (e.g. Tylenol, Aspirin, Ibuprofen etc.), or any alcoholic beverages the day before. Participants will be instructed to avoid heavy exercise on the morning of the visit. They also should be told that they can drink water (and are encouraged to do so).

Measures completed at this visit include:

- Blood Pressure
- Weight
- Venipuncture
- Urine collection
- Availability for recalls (Period 4 &5)
- Study Survey
- CONFIRM LIST IS COMPLETE

The Project Coordinator will have a participant materials packet, double checked for completeness, for each participant that day. Materials include:

- ❑ Week 12 Assessment Form
- ❑ Biospecimen Collection Kit (i.e. Labeled storage vials and assembled lab kits)
- ❑ Laptop for participants to take surveys
- ❑ Snacks
- ❑ Gown
- ❑ Compensation ($100 cash)

8.10. Week 18 visit - FASTING

The visit requires a fasting (≥ 10 hours) blood draw, so will likely occur in the morning. Participants will also be reminded to avoid any dietary supplements, OTC pain meds (e.g. Tylenol, Aspirin, Ibuprofen etc.), or any alcoholic beverages the day before. Participants will be instructed to avoid heavy exercise on the morning of the visit. They also should be told that they can drink water (and are encouraged to do so).

Measures completed at this visit include:

- Blood Pressure

- Weight
- Venipuncture
- Availability for recalls (Period 5)
- Study Survey
- CONFIRM LIST IS COMPLETE

The Project Coordinator will have a participant materials packet, double checked for completeness, for each participant that day. Materials include:

❑ Week 18 Assessment Form
❑ Biospecimen Collection Kit (i.e. Labeled storage vials and assembled lab kits)
❑ Laptop for participants to take surveys
❑ Snacks
❑ Gown
❑ Compensation ($40 cash)

8.11. Week 22 visit

At this non-fasting visit, participants will:

- have an activPAL placed on their right thigh
- have a CGM device placed on their non-dominant upper arm
- be given a gut microbiome kit for fecal collection
- provide availability for recalls (Period 5)

Preparation of participant materials for this visit:
Book an examination room ahead of time for this visit. The Project Coordinator will have a participant materials packet, double checked for completeness, for each participant that day. Each packet will contain:

❑ Week 22 Visit Form
❑ Waterproofed activPAL and related materials
❑ FreeStyle Libre Pro sensor and reader
❑ Gut Microbiome kit with pre-addressed mailing label and plastic disposable cup
❑ Printed patient care instruction sheet
❑ Alcohol wipes
❑ Gloves
❑ Gown (optional if arm & thigh aren't accessible)
❑ Compensation ($10)

8.12. Week 24 visit - FASTING

The visit requires a fasting (≥ 10 hours) blood draw, so will likely occur in the morning. Participants will also be reminded to avoid any dietary supplements, OTC pain meds (e.g. Tylenol, Aspirin, Ibuprofen etc.), or any alcoholic beverages the day before. Participants will

be instructed to avoid heavy exercise on the morning of the visit. They also should be told that they can drink water (and are encouraged to do so).

Measures completed at this visit include:

- Blood Pressure
- Weight
- Venipuncture
- Urine collection
- Availability for recalls (Period 3 & 4)
- Study Survey
- CONFIRM LIST IS COMPLETE

The Project Coordinator will have a participant materials packet, double checked for completeness, for each participant that day. Materials include:

- ❑ Week 24 Assessment Form
- ❑ Biospecimen Collection Kit (i.e. Labeled storage vials and assembled lab kits)
- ❑ Laptop for participants to take surveys
- ❑ Snacks
- ❑ Gown
- ❑ Compensation ($100 cash plus, if applicable, $40 bonus for 7x Diet Recall recompletion, and $10 bonus for 3x CGM wear)

After the participants complete the main part of the study their participation will be finished. We will only ask open ended questions (questionnaire TBD) about their participation in the study to inform future related research and inform the scientific reports that result from this research.

9. Measures

The following measures will be collected at various time points throughout the study, summarized in the table below. Each visit will have a corresponding visit form that outlines all measures to be collected at that time.

Time Frame	Height	CGM & ActivPAL	Blood Pressure	Veni-puncture	Urine & Fecal Collection	Survey & medication review	Weight
Screening							
Baseline	x	x	x	x	x	x	x
6 weeks			x	x		x	x
12 weeks		x	x	x	x	x	x
18 weeks			x	x		x	x
24 weeks		x	x	x	x	x	x

*Note: this table does not include the assessment of dietary intake as those are completed on a different schedule

9.1. Continuous Glucose Monitoring (CGM)

Please refer to the CGM Protocol for more information. In short, a FreeStyle Libre Pro will be placed on patient's non-dominant upper arm by the study coordinator by cleaning the area with an alcohol wipe and applying the sensor by pushing down firmly on the skin. The coordinator will make sure that the FreeStyle Libre Pro Sensor is activated by the reader before the patient leaves the clinic. The reader needs to be held about 1.5 inches from the sensor on patient's arm and sensor will be started by pressing "start new sensor" button on the reader. The coordinator will wait for the beep to confirm sensor has started, and wait for 2 minutes to get the sensor status. The reader will show a reminder in 2 minutes to check sensor status and that time the coordinator will press "Yes" and hold the reader within 1.5 inches of the patient's arm to verify that the sensor is working. **Green Check on the screen confirms that the sensor is activated and working.** The patient is instructed to wear the CGM for 14 days (with a minimum of 7 days), and let the study team know if there are any problems associated with the CGM. The patient will be scheduled to come back to the clinic in 14 days and the CGM will be removed by the study coordinator. All sensors need to be saved with Patient ID and visit week written on top of the sensor with a sharpie.

9.2. ActivPAL

Please refer to the ActivPAL Protocol for more information. In short, the activPAL should be fully charged, initialized and waterproofed before the visit. The study coordinator will follow the protocol to affix activPAL on patient's right upper leg. The patient is instructed to wear the activPAL for 7 days (with a minimum of 4 days), and let the study team know if there are any problems associated with the activPAL. The patient is also given a Ziploc bag to store and save their activPAL after completing the 7 day wear, and to bring it back to the clinic at their next scheduled visit.

9.3. Dietary Intake

Please refer to the Nutrition Coordinating Center's SODAS Manual of Procedures for Collecting Dietary Recalls for more information.

In summary, 7 recalls will be collected from each participant over the course of the study; two recalls during the Run-In period and 5 additional recalls spread across the 24-week intervention.

All dietary recalls will be conducted by the UMN Nutrition Coordinating Center. via a phone call from NCC (one will be done on a weekday and one on a weekend) – The study coordinators will send the NCC Data Manager (Mary Austin) and Service Center Manager (Julia Lorenzana Peasley) an Excel file via Box, a secure file exchange program through U of MN, that includes the following information for each study participant:

- Participant ID
- first name of participant
- gender (for pronoun purposes when calling and asking for participant)

- phone number(s)
- availability information
- Language preference if other than English
- Date that collection of two baseline recalls can begin. (Collection windows for following periods will be imputed from that date.)

This information will then be imported into the NCC Participant Tracking system for reference by the dietary interviewers at NCC where they will track each call made to participants to attempt to collect the recalls and track details on when each recall is collected.

9.4. Blood Pressure

Blood pressure will be measured at the Baseline visit and at the visits during weeks 6, 12, 18, and 24. It should be taken first in case the participant finds the visit stressful. Participants will sit quietly in a private exam room with feet flat on the floor and arms comfortably resting for at least 5 minutes. Then the study coordinator will take blood pressure measurements **in triplicate, with each reading separated by a 30-second break.** Record BP on the left arm (if the size of cuff is not compatible with size of patient's arm; then blood pressure will be taken on the left forearm and this will be noted in a log) and the average of the lowest two values will be used for analyses.

9.5. Anthropometry

Refer to the Anthropometric Protocol for more detail.

In summary, height will be measured in duplicate at the Consent & Screening Visit only in cms using a wall-mounted stadiometer. Ask the participant to remove their shoes, and hats (or any other hair ornaments from top of their head) and stand up straight against the backboard with both feet flat on the platform. Instruct the participant to stand with heels together and toes apart. Participants will be asked to look straight ahead with their head in proper alignment. Instruct the participant to stand as tall as possible, take a deep breath and hold this position. With the participant in correct position and holding the breath, lower the stadiometer head piece so that it rests firmly on top of the participant's head, with sufficient pressure to compress the hair. Record the measurement.

Weight will be measured in duplicate at the Baseline visit and at the visits during weeks 6, 12, 18, and 24. It will be measured in kgs using a daily-calibrated digital scale by asking the participant to be in either light clothing (e.g. shorts and t-shirt or a gown), remove their shoes and step on to the center of the scale, facing the recorder, hands at sides and looking straight ahead. Study coordinator will record the reading on the screen.

9.6. Biospecimen Collection

See the Biospecimen Collection Protocol for more detail on the collection and processing of all specimens. Assays to be conducted on these samples are also detailed in this protocol.

9.6.1. Venipuncture

The ICTS nursing staff (or ECRC phlebotomist) will draw blood with the participant in a seated position and process according to the lab protocol for the following measures:
HbA1c, Lipid Panel, Serum Creatinine, Fasting Glucose, Fasting Insulin and Fructosamine/Glycated Albumin.

9.6.2. Urine

For collection for future analyses or potential analyses, participants will also provide a urine sample to test for artificial sweeteners in the urine.

9.6.3. Fecal Sample

Patients will be provided with a pre-assembled Gut Microbiome collection kit at the run-in, week 10 and week 22 visits. Refer to Gut Microbiome protocol for more details.

9.7. Study Survey

The study survey will be administered at Baseline, and at visits during weeks 6, 12, 18, and 24. The survey itself is comprised of a series of short questionnaires from various domains of scientific interest and necessity for GCP guidelines will be administered. These questionnaires will be embedded in REDCap for security and data processing purposes. Included in the survey are questions assessing:

- Beverage habits (modified BEV-Q)
- Dietary habits (instrument needed)
- Sleep habits (PSQ-I)
- Diabetes health profile (DHP-18)
- Food Craving Inventory (FCI-II)
- Side Effects Form

9.8. Medicine Use/Change Form

Patients will fill out a medication use/change form at Baseline, and at visits during weeks 6, 12, 18, and 24. The medication form is comprised of questions related to patient's type 2 diabetes medication and they are asked for any changes in the medication itself or its dosage in the past month. This form will also be embedded in REDCap for security and data processing purposes.

10. Timing and Payment of Clinic Visits

Participants will be compensated with cash at the completion of each visit. Study coordinators will provide cash to participants upon completion of each visit, ensuring each cash distribution is appropriately logged on the UCI Cash Disbursement tracking form (i.e. include date, study ID number, and staff signature).

Visit Number	Visit Name	Payment
1	**Baseline visit**	**$75**
2	**Week 6 visit**	**$40**
3	**Week 10 visit**	**$10**
4	**Week 12 visit**	**$100**
5	**Week 18 visit**	**$40**
6	**Week 22 visit**	**$10**
7	**Week 24 visit**	**$100**
7	**BONUS: completion of all 7 dietary recalls**	**$40**
7	**BONUS: completion of all 3 CGM wears**	**$10**
	COMPENSATION TOTAL	**$425**

Note: There is no reimbursement for travel, only compensation for the visit. Parking at ICTS and ECRC is free.

11. **Adverse Events Reporting:** Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. All adverse events whether volunteered by the participant at a clinic visit or over a phone call, or discovered by study personnel during questioning, should be inputted into the study database and the study investigator should be notified immediately.

12. **Adherence*:*** A tool to increase adherence in clinical trials is to maintain frequent contact with the individual beyond the scheduled intervention sessions. A simple email, brief phone call, or text message during non-intervention visit weeks are likely the best options and the participant can suggest what is best for them.

13. **Participant Data**

    Following the completion of the study, participants can be sent a copy of their CGM reports and activPAL outputs for all three time points that these devices were worn.
    Blood results will be available at the end of the study, upon request.

14. **Data Management**

    All paper forms such as consent, payment receipts for participation, etc. will be stored in a locked file cabinet in a folder specific for the participant.

    All recruitment and enrollment files will be stored securely on the REDCap space for the study.

    All dietary data, CGM data and sensors, ActivPal data (activity, sleep), clinical measured data that is downloaded and central to the study aims will be stored on the secure, password protected network server accessible to both sites. All original files will be saved for quality control and assurance purposes.