# Advancing Care for
# Type 1 Diabetes and Obesity Network (ACT1ON)

**NCT number** NCT03651622
**Document Date** 06/15/2020

## STUDY PROTOCOL

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| **Complete Title:** | **Accelerating Solutions to Optimize Glycemic Control and Weight Management in Young Adults with Type 1 Diabetes** |
| **Short Title:** | **ACT1ON Phase 2 (SMART Pilot) and Phase 3 (Efficacy trial development)** |
| **Sponsor:** | **National Institutes of Health/NIDDK DP3DK113358-01** |
| **Original Protocol Date:** | **May 30, 2018** |


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Protocol Version: 7
Version Date: June 15, 2020

I confirm that I have read this protocol and understand it.

Principal Investigator Name: _____Beth Mayer-Davis_____

Principal Investigator Signature: ___Elizabeth G Mayer-Davis_____

Date: June 15, 2020_____

**List of Modifications**

*Version 8, June 15, 2020*

Our team has made the decision to cease recruitment and enrollment of new subjects. We have changed our target enrollment numbers in the protocol and IRB application to reflect this.

We are adding an incentive of $50 as compensation for the extra time that participants have spent in the study due to COVID-19 related delays.

We are amending the protocol to reflect a change to microbiome collection. Currently enrolled participants who agreed to microbiome and delivered a sample at baseline, will be eligible to collect a sample at M3 and M4 as well for an additional incentive.

We are making it clear that now that we are no longer doing a blood draw and not collecting stored whole blood and plasma, and therefore are not asking participants to fast, that we will not ask participants to report their blood sugar or whether or not they have had anything to eat in the last 8 hours. The only fields of the 'specimen collection form' that we will complete are those that pertain to the HbA1c collection, that is, time and date of collection along with any problems the participant may have had.

**List of Modifications**

*Version 7, April 27, 2020*

Continued **response to COVID-19: moving entire study to virtual measurement visits.**

As it becomes clear that the ramifications of the COVID-19 will hinder our ability to conduct study processes as originally designed for the indefinite future, the study team has decided to transition all data collection to remote conduct. All measurement visits will be accomplished virtually, as described in the protocol, and new participants at each site will be enrolled into the study via a virtual visit in order to meet our original recruitment goals.

- Some elements of data collection that were not necessary for randomization cannot be accomplished remotely. This includes:
  - DXA body scan
  - Stored whole blood for future analysis

  These elements of the study will be discontinued.

**We are reinitiating microbiome stool collection at Baseline and 3-months for eligible participants, as this can be done remotely. Additionally, we will add microbiome collection at 6- and 9-months for those participants who have provided baseline samples. This will allow for achievement of our originally intended sample size, given the need to stop recruitment in light of COVID-19. Incentives will increase and be $70.00 for 6-month stool samples and $90.00 for 9-month samples. Included, but separate from COVID-19 Provisions**

Additionally, we are adding a physical activity tracking part of the study, described in Appendix 1. All participants will be given the opportunity to participate in this new addition to the study.

Ketone data collection will also be discontinued as participants are not monitoring their ketones even though kits are being provided.

**List of Modifications**

*Version 6, March 19, 2020*

**AMENDMENT TO CLARIFY PROCEDURES IN LIGHT OF COVID-19**

Due to efforts to minimize the spread of Coronavirus, as of 3/19/2020, all form collection will be done online (or Zoom/phone interview if participants need help with completing). For the in-person part of the visit, this will be limited to A1c draw only and physical measures. We are stopping DXA, microbiome, and CGM for the time being, as these are not necessary to participant's safety and well-being.

The only procedures that will be conducted at in-person visits are:

- Height/weight/waist (completion of physical exam form by staff)
- A1C draw (completion of specimen form by staff)

Should the University move to restrict all participant in-person visits, we will promptly inform our participants utilizing the attached letter that they will remain on their current diet for an extended period of time and resume measurement visits and potential re-randomization only when it has been deemed safe to do so.

In this scenario, participants will remain on the diet they are currently assigned to and have virtual check-ins every other week with their study RD.

RDs will use their skills and rapport with participants to work through issues related to the diet, anticipating that this is a time of increased stress due to financial, health, and other concerns.

If it is necessary for participants to remain on diets for longer than the predetermined intervention period, analysis will take time difference into account.

We will resume regular visit protocol once the University's guidance changes and we are permitted to conduct measurement visits in-person again.

**List of Modifications**

*Version 5, January 17, 2020*

- Protocol amendment to include that screening A1C must be from within last 6 mos (not formally stated)
- We are making a change in the protocol that we will replace people who dropped out of the study before randomization. This will change our total number to be enrolled at UNC from 42 to 44.

**List of Modifications**

*Version 4, March 18, 2019*

- Changes throughout protocol to update with new screening process

- Changed order of inclusion and exclusion criteria
- Reordered information about the participant targets at each site to improve protocol flow
- Added that we will use EPIC and a subscription service 'Accurint' will be used to search for updated contact information if previously obtained contact info is not working
- May use messaging through MyChart for recruitment (TraCS is checking study eligibility).

**List of Modifications**

*Version 3, October 10, 2018*

- Protocol Synopsis and Intervention section: edited dietary fat information in the low carb diet
- Protocol Synopsis and Recruitment section: Exclusion criteria- Added exclusion criteria of having lost 10 or more pounds in the last 6 months. *(Note: this is already on the IRB-approved screening form, but language is being added to the protocol*). Updated inclusion criteria to reflect BMI of 27-39.9 (revised from 27-39)
- Section 6. Process of Obtaining Consent
    - Added description of the consent comprehension checklist, which will be used to guide the conversation between study coordinators obtaining consent and participants. The purpose of this form is to ensure participant understanding of what they are consenting to and informed consent itself.
- Recruitment – exclusion criteria: took out that those with prohibitive dietary restrictions would be excluded as this has been subsumed by those unwilling to follow study diet will be excluded.
    - Added emailing as an option to deliver recruitment materials to participants at all stages of recruitment, beginning with the initial mailing.
- Section 12: Edited blood volume from DNA storage from 8.5 ml tube to 10 ml tube. Total blood volume drawn at baseline visit increased from 20.5 to 22 ml.

**List of Modifications**

*Version 2, August 2018*

Abbreviation List

- Changed DEXA to DXA in abbreviation list and throughout. Added DXA-related abbreviations (LM, FM, VAT, AG, and FFM) to list of abbreviations.

Protocol Synopsis

- Edited total study time to be 10.5 months (this change comes from adding 14-day wear time for CGM following each measurement visit)
- Updated inclusion criteria to reflect BMI of 27-39 (revised from 25-39)
- Updated exclusion criteria to remove exclusion based on celiac disease. Edited language related to diet-related exclusion. Edited language to exclude individuals that have delivered a baby in the last 12 months. Edited exclusion criteria to reflect individuals unwilling to follow any of the three study diets (rather than unwilling to adjust insulin dosing to accommodate the three study diets)
- Updated Efficacy Evaluations to reflect 14-day CGM wear time (changed from 7-day CGM wear time)

Section 1. Executive Summary

- Edited total study time to be 10.5 months

Section 3. Study Objectives

- Edited total study time to be 10.5 months

Section 5. Selection & Recruitment of Subjects

- Updated exclusion criteria to remove exclusion based on celiac disease. Edited language related to diet-related exclusion. Edited language to exclude individuals that have delivered a baby in the last 12 months. Edited exclusion criteria to reflect individuals unwilling to follow any of the three study diets (rather than unwilling to adjust insulin dosing to accommodate the three study diets)
- Updated inclusion criteria to reflect BMI of 27-39 (revised from 25-39)
- Added email as option to share materials during the recruitment process

Section 6. Process of Obtaining Consent

- Added language to detail providing instructions to participants accessing the online data management system for self-administered forms
- Added language regarding completion of study forms prior to the baseline visit if consent is provided via an online consent form
- Added clarification on involuntary withdrawal to include difficulties with glycemic control (per investigators' discretion).

Section 7. Randomization

- Edited total study time to be 10.5 months

Section 8. Standardized Measurements

- Updated CGM wear time to 14 days (from 7 days) and CGM procedures to reflect initiation of CGM at each in person visit
- Clarified DXA scan will be full body scan and added details regarding scan procedures and outcomes of interest
- Moved waist circumference under additional measures (from primary measures)
- Removed insulin dosing from measurements
- Listed Demographics separate from Health History (now on separate form)
- Stored blood will now be collected as a fasting sample
- Adding collection of blood ketones (weekly for individuals on a low carbohydrate diet)

Section 9: ACT1ON SMART Pilot Intervention

- Edited total study time to be 10.5 months
- Corrected intervention description to show 8 in person sessions and 15 phone "check-in"
- Edited the fidelity description to clarify details of fidelity review

Section 12: Potential Risks, Discomforts, Inconveniences and Precautions

- Updated blood draw volume to reflect total amount of 20.5 ml per visit at the baseline visit and 12 ml at other study visits.

- Remove that study HbA1c results will be shared with participants and providers
- Changed time for storage of blood/plasma from 5 to 10 years after study has ended.

Section 15: Privacy and Confidentiality

- Added details regarding local Microsoft Access database to track participant contact information and contacts.

Section 16: Study Timeline

- Updated study timeline to reflect recruitment beginning in September and data collection ending in November 2020

## CONTENTS

## List of Abbreviations:

AE – Adverse Event
AG – Android/Gynoid
BF% - Body Fat Percentage
CGM – Continuous glucose monitoring
DCCT – Diabetes Control and Complications Trial
DXA – Dual-Energy X-ray Absorptiometry
DKA – Diabetic Ketoacidosis
DSMB – Data Safety and Monitoring Board
FDA – Food and Drug Administration
FFM – Fat Free Mass
FM - Fat Mass
LM - Lean Mass
MI – Motivational Interviewing
PSST – Problem Solving Skills Training
SAE – Serious Adverse Event
SMBG – Self Monitored Blood Glucose
SMART– Sequential, Multiple Assignment Randomized Trial
T1D – Type 1 Diabetes
TRI-MD – Translational Research Institute for Metabolism and Diabetes
VAT - Visceral Adipose Tissue

## Protocol Synopsis

| | |
|---|---|
| Study Title | Accelerating Solutions to Optimize Glycemic Control and Weight Management in Young Adults with Type 1 Diabetes |
| Funder | National Institutes of Health/NIDDK |
| Clinical Phase | Phase 1 |
| Study Rationale | The prevalence of overweight and obesity among individuals with type 1 diabetes now parallels that of the general population and contributes to cardiovascular disease. There is a compelling need to develop behavioral interventions that are designed to optimize not just one, but two key outcomes—glycemic control and weight status—and that are responsive to the unique metabolic, clinical, and behavioral context of T1D. Upon completion of the work, we will have established a rigorous adaptive design for an efficacy trial of behavioral interventions that will be acceptable to young adults with T1D. |
| Study Objectives | Primary<br>• To assess acceptability and adherence to three distinct, evidence-based dietary approaches designed to address weight management and glycemic control.<br>• To generate data required to inform and develop a fully powered SMART design trial. |

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| Test Article(s) | ○ *Diet 1*: hypocaloric, moderate low fat (30% calories from fat) weight management based on the Look AHEAD study<br>○ *Diet 2*: hypocaloric, low carbohydrate (15-20% calories from carbohydrate with fats being at least 37% monounsaturated fat and <10% as saturated fat)<br>○ *Diet 3:* advice to select a healthy Mediterranean dietary pattern with no caloric restriction<br><br>Behavioral counseling strategies, use of carbohydrate counting for insulin dosing, and encouragement of usual level of physical activity will be the same across the 3 diets. |
| Study Design | This is an initial pilot and feasibility study using a Sequential, Multiple Assignment, Randomized Trial (SMART) design to identify acceptable and effective dietary strategies to optimize both glycemic control and weight management. This pilot study will be done at UNC and Stanford.<br><br>Sequential randomization will occur following the baseline, 3 months, and 6 months. Following the baseline data collection and a short run-in period, participants will be randomized to one of the three diets (stratified by site with block size of 4). Using *a priori* decision rules following the 3 and 6 month visit post-initial randomization, those for whom the diet assigned is not acceptable or is not effective will be re-randomized. A total follow-up time of 10.5 months allows for evaluation of the effect of the diets on initial weight loss and on early maintenance of initial weight loss. The decision criteria for re-randomization will incorporate both clinical outcomes (glycemic control and weight change) and acceptability of the diet to the participant. |
| Subject Population Key Criteria for Inclusion and Exclusion | Inclusion Criteria<br>1. Individuals ages 19-30 years old<br>2. History of type 1 diabetes for greater than one year<br>3. HbA1C less than 13% within the last 6 mos.<br>4. BMI of 27-39.9 at time of phone screening<br><br>Exclusion Criteria<br>The study will exclude based on the following criteria:<br>1. Individuals with other metabolic disorders, diagnosed eating disorder, prohibitive strict dietary restrictions, or those with other serious condition that renders participation inappropriate.<br>2. Individuals that have experienced DKA or severe hypoglycemia requiring outside assistance in the last 6 months.<br>3. Females who are pregnant, breast feeding, planning to become pregnant during the study period or delivered a baby in the last 12 months<br>4. Individuals unwilling to follow any of the three study diets.<br>5. Individuals who are unwilling to monitor blood glucose at least three times a day.<br>6. Individuals who have lost 10 or more pounds in the last 6 months. |
| Number of Randomized Subjects | 84 randomized subjects (42 at UNC, 42 at Stanford)<br>Participants withdrawn from the study before randomization will be replaced. |
| Study Duration | Each subject's participation will last approximately 10.5 months. |

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| | Study data collection is expected to end by November 2020. Grant funding ends April 2021. |
| Study Phases | 1. Screening: screening for eligibility, recruiting and obtaining consent<br>2. Intervention: study intervention (randomization to diets)<br>(Note: Each clinical site will recruit approximately four participants a month over 12 months. Intervention will be ongoing once enrollment has begun.) |
| Efficacy Evaluations | Glycemic control: HbA1c and percent time in hypoglycemia (continuous glucose monitor worn for 14-days at each measurement visit). Change in weight. |
| Safety Evaluations | Participants will be asked about hypoglycemic events at each study visit and RD session (in person and telephone). The RDs will communicate regularly with the study endocrinologist to review labs and self-monitored blood glucose (SMBG) data to ensure appropriate insulin dosing. |
| Statistical and Analytic Plan | We will primarily compare the 3-month response rates to each of the 3 initial diets using standard statistical comparison procedures (e.g., t-tests and ANOVA) for differences in glycemic control (HbA1c and percent time in hypoglycemia) and change in weight.<br><br>In addition, we will conduct a series of secondary, hypothesis-generating analyses using standard statistical approaches as well as more complex fixed and mixed effect regression methods such as generalized additive models and random forests for these outcomes plus body fat and fat free mass. |
| Data and Safety Monitoring Plan | Data quality and safety monitoring will occur both within the research team (data quality committee) (monthly) and a 4-member DSMB (to meet twice yearly).<br><br>Participant accrual and retention, progress, completeness of standardized measures, and attendance at intervention sessions will be monitored. All aspects of data collection and data storage will be carefully monitored to ensure rapid detection of errors, inconsistencies or other problems. Distributions of key variables will be monitored for data quality and safety. AE and SAE, as defined by NIH, will be reported to the local site investigator and corresponding IRBs. AE/SAEs will be reviewed monthly. |

**Summary of changes related to COVID-19 Provisions, submitted with Protocol Version 7:**

As of April 2020, we are transitioning the entire study to a virtual format. All follow-up visits will be conducted virtually, and we will continue to enroll new subjects remotely as well. We are making changes according to the following table, described in detail in the protocol document:

| Data element | Method and timepoint conducted previously | Method and timepoint conducted now | Major changes |
|---|---|---|---|
| **Anthropometrics** | | | |
| Height | **In-person, all visits** | **At home, baseline only** | For existing participants, will use baseline height (avg of 2 closest). For new participants, the home height procedures (Section 8a) will be used. |
| Weight | **In-person, all visits** | **At home, all visits** | Participants will use their BodyTrace scale provided as part of their study participation to measure their weight |

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| | | | according to the home weight procedures (Section 8a). |
| Waist circumference | **In-person, all visits** | **At home, all visits** | Participants will be mailed a tape measure and provided with instructions as to how to collect this measurement at home (Section 8e). |
| **Lab-based** | | | |
| HbA1c | **In-person, all visits** | **At home, all visits** | At home collection kits will be used (Section 8a). |
| Fasting stored blood | **In-person if fasting and consented, all visits** | **No longer collecting** | This was not a primary outcome measure and is not feasible to collect at home (Section 8e). |
| Stool sample collection/storage (gut microbiome) | **Kit offered for home collection at baseline, Meas 2, Meas 3, and Meas 4** | **Kit shipped for home collection, Baseline, Meas 2, Meas 3, and Meas 4** | The only change to procedure is that the kit will be shipped directly to participants and they will receive their instructions remotely (Section 8e). |
| **BG/Ketones** | | | |
| Blood ketones | **Weekly at-home monitoring by participants on low-carb diet** | **No longer collection** | Participants have not been doing data collection for the most part and this data is not essential for outcomes (Section 8e). |
| CGM (% time in hypoglycemia and other measures of glycemia | **CGM sensor inserted by staff at all visits** | **CGM inserted at home by participant, all visits** | The Libre Pro Reader and sensor, along with all other necessary supplies for insertion, will be shipped to participants ahead of each virtual visit for at-home insertion. Participants will be provided with an instructional video link and written instructions (Section 8a). |
| **Self-Admin Questionnaires** | | | |
| All Self-Admin Questionnaires, including diet acceptability | **Completed online or in-person at all visits by participant** | **Completed online at the time of each measurement visit by participant or via phone or zoom interview with staff** | Participants will now complete the CES-D online. This form was previously completed by participants on paper at the in-person measurement visit (Section 8e). |
| COVID-19, Stress, Resilience, Food Security Form | **NEW** | **Completed online** | This form will be administered via CDART as an interview and completed at each virtual visit (Section 8e). |
| **Physical Activity** | | | |
| 24-Hour Diet and Physical Activity Recalls | **Phone interview by NORC staff after each meas visit** | **No change** | No change except participants will now be mailed the Food Amounts Booklet at their baseline visit or ahead of any visit if they have misplaced it (Section 8c). |
| Global Physical Activity Questionnaire | **In-person interview, all visits** | **Phone or Zoom interview, all visits** | Completed at time of 'virtual visit.' Showcards will be emailed to participants (Section 8c). |
| Garmin Wearable Component | **NEW** | **Home setup and wear** | Participants will receive written instructions and be guided through the setup process during a phone or zoom call (Section ?). |

| Other | | | |
|---|---|---|---|
| DXA (Body composition) | **In-person, all visits** | Discontinued | Cannot do virtually (Section 8b). |
| Urinalysis Pregnancy Test | **In-person, ahead of DXA scan, all visits** | Female participants will be asked to self-report pregnancy at the time of each virtual visit. | Pregnancy result will be recorded on DXA form. Participants will simply be asked if they are pregnant, no urinalysis will be required. Safety concerns of pregnancy are lessened now that DXA is discontinued (Section 8b). |

# 1. Executive Summary

Young adults with type 1 diabetes (T1D) commonly struggle with both glycemic control and weight. The prevalence of overweight and obesity among individuals with T1D now parallels that of the general population and contributes to central obesity, dyslipidemia, elevated blood pressure, and insulin resistance, increasing risk for cardiovascular disease. There is a compelling need to develop a program of research designed to optimize not just one, but two key outcomes – glycemic control and weight status – and to address the underlying metabolic processes and behavioral challenges unique to T1D. **Accordingly, our main objective is to develop a rigorous adaptive design to test the efficacy of a behavioral intervention to simultaneously optimize glycemic control and facilitate weight management among overweight young adults with T1D.** The intervention must be appropriate to the unique metabolic phenotype in T1D, and to biological and behavioral responses to glycemia (including hypoglycemia) that relate to weight management. The intervention must be safe, feasible to implement, and accepted by overweight young adults with T1D. In June 2015, we established a consortium called **ACT1ON**: **A**dvancing **C**are for **T**ype **1** Diabetes and **O**besity **N**etwork, which includes a transdisciplinary team of scientists at three institutions: University of North Carolina at Chapel Hill (UNC), Florida Hospital Translational Research Institute for Metabolism and Diabetes (TRI), and the Division of Pediatric Endocrinology and Diabetes at Stanford University. Together, we propose **Specific Aims** in three phases focused on young adults (age 19-30 years) with T1D. **This protocol covers one aim of the funded grant: Aim 2 (Phase 2).**

**Aim 2, Phase 2:** In Phase 2, an initial pilot and feasibility study will be conducted using a Sequential, Multiple Assignment, Randomized Trial (SMART) design to identify acceptable and effective dietary strategies to optimize both glycemic control and weight management in young adults with T1D. This pilot trial will include 84 randomized participants (42 at UNC, 42 at Stanford) in a 10.5 month behavioral intervention, with co-primary outcomes of glycemic control (HbA1C and hypoglycemia) and weight loss. (Note: data from Aim 1, Phase 1 approved under separate IRB approval will be utilized to inform the SMART pilot. Phase 1 Study 1 will inform calorie goals. Phase 1 Study 2 will inform potential counseling strategies related to dietary response to hypoglycemia).

## 2. Background and Significance

Young adults with type 1 diabetes (T1D) commonly struggle with both glycemic control and weight. The prevalence of overweight and obesity among individuals with T1D now parallels that of the general population[1,2] and contributes to central obesity, dyslipidemia, elevated blood pressure, and insulin resistance,[3–5] increasing risk for cardiovascular disease.[4,5] There is a compelling need to develop a program of research designed to optimize not just one, but two key outcomes – glycemic control and weight status – and to address the underlying metabolic processes and behavioral challenges unique to T1D.

**Glycemic Control in Young Adults with T1D:** The benefits of intensive glucose control were demonstrated by the DCCT,[6,7] with persistent benefit over 30 years later.[8] Higher HbA1c in teens/young adults as compared to adults over age 30 was well documented in the DCCT trial.[9] Recent T1D Exchange data demonstrate elevated HbA1c with a peak mean of over 9% in 17-year-olds, which remains elevated above 8% until a mean age of 30 years.[10] Thus, a significant number of young adults with T1D have glucose control similar to and even worse than DCCT participants in the conventional glycemic control arm, despite advances in technology and therapeutics.

**Prevalence and Consequences of Overweight and Obesity in T1D:** Historically, people with T1D were thin or of normal weight, in part due to poor glucose control. Many participants in the DCCT intensive treatment arm experienced weight gain,[11,12] which was associated with a poorer cardiometabolic profile.[3] Now, with common use of intensive insulin therapy, and paralleling trends in the U.S. population, there is a high prevalence of overweight and obesity among people with T1D.[1,2] Among young adults in the T1D Exchange Registry, 31% were overweight and 15% were obese.[10] Longitudinal studies show that obesity increases in people with T1D as they age.[13,14] Obesity is now accepted as an important contributor to long term cardiovascular risk in people with T1D.[4,5,15]

**Determinants of Energy Balance in T1D:** Standard equations for estimating energy expenditure and dietary requirements in healthy individuals are not adequate for those with T1D. First, in patients with uncontrolled T1D, glucosuria can account for 300-400 kCal/day in obligate energy losses.[16] Second, most studies demonstrate a modest increase in resting energy expenditure (REE; range=100-300 kCal/day) in people with T1D relative to healthy controls or predicted values.[16–20] The REE increase in T1D appears to be proportionate to the degree of hyperglycemia and has been attributed to increased hepatic gluconeogenesis, driven by hyperglucagonemia.[21] Other factors, including increased sympathetic nervous system activity, increased protein turnover and substrate transport across cellular membranes, alterations in the gut microbiome, [22] and increases in size of metabolically active organs,[23] may contribute to alterations in T1D energy expenditure. While exploration of these factors is beyond the scope of this proposal, there is an urgent need for a new and comprehensive assessment of the 24-hour energy requirements in people with T1D.

In addition to alterations in energy balance, T1D is characterized by impairments in metabolic flexibility, which is the ability of an organism to shift substrate oxidation rates to accommodate changes in substrate availability[24] and is important in the development of metabolic syndrome.[25] Compared to controls, people with T1D had

marked differences in substrate oxidation rates – with increased lipid oxidation during basal conditions – blunted ability to shift to carbohydrate oxidation during meals, and decreased thermic effect of food.[16–21] Metabolic inflexibility is implicated in the development of insulin resistance in obesity and T2D, and may similarly contribute to the metabolic syndrome and increased risk of CVD in T1D.[24,25]

**Weight Loss and Eating Behaviors Unique to T1D:** Successful weight loss strategies address both behavioral and psychosocial elements,[26,27] grounded in established theoretical frameworks to promote behavior change, such as the Health Belief Model,[28] Transtheoretical Model,[29–31] and Theory of Reasoned Action.[27,32] Self-monitoring of dietary intake and weight, use of caloric restriction, fewer calories from fat, and high levels of physical activity contribute to sustained weight loss and weight gain prevention in the general population.[12,26,27,33] Conditions unique to T1D – including fear of hypoglycemia,[34] diabulimia,[35] or hypoglycemia-induced binging – may interfere with weight loss and maintenance efforts.[5]

The process of glycemic management in T1D may interfere with achieving and maintaining healthy weight via unintended consequences of dietary restriction. Dietary restraint refers to intentional and sustained restriction of caloric intake to achieve weight loss or maintenance.[36,37] T1D is described as a food culture of dietary restraint in that a strict dietary regimen[38,39] characterized by carbohydrate counting drives imposed food preoccupation.[40] Self-report measures of dietary restraint in T1D patients showed higher dietary restraint was associated with poorer glycemic control.[41] Recurrent hypoglycemia and its associated intense hunger and permission to eat forbidden sugary foods may lead to over-eating, guilt, restriction, and possibly more episodes of hypoglycemia, creating a self-perpetuating cycle of disordered eating behavior resembling binge eating disorder and bulimia.[42] As this restrictive-excess intake cycle repeats, individuals may increase their risk for weight gain[43–46] and worsening glycemic control. Thus, models for disordered eating behaviors in T1D have expanded from insulin manipulation for weight loss to identify hypoglycemia as an important part of a cycle of dietary restraint[39,40,47] in which hypoglycemia and its treatment can disrupt physiological hunger cues and result in a net surplus of calories with potential weight gain and worsened glycemic control.[48]

**Dietary Approaches to Weight Loss:** According to the American Diabetes Association (ADA)'s Nutrition Therapy Recommendations, **individualization of dietary recommendations is recommended** to account for metabolic status, clinical goals, preferences, and sociocultural considerations.[49] Optimal dietary approaches to weight management and metabolic control are highly controversial: studies (essentially all in T2D) vary in dietary approach, sample population, T2D duration and T2D treatment regimen, and importantly, in participant retention, particularly in the more restrictive dietary approaches.[50,51] As reviewed by Evert et al.,(2013)[49] weight management approaches in Look AHEAD[52] (low fat diet) and a Mediterranean dietary pattern approach[53] were effective in weight loss and HbA1c improvement. Both approaches incorporated relatively high carbohydrate intake (~50-55% of calories). Current ADA Standards of Medical Care[54] emphasize that, for T2D patients, weight loss can be achieved with hypocaloric diets with macronutrient composition based on the individual patient's medical status and preferences. However, in a subset of

individuals with T2D from PREDIMED, a Mediterranean diet supplemented with either olive oil or nuts, but not explicitly calorically restricted, led to significant weight loss.[55]

On average, people with T1D consume 45% of calories from carbohydrates,[51,56] significantly less than the general US population.[53] Further, in T1D, higher intake of carbohydrate is associated longitudinally with higher HbA1c.[57] In T2D, a one-year hypocaloric low carbohydrate (14%) diet was effective in promoting weight loss, improving glycemic control and variability, and improving CVD risk factors.[58] Thus it is reasonable to consider that, in T1D, a lower carbohydrate diet may be acceptable and beneficial in promoting weight loss and glycemic control. **Randomized controlled clinical trials that evaluate dietary approaches to optimize both weight management and glycemic control in T1D have not been conducted. Our proposed work will provide critically needed information to optimally design such a trial.**

**Sequential, Multiple Assignment Randomized Trial (SMART) Designs:** Sequential multiple assignment randomized trials (SMARTs) have become increasingly important tools in biomedical research because of their ability to efficiently address practical treatment comparison questions in clinically realistic settings. SMART designs address intervention decisions that unfold over time and can adapt dynamically based on patient response,[59–61] as is crucial in T1D treatment. The proposed pilot SMART design will evaluate the effectiveness of experimental diets in the context of anticipated variation in patient response, both across patients and within patients over time.

## 3. Study Objectives

Our main overall objective is to develop a rigorous adaptive design to test the efficacy of a behavioral intervention to simultaneously optimize glycemic control and facilitate weight management among overweight young adults with T1D. We propose **Specific Aims** in three phases focused on young adults (age 19-30 years) with T1D. ***This protocol covers Aim 2 (Study Phase 2).***

**Aim 2, Phase 2:** Phase 2 is an initial pilot and feasibility study using a Sequential, Multiple Assignment, Randomized Trial (SMART) design to identify acceptable and effective dietary strategies to optimize both glycemic control and weight management in young adults with T1D. This pilot trial will include 84 randomized participants (42 at UNC, 42 at Stanford) in a 10.5 month behavioral intervention, with co-primary outcomes of glycemic control (HbA1C and hypoglycemia) and weight loss. (Note: data from Aim 1 Phase 1, approved under separate IRB approval, will inform the SMART pilot. Phase 1 Study 1 will inform calorie goals. Phase 1 Study 2 will inform potential counseling strategies related to dietary response to hypoglycemia.)

**Specific objectives of SMART pilot work are as follows:**

- **To assess acceptability and adherence to three distinct, evidence-based dietary approaches designed to address weight management and glycemic control.** Behavioral counseling strategies, use of carbohydrate counting for insulin dosing, and encouragement of the participant's usual level of physical activity will be the same across the 3 diets. Diets are as follows:
  - *Diet 1*: hypocaloric, moderate low fat (30% calories from fat) weight management based on the Look AHEAD study[52]
  - *Diet 2*: hypocaloric, low carbohydrate (15-20% calories from carbohydrate, 59-63% as total fat (<10% saturated fat, at least 37% monounsaturated fat, remaining as polyunsaturated fat)[58]
  - *Diet 3:* advice to select a healthy Mediterranean dietary pattern[49,55] with no caloric restriction

- **To generate data required to inform a fully powered SMART design by**:
  - estimating the reduction in weight and body fat for each of the three diets
  - estimating the improvement in glycemic control (HbA1c, hypoglycemia) for each of the 3 diets
  - comparing the effectiveness and acceptability of the 3 dietary approaches to concurrently optimize weight and glycemic control outcomes

## 4. Site Descriptions and Targets

The two clinical sites include the 1) University of North Carolina at Chapel Hill (UNC-CH) and 2) Division of Pediatric Endocrinology and Diabetes at Stanford University. Both clinical sites are well-established academic medical centers with vast experience in diabetes translational research. UNC-CH will also oversee coordination of the SMART pilot. Northwest Lipid Research Laboratory in Seattle, Washington will complete the required laboratory (blood sample) analysis for the SMART Pilot. **COVID-19 PROVISIONS:** *Due to ramifications of the COVID-19 Pandemic, we are no longer able to have samples assayed with Northwest Lipid Metabolism and Diabetes*

*Research Laboratories in Seattle, Washington. We will be using the Diabetes Diagnostic Laboratory at the University of Missouri. Existing specimens stored at the Northwest Research Laboratories will be transferred to the Stanford University School of Medicine for storage.*

Participant Recruitment: Stanford: The recruitment goal for Stanford will be 42 participants (~ 4/month over 12 months). Among the current patient population at Stanford, approximately 300 are between the ages of 19-30 and meet study inclusion criteria for weight and HbA1c.

Participant Recruitment: UNC: The recruitment goal for UNC is 42 (~4/month over 12 months). The number of patients in the UNC Health Care System who meet our inclusion criteria is approximately 150 and in addition, the UNC Student Health center follows about 100 T1D patients. If necessary, UNC-CH may also recruit from T1D patients seen at the nearby Duke Diabetes clinic.

Only those participants who withdraw from the trial *before randomization* will be replaced.

## 5. Selection & Recruitment of Subjects

**Inclusion criteria**

Males and females ages 19-30 years old with a diagnosis of type 1 diabetes for greater than one year. Individuals must have most recent HbA1c (measured within last 6 months at time of phone screening) of less than 13% and BMI of 27-39.9 at time of phone screening.

**Exclusion criteria**

The following individuals will be excluded from study participation: individuals with other serious metabolic disorders that would render participation unwise, diagnosed eating disorder, or those with other serious conditions that renders participation inappropriate. Individuals who have experienced DKA or severe hypoglycemia requiring outside assistance in the past 6 months will be excluded. Females who are currently pregnant, breastfeeding, planning to become pregnant during the study period or who have delivered a baby in the last 12 months will be excluded. Individuals who are unwilling to follow any of the three study diets will be excluded. Individuals who are unwilling to self-monitor blood glucose levels at least three times a day will be excluded. Individuals who have lost 10 or more pounds in the last 6 months will be excluded.

Medical records will be used to identify patients who potentially meet the eligibility criteria for this study. Medical records will also be used to collect information related to the participant's diabetes care, as well as demographic information. For individuals contacting us about study participation, medical record review will not be required; instead, we will rely on self-report of relevant screening criteria.

Participants may reach out to us after seeing the study on Join the Conquest or through another Type 1 diabetes support network. We will work with NC TraCS to establish recruitment through MyChart.

***Strategies to Optimize Recruitment and Retention:*** Study staff at UNC-CH and Stanford will be responsible for local recruitment activities. Recruitment will use a combination of targeted mailings/emails with phone follow-up and in-person clinic-based strategies. Our recruitment process will utilize the highly successful two-step recruitment strategy used in the FLEX study, consisting of sending an informative recruitment letter/email to eligible participants and following with a series of phone calls by research staff.

***COVID-19 VIRTUAL VISIT TRANSITION (4/2020) -*** *All recruitment of new subjects will be conducted electronically. The protocol has been altered to reflect this.*

Recruitment Step 1: Initially, prospective participants will be emailed an invitation letter with an electronic study brochure. Research staff will follow-up with a brief telephone call to explain the study and ascertain participant interest. If participants are interested, research staff will schedule a second follow-up call (described in recruitment step 2).

If we are unable to reach participants because of what seems to be outdated or incorrect contact information, we may use EPIC and a subscription service 'Accurint' to search for updated contact information.

Recruitment Step 2: Potential participants who remain interested following the initial telephone contact will be emailed a document providing additional details about the study ("Frequently Asked Questions" (FAQ)), which will include common barriers or issues that could impede participation in the study. This mailing/email will also include the Participant Study Flowsheet, which displays the schedule of measurement activities and RD encounters, and the Microbiome Information Sheet, which provides information about the optional stool collection activity in the study. Staff will review these documents and specific barriers or concerns for the potential participant during a follow-up telephone call with the potential participant. The conversation will be individualized and will incorporate strategies of motivational interviewing as a way to allow the potential participant to identify, express, and discuss any of their concerns about participation. This two-step recruitment process will help ensure the participant understands the study fully before deciding to participate.

Recruitment materials will also be prominently displayed in the diabetes clinic waiting area and exam rooms at both sites. ACT1ON study personnel may also utilize in-person recruitment of eligible participants during usual care visits.

***COVID-19 VIRTUAL VISIT TRANSITION (4/2020) –*** *Recruitment materials will no longer conducted in-person.*
Additionally, we will incorporate successful retention strategies from FLEX (e.g., offering flexible visit options, incentives that increase over time {baseline: $100, 3-mo: $150, 6-mo: $200, 9-mo: $250}.

## 6. Process of Obtaining Consent

Participants will have opportunity to provide informed consent following the two-step recruitment process detailed above. For participants who agree to participate and schedule a baseline visit, the study consent form will be emailed to the participant prior to the Baseline Visit, so that the individual has ample time to review it on their own ahead of the visit. Participants will also be provided with instructions on how to use CDART, the data management system that we will employ to house participant data and house self-administered questionnaires. This email will also include a personalized link to a Qualtrics questionnaire, which provides participants the chance to read a consent form specific to completing baseline forms ahead of the virtual visit with the ACT1ON team coordinator.

***COVID-19 VIRTUAL VISIT TRANSITION (4/2020) -*** *Participants will have opportunity to provide informed consent following the two-step recruitment process detailed above. Prior to the virtual visit, study staff will review the full study consent via Zoom or telephone in detail before standardized data collection begins. For participants who agree to participate and schedule a baseline visit, the study consent form will be emailed prior to the consent conversation so that the individual has ample time to review it on their own ahead of the visit. The participant will be given as much time as needed to review the consent form and ask any questions prior to signing it. Participants will be informed that participation in the study is voluntary and they are free to withdraw their consent and discontinue participation in this research at any time. Study staff obtaining consent will utilize the tailored Consent Comprehension Checklist to guide a conversation with the participant that aims to ensure that she or he understands what she or he is consenting to and the nature of informed consent itself. Following the consent conversation, participants will be provided with instructions on how to use CDART, the data management system that we employ to house participant data and house self-administered questionnaires.*

*We will reconsent all currently enrolled participants using the consent addendum. This will be completed with participants prior to the beginning of any data collection for their next upcoming measurement visit.*

Following consent, participants may be involuntarily withdrawn from the study per the investigator's discretion if they develop a serious condition that would render participation unwise, including difficulties with glycemic control and/or serious physical or psychiatric conditions. Females who become pregnant will also be withdrawn from study participation.

## 7. Randomization

*Sequential randomization (Baseline, ~3 months, and ~6 months*). At the start of the study, diet randomization schemes will be determined by computer for each individual.

Permuted block randomization with blocks of size 24 will be used to assign all 12 potential treatment regimes using R statistical software. This will be confidentially generated by the statistician and placed into CDART data management software to be revealed only at the point of treatment (diet) assignment for each patient.

Following the baseline data collection and a short run-in period, the initial diet randomization will be revealed to the participant. Based on a priori decision rules at 3 and 6 months post-initial randomization, those for whom the diet assigned is not acceptable or is not effective will have the next diet assignment revealed (be re-randomized). A total follow-up time of 10.5 months allows for evaluation of the effect of the diets on initial weight loss and on early maintenance of initial weight loss. The decision criteria for re-randomization (Table 7.1) will incorporate both clinical outcomes (glycemic control and weight change) and acceptability of the diet to the participant as indicated on the Diet Acceptability Form.

Following Measurement Visit 2, participants meeting one or more criteria for re-randomization will have the next diet in their individual randomized diet scheme revealed (one of two diets not yet experienced); otherwise, participants will continue their original diet assignment. Following Measurement Visit 3, decision criteria will be applied again. Participants meeting re-randomization criteria will have the next diet in their individual randomized diet scheme revealed (for participants who had continued on the original assignment at the 3-month mark, this will be one of the two remaining diets; for those who received a new diet, the only remaining untried diet will be assigned). By the end of the study, each participant will have either been on a diet that was acceptable and effective for a period of time or will have tried all 3 diets. For individuals assigned to one of the hypocaloric diets (low carbohydrate or Look AHEAD), at Measurement Visit 2 and/or Measurement Visit 3 the calorie prescription will be re-calculated to incorporate body weight and composition at that time. Note that at 3 and 6 months, if weight loss has been achieved that classifies participant as "normal weight" then 'weight change' criteria (see Table 7.1) does not apply for re-randomization. For these individuals, the RD will advise the participant regarding weight loss maintenance in the context of their assigned diet.

**Table 7.1 Re-Randomization Criteria. Re-assignment of diet will occur if one or more criteria are met.**

| Time post-initial randomization | Diet acceptability | Weight change | Glycemic control since baseline |
|---|---|---|---|
| **3 and 6 months** | Unacceptable based on Diet Acceptability Form | Not achieving at least 2% loss in body weight from previous measurement visit. Exception: if weight loss has been achieved that classifies participant as "normal weight" then this criteria does not apply | Self-report of increased hypoglycemia<br>or<br>HbA1c ↑ ≥ 0.5% |

## 8. Standardized Measurements

### 8a. Primary Outcomes

*Anthropometric Measurements:*

The primary outcome of weight change will be assessed through measurement of anthropometrics. Study visits completed prior to the virtual transition included a height and weight measurement at each study visit utilizing standardized methods described in the SEARCH study protocol (available online, www.searchfordiabetes.org).

***COVID-19 VIRTUAL VISIT TRANSITION (4/2020) -*** *Height will be obtained either from medical record or via self-report. Weight will be measured at home using the BodyTrace scale provided by the study for intervention support. We will calculate body mass index (BMI) from these measurements.*

*Glycemic control*: HbA1c (assayed at the Diabetes Diagnostic Laboratory at the University of Missouri as of virtual visit transition, using HPLC) will be used as a measure of long-term glycemic control. Continuous Glucose Monitoring (CGM): The Freestyle Libre Pro CGM will be used to collect short-term glycemia, including frequency and time spent in hypoglycemia. Study visits completed prior to the virtual transition included use of CGM applied by a study staff member. With transition to virtual visits (4/2020), the CGM will be applied at home by participants at the time of each virtual visit. Participants will be provided with written instructions as to how to apply the CGM, along with a link to a video outlining and demonstrating the process. The CGM will continue to be worn for 14 days. At the baseline visit, the participant will have been instructed on the use of the study CGM (for participants enrolled remotely, this will occur at the virtual baseline visit), namely duration of wear and how to remove the CGM after the wear period. During CGM wear, participants will be instructed to perform blood glucose measurements as they normally do according to physician guidance. Participants who are already using a CGM for glucose management will be advised to continue to do so.

Additionally, participants will be queried regarding occurrence of both non-severe and severe hypoglycemia by their RD at each encounter (check-in and longer remote sessions). Participants will also be queried regarding increased hypoglycemia on the short and long diet acceptability forms, completed between and at measurement visits. Consistent with a recent report on consensus guidelines for the use of continuous glucose monitoring, contributed to by MPI Maahs,[62] we define hypoglycemia as CGM-based glucose <70mg/dl for more than 10 min, not requiring help from another person.

### 8b. Secondary outcomes:

*Body Composition*:

Body composition will be assessed via a full body dual energy x-ray absorptiometry scan. For female participants, a urinalysis pregnancy test will be performed at each in-person measurement visit prior to the DXA measurement. Participants who become pregnant will be withdrawn from the study. Participants will be asked to remove any

clothing that might contain metal, hard plastic, or any other materials that could interfere with the DXA scan. A trained DXA technician will enter the height, weight, gender, and ethnicity of each subject into the device's default software prior to performing each scan. During each scan, participants will rest in a supine position in the center of the scanning table with their hands at their sides, while minimizing movement as much as possible. Outcomes of interest for the current study included lean mass (LM), fat mass (FM), body fat percentage (BF%),visceral adipose tissue (VAT), android/gynoid (AG) fat mass ratio, and fat free mass (FFM). To ensure the accuracy of this measurement, participants will be advised to arrive at all DXA measurement visits having fasted and avoided exercise for at least 2 hours prior.

**COVID-19 PROVISIONS-VIRTUAL VISITS:**
*Body composition will **no longer be** assessed as of modifications submitted in April of 2020, as DXA scans cannot be completed virtually. For participants attending in-person visit prior to the virtual transition, body composition was assessed via a full body dual energy x-ray absorptiometry scan. For female participants, a urinalysis pregnancy was performed at each in-person measurement visit prior to the DXA measurement for safety purposes. **With transition to virtual visits (4/2020),** participants will no longer be tested for pregnancy. Rather, female participants will be queried at each measurement visit regarding current pregnancy status.*

*Other Glycemia Measures:* We will use CGM data to explore additional measures of glycemic variability.[62]

*As we are no longer doing a blood draw and not collecting stored whole blood and plasma, and therefore are not asking participants to fast, that we will not ask participants to report their blood sugar or whether or not they have had anything to eat in the last 8 hours. The only fields of the 'specimen collection form' that we will complete are those that pertain to the HbA1c collection, that is, time and date of collection along with any problems the participant may have had.*

**Table 8.1**

| Outcome/Measure | Meas. Visit 1 (Baseline; -14 days) | ~ 1 mo | Meas. Visit 2 | ~ 4 mo | Meas. Visit 3 | ~ 7 mo | Meas. Visit 4 (End of Study) | Conducted remotely? |
|---|---|---|---|---|---|---|---|---|
| **Anthropometric Measurements** Height | X | | X | | X | | X | Baseline only |
| Weight | X | | X | | X | | X | Yes |
| Waist | X | | X | | X | | X | Yes |
| **Glycemic Control** HbA1c | X | | X | | X | | X | Yes |
| % time in hypoglycemia (CGM) | X | | X | | X | | X | Yes |
| **Secondary Outcomes** | | | | | | | | |
| DXA (Body composition) | X | | X | | X | | X | No |
| CGM (Other measures of glycemia) | X | | X | | X | | X | Yes |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Urinalysis Pregnancy Test (biologically female participants only, prior to DXA) | X | | X | | X | | X | No |
| **Dietary Intake and Physical Activity** | | | | | | | | |
| 24-Hour Diet and Physical Activity Recalls | X | | X | | X | | X | Yes |
| Global Physical Activity Questionnaire | X | | X | | X | | X | Yes |
| **Potential Mediators** | | | | | | | | |
| Diet History Questionnaire III | X | | X | | X | | X | Yes |
| Diabetes Eating Problem Survey | X | | X | | X | | X | Yes |
| Weight Related Eating Questionnaire | X | | X | | X | | X | Yes |
| Barratt Impulsiveness Scale | X | | X | | X | | X | Yes |
| Food Craving Inventory | X | | X | | X | | X | Yes |
| Nutrition Knowledge Questionnaire | X | | X | | X | | X | Yes |
| **Additional Measures** | | | | | | | | |
| Demographics | X | | | | | | | Yes |
| Health History | X | | X | | X | | X | Yes |
| Diabetes-Specific Quality of Life | X | | X | | X | | X | Yes |
| Generic Quality of Life | X | | X | | X | | X | Yes |
| Low Blood Sugar Survey | X | | X | | X | | X | Yes |
| Sleep Disorders Questionnaire | X | | X | | X | | X | Yes |
| Centers for Epidemiologic Study - Depression Scale (CES-D) | X | | X | | X | | X | Yes |
| Diabetes Stigma Assessment Scale | X | | X | | X | | X | Yes |
| Fasting stored blood (future assessment of genetics, lipids and other parameters TBD) | X | | X | | X | | X | No |
| Stool sample collection/storage (gut microbiome) | X | | X | | X | | X | Yes |
| Blood ketones | At home weekly check for those on a low carbohydrate diet. | | | | | | | Discontinued 4.8.2020 |
| **Study Acceptability** | | | | | | | | |
| Diet Acceptability-Long Form | | | X | | X | | X | Yes |
| Diet Acceptability-Short Form | | X | | X | | X | | Yes |
| Exit Interview | | | | | | | X | Yes |
| **Added after virtual transition** | | | | | | | | |
| Stress/Resilience/Food Security/COVID-19 questions | X | | X | | X | | X | Yes |
| Pregnancy self-report | X | | X | | X | | X | Yes |

## 8c. Dietary Intake and Physical Activity

Dietary adherence will be monitored via 24-hour dietary recalls. Recalls will be done on two unannounced days during the 14-day CGM wear time after each measurement visit. These recalls will be obtained by telephone by trained and certified interviewers from the UNC NIH/NIDDK Nutrition Obesity Research Center (NORC) staff (P30DK056350; MPI Mayer-Davis) under the direction of Dr. Mayer-Davis (Diet Assessment Core Director), using the Nutrient Data System for Research (NDSR) software and the multiple pass interviewing method.[63,64]

The validated[65,66] *Previous Day Physical Activity Recall (PDPAR)* will be under the direction of the UNC NORC, to be administered concurrent with the 24-hour dietary recalls, as we have done previously.[67] The PDPAR divides the day into half-hour time blocks and queries the dominant activity and the approximate intensity of that activity for that period, categorized as ‘‘light,’’ ‘‘medium,’’ ‘‘hard,’’ or ‘‘very hard.’’

As an additional measure of physical activity, we will administer the *Global Physical Activity Questionnaire (GPAQ)*, via interview during virtual measurement visits. The GPAQ is an adaptive, interview-based questionnaire developed by the World Health Organization (WHO), collects information on physical activity in three areas: activity at work, traveling from place to place, and recreational activities. It also collects information on sedentary time.[68]

## 8d. Potential Mediators

We will assess food frequency and habitual dietary patterns using the Diet History Questionnaire III (DHQ III).[69,70] To capture disordered eating behavior, the Diabetes Eating Problem Survey[71] will be combined with non-T1D specific ingestive behavior questionnaires. The Weight-Related Eating Questionnaire (WREQ) assesses emotional eating, disinhibition, and restrained eating behavior/cognitive restraint.[72] The Barratt Impulsiveness Scale[73] (BIS-15), assesses trait impulsivity, including non-planning, motor impulsivity, and attention impulsivity.[74] The Food Craving Inventory[75] assesses the degree of craving for a variety of foods. Finally, the Nutrition Knowledge Survey, validated in people with T1D,[76] assesses healthful eating knowledge, carbohydrate counting, blood glucose response to foods, and nutrition label reading.

## 8e. Additional Measures

*Anthropometric Measurement:*

Waist circumference will be measured at each study visit utilizing standardized methods described in the SEARCH study protocol (available online, www.searchfordiabetes.org). **COVID-19 PROVISIONS - VIRTUAL VISITS -** *Waist circumference will be measured at home at the time of each virtual study visit by the participant. Participants will be provided with instructions as to how to measure their natural waist by holding the tape level and using the aid of a mirror.*

At the Baseline (Measurement 1) virtual visit, participants will complete the Demographics Form to collect basic demographics, including birthdate, gender,

ethnicity, race, date of diabetes diagnosis, and information about education and employment. Also at baseline, participants will complete the Health History Baseline Form to ascertain information related to health history, diabetes care, and health insurance.

The Health History Follow-Up form will be administered at Measurement Visits 2, 3, and 4, to update information related to health history, diabetes care, and health insurance as needed.

To assess diabetes-related quality of life, we will administer the DCCT-validated measurement form Diabetes-Specific Quality of Life (DQOL).[77] We will assess non-T1D specific quality of life using the MOS 36-item short form (SF-36), created as part of the Medical Outcomes Study (MOS)[78] to assess health-related quality of life. We will also assess behaviors and worries related to hypoglycemia using the Low Blood Sugar Survey.[79]

The Sleep Disorders Questionnaire will be used to obtain sleep duration and quality over the preceding month.[80] We will assess depressive symptoms using the Centers for Epidemiologic Study Depression Scale (CES-D).[81] The Diabetes Stigma Assessment Scale (DSAS-1) will assess experience and views related to stigma and T1D.[82]
We will administer the four part data collection form: COVID-19, Stress, Resilience, Food Availability Form, which is a combination of questions based of the newly developed World Health Organization Survey Tool and Guidance: Rapid, simple, flexible behavioural insights on COVID-19[112]; a globally validated 14-item Perceived Stress Scale (PSS)[113]; and the Connor-Davidson Resilience Scale 25 (CD-RISC-25)©[114]; and USDA Food Security Screener (2019).[115]

Fasting blood will be collected at each study visit to allow for storage of blood and plasma for future testing. Samples will be stored for future testing of lipids and other analyses. We will also include storage of whole blood from the baseline visit only for future DNA/genetics work.

**COVID-19 PROVISIONS-VIRTUAL VISITS:** *With the transition to virtual visits, fasting blood and plasma for storage will no longer be collected.*

Participants will complete at home stool collection after the Baseline (Measurement 1) Visit and Measurement Visit 2. Stool samples will be analyzed using 16s rRNA sequencing and analysis of short chain fatty acids using liquid-chromatography mass-spectrometry.

**COVID-19 PROVISIONS-VIRTUAL VISITS:** *Participants who have not taken antibiotics in the past 4 weeks will still be eligible to complete a stool sample at the time of the baseline and measurement visit 2. The stool kits and written instructions with step-by-step photographed procedures will be mailed directly to participants and further instructions will may be provided remotely, through a phone/zoom call.*

Participants on the low carbohydrate diet may be asked to check their blood ketones once weekly using the Nova Max© Plus glucose monitoring system, along with Nova Max ketone testing strips, provided by the study. **Note: as of 4/2020**, the study is discontinuing weekly checks of blood ketones for participants on the low carbohydrate diet due to lack of participation by study participants.

### 8f. Study Acceptability

*Diet Acceptability*: An appropriate instrument with known psychometric properties to systematically assess acceptability of specific diets could not be identified in the literature. Therefore, we developed and piloted a simple five-item assessment for this purpose. From a pre–test, Chronbach's alphas were 0.89 and 0.87 for weeks four and ten, respectively, indicating high internal consistency among questionnaire items.

Two versions of the diet acceptability will be utilized in this study. The Diet Acceptability Long Form includes the five-item assessment of diet acceptability along with five items associated with blood glucose management and hypoglycemia relative to the study diet. This form will be used to assess acceptability of diet at Measurement Visits 2, 3, and 4. The Diet Acceptability Short Form includes only the five questions relative to study diet acceptability. Participants will be asked to respond to this form approximately one month after beginning a study diet period (months 1, 4, and 7).

Overall study acceptability will be ascertained at the conclusion of the intervention period. Study staff will conduct an exit interview with study participants to gather feedback on the study, including intervention design, process, and education materials.

## 9. ACT1ON SMART Pilot Intervention

### 9a. SMART Pilot Overview

*Intervention Arms*: Through the sequential randomization process, three evidence-based diets will be evaluated. Diets were selected purposefully to vary substantially in macronutrient composition and in whether or not calories are explicitly restricted.

Diet 1: Look AHEAD (hypocaloric): The Look AHEAD "intensive lifestyle intervention" will be followed, except that the calorie prescription will be T1D-specific and individualized based on findings from energy balance modeling in Phase 1 Study 1, calculated to attain the Look AHEAD weight loss goal of 7% body weight loss/1 year. The caloric distribution will be <30% fat, <10% saturated fat, and ≥15% protein.[83]

Diet 2: Low Carbohydrate (hypocaloric): We will implement a low carbohydrate diet similar to the diet described by Tay et al.,(2015)[58] which resulted in significant weight loss and improved metabolic status with no adverse impact on LDL cholesterol in patients with T2D over 12 months. The caloric distribution will be: 15-20% from carbohydrate, 22-27% from protein, with fats being at least 37% monounsaturated fat and <10% as saturated fat). Individualized calorie goals will be established in the same manner as for Diet 1.

Diet 3: Healthy (Mediterranean) Dietary Pattern (not calorically restricted): This approach is justified by the PREDIMED diet, which employed Mediterranean diets without caloric restriction and resulted in reduced weight and waist circumference

among people with T2D, despite supplementation with either olive oil or nuts.[55] Current ADA guidelines also support use of healthy dietary patterns such as the Mediterranean diet.[49] In patients with T1D, common current clinical practice for weight loss is to advise reduced consumption of energy dense, nutrient poor foods and encourage consumption of healthy foods with ongoing carbohydrate counting for glycemic management. Diet 3 will use this approach and clarify appropriate food choices consistent with PREDIMED dietary guidance, but without the direct provision of olive oil or nuts, which is not practical. Dietary guidance includes: (1) abundant use of olive oil for cooking and dressing; (2) increased consumption of fruits, vegetables, legumes and fish; (3) reduction in total meat consumption, recommending white meat instead of red or processed meat; (4) preparation of homemade sauce with tomato, garlic, onion, and spices with olive oil to dress vegetables, pasta, rice and other dishes; (5) avoidance of butter, cream, fast food, sweets, pastries and sugar-sweetened beverages; and (6) in alcohol drinkers, moderate consumption of red wine.[55]

### 9b. SMART Pilot Procedures

***All RD sessions are conducted remotely following the restrictions placed on in person visits due to COVID-19.***

The initial counseling session, following baseline measurement but prior to initial randomization, will be designed to explore the participant's past experiences with both glycemic control and weight management. An overview of healthy diet and general concepts related to weight management will be discussed. Motivational interviewing will be used to facilitate discussion of the participant's perceptions of challenges and strengths related to diabetes self-management, including glycemic control, dietary choices, and weight management. Problem-solving skills training will be initiated. This initial session will establish the MI/PSST process, which will be used for all diets. Depending on results of Phase 1 Study 2 project on hypoglycemia, this initial counseling session will incorporate a discussion of problem-solving related to dietary response to hypoglycemia. Because self-monitoring will be used for all diets, we have designed a simple, one-week run-in period during which participants will monitor carbohydrate grams and weight. Participants will be shown how to use "MyFitnessPal," an app commonly used by individuals with T1D for carbohydrate counting. Participants will also be provided with a Body Trace scale for home use. This scale transmits weight using the cellular network, through which we can confirm self-monitoring.[84]

Further virtual counseling sessions will provide specific instruction and ongoing MI and PSST related to dietary adherence and glycemic control in the context of diet assignment. Self-monitoring of dietary intake and weight as relates to goal setting and attainment will be reviewed, and problem-solving skills developed to address barriers to adherence will be encouraged. The participant will be queried and any difficulties related to blood glucose management in the face of the experimental diet will be addressed.

Periodic shorter phone check-in sessions will focus on review of goal attainment and problem-solving strategies.

For an overview of measurement and intervention contacts, see Figure 9.1.

## 9c. Intervention Components

*Behavioral Framework for Dietary Interventions:* We will deploy the behavioral framework established and refined by the FLEX study team as an adaptive method to help individuals accomplish individualized goals that improve self-management.[85] Theories of health behavior,[86,87] and analysis and integration of theory in social and health psychology,[88,89] suggest a conceptual framework positing knowledge, motivation, and skills as necessary for behavior change. Our application of this theory is to integrate motivational interviewing (MI) and problem-solving skills training (PSST) approaches into a coherent intervention and to supplement these with pragmatic tools tailored to overcome specific barriers to adherence. MI, an effective,[90–92] patient-centered approach to health behavior change, is used to help individuals resolve ambivalence about change and to enhance intrinsic motivation by creating a motivational frame for change.[93–95] Once this motivation for change is achieved, PSST, a systematic approach to problem-solving, is presented as a way to make desired changes.[91–100]

*Registered Dietitian (RD) Counseling:* Shown in Figure 9.1, RDs will conduct 18 sessions over 10.5 months: 8 longer virtual counseling and education sessions and 15 phone "check-in" sessions, a framework similar to the ADA guidelines for intensive lifestyle counseling for weight management.[54] Study RDs will be centrally trained and certified to deliver the proposed intervention, including use of the MI and PSST counseling strategies, and delivery of education related to adherence to the specified experimental diets. All RD sessions will be documented, including audio-recording of the in-person sessions to enable ongoing assessment of fidelity of intervention delivery. For all 3 diets, self-monitoring of diet and weight will be encouraged in the context of individual goal-setting. Participants will be encouraged to continue on with their usual level of physical activity throughout the study, as this study is focusing on changes to diet. Counseling related to glucose management and physical activity will be provided as needed, and carbohydrate counting will be reinforced for insulin dosing. Participants on the low carbohydrate diet will learn about necessary insulin dosing adjustments related to higher protein and fat intake. The participants will be queried and any difficulties related to blood glucose management in the face of the experimental diet will be addressed.

*Intervention Materials:* The study team developed intervention materials for each of the study diets. Materials will utilize motivational interviewing (MI) techniques and problem solving skills training (PSST). MI[94] is a collection of patient-centered interviewing techniques that can be used as the context for virtually any psychological or behavioral intervention. MI is designed to create a collaborative environment in which patients can develop arguments for change, understand and resolve their ambivalence to change, develop strategies for change, and increase their confidence in their coping abilities.[93,94] PSST teaches problem-solving as a behavior process through which individuals can accomplish the task of self-management.[95,96]

The initial RD session focuses on providing an overview of healthy eating strategies, reviewing use of MyFitnessPal and the BodyTrace scale, use of nutrition labels, and an introduction into PSST strategies. Additional intervention sessions will utilize study diet materials to teach use of the specific diet to help the study participant achieve a healthy

diet within the guidelines of the specific study diet. Materials will include guidance on insulin dosing, caloric intake (for the two hypocaloric study diets), self-monitoring of dietary intake and weight, modification of a typical daily intake to meet guidelines of the specific study diet, use of nutrition labels, and PSST to identify specific goals within the context of use of the study diet in day-to-day life. Additional materials to be provided include guidance for eating out, recommendations for exercise for individuals with T1D, sample meal plans for each of the study diets, guidance for alcohol intake for individuals with T1D, and recognition of signs and symptoms for hyperglycemia, hypoglycemia, and diabetic ketoacidosis.

*Fidelity:* All full-length intervention sessions will be audio-taped. Fidelity assessment will include review using a content fidelity checklist. Initially, the first two of each session type (initial, introduction to each diet, follow-up to each diet) by each RD will be reviewed. A random sample of other sessions will be reviewed in a timely fashion to provide feedback to the interventionists throughout the intervention.

## 10. Data management

An online data management system utilizing CDART from the Collaborative Studies Coordinating Center will be developed for this SMART pilot. The system will include online data collection and tracking of participant randomization. CDART has robust security features including unique user logins with expiration dates and complex password requirements; storage of hashed passwords only; granular permissions based on user requirement; and encrypted data transmission. The secure server environment where the systems that host CDART reside is located within a hardened data center on the UNC campus, and is governed by standard UNC information security guidelines. Weekly vulnerability detection scans are performed by a third-party vendor, which include full administrative credentials to perform maximum detection techniques. Real-time virus protection software is implemented, and weekly full system virus scans are performed. Daily backups of the data are made and stored in an off-site location. CDART is 21 FDA Part 11 compliant.

Upon entry into the study, a unique identifying number will be assigned to each participant. This number will be used to identify the information and specimens collected and stored during this study. Specimens collected and transferred to the central laboratory will have no identifier other than the unique identifying number assigned to the participant. The roster containing the unique identifying number and direct participant identifiers will be kept in a local password-protected database on a secure network drive at the clinical sites.

## 11. Statistical Considerations

We will primarily compare the 3-month response rates to each of the three initial diets using standard statistical comparison procedures (e.g., t-tests and ANOVA) for differences in glycemic control (HbA1c and percent time in hypoglycemia) and change

in weight. In addition, we will conduct a series of secondary, hypothesis-generating analyses using standard statistical approaches as well as more complex fixed and mixed effect regression methods such as generalized additive models[101] and random forests[102] for these outcomes plus body fat and fat free mass. We will compare all diet sequences (there are 12) using the same outcomes and will incorporate evaluation of measures of ingestive behaviors. After adjusting for multiple comparisons, the proposed sample size of n=84 is sufficient to ensure 60% power to detect a moderate effect size (Cohen h=0.68) and 80% to detect a large effect size (Cohen h=0.85) at a significance level of 0.10 for comparing response rates among the 3 diets. Based on data reported in Wing et al (2016)[103] and Russell et al (2014)[104] and other preliminary data, we estimate for the same significance level and with 80% power that we will be able to detect a difference of about 3.0kg for weight change, 1.3% for HbA1c change, and 1.3 percentage point change in percent time <70mg/dl. Here we emphasize that, by design, our primary goal for this pilot work is to inform the final efficacy design, and we have therefore not designed this pilot SMART to be fully powered for all analyses.

An advantage of SMARTs is that they allow for efficient estimation of precise (i.e., deeply tailored) diet strategies. A precise diet strategy adapts treatment to the evolving health status of each participant. We will use a regression-based approximate dynamic programming algorithm known as Q-learning[61,105,106] to estimate the precise diet strategy that maximizes weight loss while improving suboptimal or maintaining good glycemic control over the duration of the trial. The form of this estimated optimal diet strategy will generate hypotheses about how best to choose and adapt diets to individual patients. This will require the use of SMART analysis methods for balancing competing outcomes.[107]

For treatment assignment, permuted block randomization with blocks of size 24 will be used to assign all 12 potential treatment regimes using R statistical software. This will be confidentially generated by the statistician and placed into CDART software to be revealed only at the point of treatment (diet) assignment for each patient. The 12 possible regime sequences are (1,2,2), (1,2,3), (1,3,2), (1,3,3), (2,1,1), (2,1,3), (2,3,1), (2,3,3), (3,1,1), (3,1,2), (3,2,1), and (3,2,2). To illustrate, suppose a patient is assigned treatment sequence (1,3,3). Then, at baseline, only the initial diet (Diet 1) will be revealed. At 3 months, if the response is positive, the patient will continue with the same diet (Diet 1) for the next 3 months to the 6-month follow-up time. If at 6 months the patient is not responding, the new diet (Diet 3) will then be revealed. At 6 months, if the patient response is positive, the patient will continue with the most recently assigned diet (either Diet 1 or 3 depending on the outcome at 3 months yielding one of the two treatment paths (1,1,1) or (1,3,3)). If, at 6 months, the patient response is not positive, the new diet will be revealed. The new diet is Diet 3 if the patient had a positive response at 3 months (yielding the diet sequence (1,1,3)), otherwise the patient will receive the only unused diet, Diet 2 (yielding the diet sequence (1,3,2)). Thus a single regime will provide for four treatment paths depending on patient response. Moreover, all treatment assignments remain hidden in CDART until it becomes time to reveal the new diet. We recognize that patients who do not respond at either the 3 or 6 month time points will be able to anticipate their third diet, but all other patients will not. This is as unblinded as possible for this open label setting.

Effect sizes with accompanying confidence intervals will be estimated using mean outcome at 3 months and standard ANOVA methods will be used for confidence interval construction. We have no reason to think that diets will be differentially acceptable or effective for men compared to women; however, exploratory analyses will consider sex differences in response to the three diets.

We also note that there are 21 possible diet sequences, but there are only 12 treatment regimes based on the randomization scheme. The distinction between regimes and sequences is described in Chapter 2 of *Adaptive Treatment Strategies in Practice: Planning Trials and Analyzing Data for Personalized Medicine* (Kosorok and Moodie, 2016),[108] but this can be illustrated by example. One treatment regime is the following: treat initially with Diet 1, then, if the patient responds favorably after 3 months, continue with the same diet, otherwise switch to Diet 3. After 6 months, if the patient responds favorably, continue with the same diet as given in the previous period. Otherwise, if they were on Diet 1, switch to Diet 3; If they were on Diet 3, switch to Diet 2. Although this is a single treatment regimen (reflecting a single treatment choice at each decision time), this regime is consistent with the following four treatment paths: (1) if the patient responds favorable at both time points, they will experience Diet 1 repeated three times. (2) If they respond favorably at 3 months but not at 6 months, then their diet sequence would be Diet 1, Diet 1, and Diet 3. (3) If they responded unfavorably at 3 months but favorable at 6 months, then their diet sequence would be Diet 1, Diet 3, Diet 3. (4) If they respond unfavorably at both 3 and 6 months, their diet sequence would be Diet 1, Diet 3, and Diet 2. The issue is that a regime focuses on the decision a clinician can make either initially, or when the patient experiences an unfavorable response, at either 3 or 6 months. The remaining decisions are made automatically since favorable responses do not lead to changes in diet. Note that this means that some diet sequences are consistent with more than one treatment regime, and thus the data from same patients will sometimes be used for estimating more than one of the 12 regimes. With balanced randomization, at least 6 patients will be assigned to each treatment regime.

Moreover, we will in fact be able to make valid intent-to-treat comparisons across the three starting diets using the outcomes at 9 months, based on the fact the SMART designs have greater power for intent-to-treat hypotheses than traditional randomized designs (see Chapter 3 of Kosorok and Moodie, 2016).[109] In a standard, randomized trial, failure of a diet would lead to either patient drop-out or switching of diet by the clinician. Thus two sources of bias arise: one from drop out and one from change in treatment. In contrast, with our design, we make additional diet assignments at 3 and 6 months based on diet success. We use randomization instead of ad hoc reassignment. Thus, our design more formally addresses both patient drop out and treatment changes by including diet changes in our design in a balanced way. There may still be some drop out, but it will be lower since patients do not have to leave the study to have their diet changed. Thus the design is adequate to achieve the stated objectives.

In addition, the Q-learning methodology will permit us to pool the data for regression models across similar branches among the possible treatment paths. To illustrate this, we point out that, as described in Chapter 17 of Kosorok and Moodie, 2016,[106] Q-learning is done through a backwards iteration of regression model fitting, with different

regression models at each potential randomization point. In our setting, we can integrate the multiple possible regression models at the third decision time (6 months) into one regression model by including past diets in the history variables as well as by allowing for four treatment options, one for each of the three diets and one for those patients who stay on with the previous diet. We can similarly integrate across the regression models at the 3 month decision time and also at baseline, resulting in the need for only three regression models. We will therefore have sufficient power for all of our proposed analyses. In addition, we will have sufficient sample size to use the pilot data to sample size a full SMART design using the methods described by Laber et al., (2016).[110]

## 12. Potential Risks, Discomforts, Inconveniences, & Precautions:

**Potential Risks**

Psychological and social risks are expected to be minimal (e.g., potential embarrassment about answering questions related to adherence).

Venipuncture: Drawing blood from a vein in the lower arm may cause mild pain and occasionally minor bruising at the site of the blood draw. Fainting can also occur. There is a remote chance of infection or peripheral venous phlebitis or thrombosis. For study subjects with diabetes, the requirement of a fasting blood sample may precipitate a temporary blood glucose level that is somewhat lower or higher than usual.

DISCONTINUED AS OF 4/2020. DXA scanning exposes subjects to a small dose of ionizing radiation. This dose of radiation is comparable to that obtained on a transcontinental airplane flight.

Continuous glucose monitoring (CGM). This procedure is routinely used in clinical practice. The main risks of CGM are local irritation from the sensor or tape.

Breach of confidentiality is a risk, although this is highly unlikely as data are used exclusively for research purposes and participants will be provided with information on how risks to confidentiality are minimized (see protection against risks for further details).

**Adequacy of Protection against Risks**

**Recruitment and Informed Consent**

For both clinical sites (University of North Carolina, Stanford) we will invite eligible patients to participate in this study by emailing them an introductory letter that describes the study. These letters will be followed with telephone calls to answer questions and encourage participation.

Research staff at the clinical sites will obtain written informed consent from participants. The study consent will explain the purpose of the study and measures taken to protect confidentiality (e.g., the data will not be linked with personal identifying information). A full informed consent protocol will be developed under the guidance of the Institutional Review Boards at each of the three clinical performance sites. Patients will be assured that participation is voluntary and that non-participation will not result in any

consequences to them. In addition, they will be informed that they may withdraw from the study at any time without consequences. Finally, participants will be informed that the data are used exclusively for research purposes, that identifying data will not be released by the investigators to their families or to any other individual or organization, and that any identifying information will be destroyed at the end of the project. Participants will be given adequate time prior to signing the informed consent document to ensure that they have an opportunity to ask and receive answers to any and all questions about study participation.

In soliciting the cooperation of each young adult in our study, we will stress the data safeguards that will be in place to protect the confidentiality of the survey data. Minimizing the risk of disclosure requires careful data safeguards. Most important is the need to prevent the association of an individual's name with sensitive information. We will keep participants' names separate from their survey responses and store the link between names and study identification numbers in a password-protected file that is accessible only to authorized staff at the respective clinical sites.

Participants will have opportunity to provide informed consent following the two-step recruitment process detailed above. For participants who agree to participate and schedule a baseline visit, the study consent form will be mailed or emailed to the participant prior to the scheduled baseline visit, so that the individual has ample time to review it on their own ahead of the visit. Participants will also be provided with instructions on how to use CDART, the data management system that we will employ to house participant data and house self-administered questionnaires. This email will also include a personalized link to a Qualtrics questionnaire, which provides participants the chance to read a consent form specific to completing baseline forms ahead of the in-person visit. If they choose to consent to completing these forms ahead of the visit, study staff will then email them their login information for CDART. These emails will include relevant visit reminders that have been previously reviewed during phone conversations with participants. Prior to the baseline measurement visit, participants will have a chance to complete several questionnaires in CDART, which will shorten the length of the in-person visit.

At the time of the visit, study staff will review the full study consent in detail before standardized data collection begins. The study participant will be given as much time as needed to review the consent form and ask any questions prior to signing it. Participants will be informed that participation in the study is voluntary and they are free to withdraw their consent and discontinue participation in this research at any time. Study staff obtaining consent will utilize the tailored *Consent Comprehension Checklist* to guide a conversation with the participant that aims to ensure that she or he understands what she or he is consenting to and the nature of informed consent itself.

**COVID-19 PROVISIONS – VIRTUAL VISITS:**

*Newly enrolled participants will be emailed the full consent form so that they may review it in detail. Then during a subsequent phone or Zoom call, the consent form will be reviewed verbally in detail by the Study Coordinator and participants will be given time to ask any questions and have these questions answered. Participants will be able to indicate their*

*consent using an electronic Qualtrics Survey in which they can indicate whether or not they agree to participate in the study as a whole as well as the stool kit collection and physical activity tracking opportunities. This consent process will include consent to complete online forms and thus will eliminate the use of the previous Qualtrics survey that allowed participants to complete online forms ahead of their in-person visits.*
*Follow-up participants. These participants will be emailed a link to the revised consent addendum so that they may review it in detail. The study coordinator will discuss the changes to the study with already enrolled participants and go through the consent addendum in detail via a phone or Zoom call. They will be able to indicate their consent to participate in the revised virtual study online.*

*Once participants have indicated their consent, they will be mailed their virtual measurement visit package and can begin all elements of the study visit.*

Following consent, participants may be involuntarily withdrawn from the study per the investigator's discretion, if they develop a serious condition that would render participation unwise, including difficulties with glycemic control, and serious physical or psychiatric conditions. Females who become pregnant will also be withdrawn from study participation.

**Protections against Risk**

All institutions associated with this study are experienced with handling sensitive and confidential data. Certain routine administrative, personnel, physical security, information management, and computer system or network security practices are always in place given the policies and the requirements for safeguards consistent with the management of PHI at both clinical sites. All PHI will be used or disclosed in compliance with the Health Insurance Portability and Accountability Act (HIPAA). Paper forms will be kept in locked files when not in use. Participants will be assigned identification numbers in lieu of names on data management and data analysis files. A master list of identification numbers and names will be kept separate from all database files and will be maintained in a password-protected file that is accessible only to authorized staff at the respective clinical sites. Upon completion of the study, these files will be destroyed. No individual PHI will be used in reports or manuscripts. Data entered and stored on the microcomputer will be archived daily. The data collectors will follow a strict written protocol that describes study measures for protecting data privacy. Patients always have the right to refuse to participate or to refuse to answer any individual question they might find objectionable.

Each site has a highly experienced endocrinologist as part of the local investigative team (UNC – Kirkman; Stanford – Maahs). To minimize the possibility of risks associated with the blood draw, experienced medical staff will obtain the blood samples. A local numbing medicine may be placed on the skin before the blood is drawn to decrease any pain. Participants who have a history of fainting or who develop symptoms of light-headedness will be placed in the supine position. The study physicians will review all laboratory findings for study participants in a timely fashion. Research staff will have guidance ("alert values") for when to proactively contact the study physician for guidance.

**Hemoglobin A1C**
The minimum amount of blood/plasma necessary to conduct these tests will be collected and the total amount collected will not exceed standard, weight-specific guidelines. Blood volumes will be approximately 22 ml at the baseline visit and 12 ml at the follow-up visits. Stored blood will be saved for 10 years after the end of the study. The following table describes the amount of blood required for the laboratory tests.

The minimum amount of blood/plasma necessary to conduct these tests will be collected and the total amount collected will not exceed standard, weight-specific guidelines. Blood volumes will be approximately 22 ml at the baseline visit and 12 ml at the follow-up visits. Stored blood will be saved for 10 years after the end of the study. The following table describes the amount of blood required for the laboratory tests.

| **MEASUREMENT** | **Baseline Blood Draw Volume** | **Remaining Visits Blood Draw Volume** |
|---|---|---|
| **Hemoglobin A1c** | 2 ml | 2 ml |
| **Stored plasma** | 10 ml | 10 ml |
| **Stored whole blood for DNA** | 10 ml | N/A |
| **Total maximum blood volume** | 22 ml | 12 ml |

***COVID-19 Provisions-Virtual Visits***

| **MEASUREMENT** | **Baseline Blood Draw Volume** | **Remaining Visits Blood Draw Volume** |
|---|---|---|
| **Hemoglobin A1c** | 2 ml | 2 ml |

*For the SMART pilot*, the interventionists (Registered Dietitians) and study physicians will communicate regularly (verbally and in writing per protocol) regarding glucose control so that any changes in medical management can be made in a timely fashion, as it is understood that with weight loss, adjustments in medical management will be needed.

Study personnel will be trained to identify the signs and symptoms of a blood glucose level that is low or high. They will also be trained to check the blood glucose level, using a glucometer. If low blood glucose occurs during a study visit (< 70 mg/dL), study personnel will be trained to administer 15 grams of an oral carbohydrate, and to repeat as needed every 15 minutes until the blood glucose level is > 70 mg/dL.[111] If the blood glucose level is above 300 mg/dL during a study visit, study personnel will be trained to check for urinary ketones. In cases of low or high glucose levels (with or without the presence of ketones), additional medical interventions may sometimes be

needed. Local policies dictate these procedures, which may include a one-time adjustment in the dose of insulin taken and/or the administration of glucose gel, glucagon, or intravenous glucose. If participants experience hypoglycemia or hyperglycemia outside of study visits, they will be advised to treat these situations per their usual diabetes care plan.

***COVID-19 Virtual Visit Provisions:*** *We are no longer asking participants to report their blood sugar or whether or not they have had anything to eat in the last 8 hours. The only fields of the 'specimen collection form' that we will complete are those that pertain to the HbA1c collection, that is, time and date of collection along with any problems the participant may have had.*

At each study visit and RD check-in call, hypoglycemia events will be reviewed with the participant. Participants will be asked to notify the study team within 48 hours of any severe hypoglycemic event (seizure, coma, or need for glucagon administration).

Participants will be completing a CES-D form at all the measurement visits. Although the CES-D is not considered a diagnostic tool for the identification of clinical depression, it is designed to identify people who may be suffering from a depressed mood. Whenever a participant scores high (> 24) on the CES-D, study personnel will inform the participant that the CES-D score is "high" compared to what would be expected for most adults, indicating that the participant may be clinically depressed. If the participant is currently receiving mental health counseling or treatment, study personnel will recommend follow-up with his/her mental health provider. If the participant is not being treated by a mental health provider, study personnel will make a referral based on local guidelines and procedures.

DXA scanning is performed by a certified radiology technologist, knowledgeable in the procedure and equipment. Female participants will undergo a urinalysis pregnancy test prior to each DXA scan to protect the unborn fetus from radiation exposure.
***COVID-19 VIRTUAL VISIT TRANSITION (4/2020)*** *DXA discontinued.*
There may be unknown or unforeseen risks associated with study participation.

## 13. Risk/Benefit Analysis

Participation in this research study may help to improve glycemic control and weight in some participants.

### Potential Benefits of the Proposed Research to Human Subjects and Others

The proposed research may lead to potential benefits for individuals with diabetes, including improved weight and improved diabetes control, and reduced risk of both short- and long-term complications. The risks to participants are reasonable in relation to the anticipated benefits to participants and others because: the risks are judged to be minimal and unlikely, safeguards against these risks are in place, and the potential benefits are important, both to individuals who participate in the study and to the broader population of young adults with T1D.

**Importance of the Knowledge to be Gained**

This study should yield new information contributing to the self-management of diabetes, including both weight management and glycemic control, through the use of diet and related behavioral strategies to promote adherence. This knowledge may lead to better care for young adults with diabetes. The development of a feasible and effective novel intervention for young adults with T1D far outweighs potential risk of harm.

## 14. Data Safety & Monitoring:

We will convene a 4-member Data and Safety Monitoring Board to meet twice yearly via video conference call. DSMB members will represent expertise in endocrinology, nutrition, health psychology and behavior change, and study design and statistical analysis relevant to SMART designs. Drs. Mayer-Davis, Maahs and Pratley will represent the ACT1ON consortium in interactions with the DSMB. The DSMB will review the final study protocol and any significant changes to the protocol over the course of the study especially as related to participant burden or safety. The DSMB will monitor and advise on study participant accrual and retention, progress and completeness for all standardized measurement visits and attendance at intervention sessions. Data quality will be reviewed and staff training and certification will be monitored. Adverse events will be monitored. A summary of the DSMB report will be sent to both the local site IRBs and NIDDK as part of the annual progress reports. Members of the DSMB have been identified and each individual listed below by area of scientific expertise (all with relevant expertise applied to T1D) has agreed to serve:

Endocrinology: Irl Hirsch MD, University of Washington
Nutrition: Sarah Couch PhD RD, University of Cincinnati
Health Psychology and Behavior Change: Jessica Kichler, PhD, University of Cincinnati
Study Design and Statistical Analysis: Ralph D'Agostino, PhD, Wake Forest University

**Data Monitoring**
Questionnaires will be administered to participants. Data will also be obtained via physical exam and biological specimen collection, as well as data collected based on structured interviewing of intervention acceptability. All aspects of data collection and data storage will be carefully monitored to ensure rapid detection of errors, inconsistencies or other problems. Data are reviewed systematically on a monthly basis throughout the data collection period so that data cleaning will happen close to "real time". The data collectors will follow a strict written protocol that describes study measures and details for conducting measures accurately and in a manner that protects data privacy. They will explain to each participant that s/he has the right to refuse to participate or to refuse to answer any individual question that s/he finds objectionable and emphasize the importance of telling the truth. All institutions associated with this application are experienced in training data collection fieldwork personnel how to handle, store, and process sensitive and confidential data. Certain routine administrative, personnel, physical security, information management, and

computer system or network security practices are always in place. These practices include: building an audio-tape vault security, non-disclosure pledges, and account/keyword security on computer networks. In addition, we take multiple project-specific steps to protect subjects from the risk of a breach in confidentiality. All data will be collected using study identification numbers. The list that links identification numbers to names will be kept in a password-protected file that is accessible only to authorized staff at the respective clinical sites. Only aggregate data that cannot be used to identify individuals will be included in any reports released to other agencies or for publication.
Recruitment and retention will be monitored internally by the study via the study Recruitment, Retention, and Data Quality Committee, using the report templates established for the FLEX trial that show monthly participant recruitment and randomization accrual by site and overall. Reports also detail attendance at each of the intervention sessions and at each of the standardized measurement visits. Any participants permanently withdrawn from the study are documented, including reason for withdrawal. Reports also provide information on completeness of data collection as well as distribution of key variables (e.g., weight, height) for data quality checks. Internally, these reports will be reviewed monthly, and the DSMB will review the reports when they convene twice yearly.

**Adverse Events**
For purposes of monitoring and reporting adverse events, the following NIH definitions will be used:
Adverse Event (AE): any unanticipated, untoward medical occurrence that may present itself during treatment or administration of an intervention, and which may or may not have a causal relationship with the treatment. Adverse events could arise from the study (e.g., breach of confidentiality) or could arise due to the population under study.
Serious Adverse Event (SAE): Any medical occurrence that results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalizations; creates persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

It is highly unlikely that participation in the SMART pilot intervention will cause an AE or SAE. Should an AE occur, however, the study coordinators will immediately report any AE's connected to the study physician at the local site and to the study investigators, who will keep a log of AE's and SAE's. The log will also be used to provide information about AE's in annual progress reports to participating IRBs and NIDDK. Any study participant experiencing hypo/hyperglycemia or an otherwise potentially expected symptom related to diabetes will be encouraged to consult their diabetes care provider or to go to the emergency room immediately as needed.

For monitoring, the coordinators will report AEs to the study MPIs and the overall study project manager (Thomas) on a timely basis – 24-48 hours is typical for an SAE, 10-14 days for a routine AE. Local IRB reporting requirements will be followed (rapid

reporting for SAEs only, routine AEs as part of the annual IRB renewal documentation).

All AEs will be reviewed monthly by the study Recruitment, Retention and Data Quality committee, which also serves as the clinical oversight committee in this pilot project, to ensure completeness of documentation and study relatedness. AEs will be reviewed quarterly by the study Steering Committee.

The following grading scale will be used by the Recruitment, Retention and Data Quality committee to adjudicate AE/SAEs. Consensus will be sought among all members and in the event of lack of consensus; this will be noted and reported to the DSMB.

| *Study Relatedness:* | *Action Taken:* | *Status:* |
|---|---|---|
| *1=Definitely Unrelated* | *0 = None* | *1 = Resolved* |
| *2=Possibly Related* | *1 = Counteractive Medication* | *2 = Recovered with minor sequelae* |
| *3=Probably Related* | *2 = Medical/surgical intervention* | *3 = Recovered with major sequelae* |
| *4=Definitely Related* | *3 = Hospitalization* | *4 = Condition still present and under treatment* |
| *5=Diabetes Related; Definitely Unrelated* | *4 = Other (specify under comments)* | *5 = Condition continues to worsen* |
| | | *6 = Patient died* |

All AEs will be reviewed by the study Data and Safety Monitoring Board to determine if an AE is related to the research project. Our team will file a written report to the site IRBs in accordance with local IRB requirements, and to NIDDK. Outcomes for AE's will be monitored by the DSMB and outcome information will be entered into a log for inclusion in reports to participating IRBs and NIDDK as required.

Anticipated events relative to the population under study (e.g., low or high blood glucose) or relative to study activities (e.g., fainting associated with venipuncture) will be noted as potential risks on the informed consent form. The DSMB will also monitor the occurrence of these events. In addition, resource and referral listings for community services will also be provided on a routine basis as needed. Drs. Mayer-Davis and Maahs will also work extensively with the staff at each of the clinics to ensure that if participants need to be referred, these situations are managed in a manner consistent with clinic preferences/policies.

Should any other problems or concerns arise with the data collection or intervention program, the PI or local clinical PI will be available to address these.

## 15. Privacy & Confidentiality

To protect the right of the participant's privacy, the patients' disease status will not be included on the mailing envelope or subject line of any recruitment materials or emails

for the study. In-person recruitment will occur in the diabetes clinics by study personnel. Study visits will occur in private settings.

To minimize the risk of loss of confidentiality, all information related to study subjects will be confidential and kept in secure cabinets or password-protected computer files, in compliance with NIH and HIPAA requirements as detailed in NIH Notice OD-020 issued December 30, 2004.

Each participant will be assigned a unique study identification (ID) number. Participants will be identified on all study-related documents only by their study ID numbers. The roster containing the unique identifying number and direct participant identifiers will be kept in a local password-protected database on a secure network drive at the clinical sites.

All hard copy data collection forms will be secured in a locked file cabinet or office. Data will be entered onto a secure Web-based data management system. Only the study coordinator and relevant research study staff will have access to this study database. Secure access will be assured by use of individual login codes and password protection. Entered data will be stored securely and accessed in accordance with current HIPAA standards, the HCFA's Internet Security Policy, and other state and local requirements.

All data interactions for the study by all users including participants, coaches, clinical staff, research staff, and investigators, are web-based communications between the given user's web browser and the web server running the study website and/or data management software. All of these web-based communications are configured to use the standard HTTPS protocol with 128-bit encryption. This includes online forms submitted by participants as they are transferred to the servers at UNC.

An online data management system utilizing CDART from the Collaborative Studies Coordinating Center will be developed for this SMART pilot. The system will include online data collection and tracking of participant randomization. CDART has robust security features including unique user logins with expiration dates and complex password requirements; storage of hashed passwords only; granular permissions based on user requirement; and encrypted data transmission. The secure server environment where the systems that host CDART reside is located within a hardened data center on the UNC campus, and is governed by standard UNC information security guidelines. Weekly vulnerability detection scans are performed by a third party vendor, which include full administrative credentials to perform maximum detection techniques. Real-time virus protection software is implemented, and weekly full system virus scans are performed. Daily backups of the data are made and stored in an off-site location. CDART is 21 FDA Part 11 compliant.
For the purposes of tracking recruitment and scheduling, basic participant information, including first and last name, Study ID, and dates and other pertinent information regarding scheduled appointments (reminder calls, etc.) will be kept in a password-protected Microsoft Access database stored securely at each clinical site.

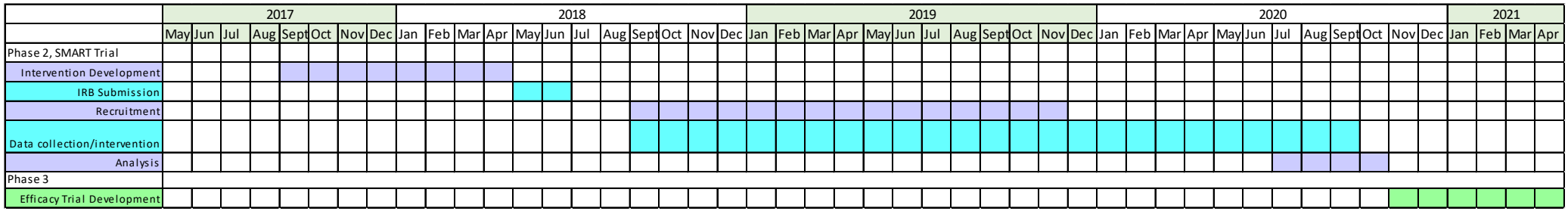
The intervention does not require transmission of PHI by any cell phone. We recognize that participants may take the initiative to send PHI by cell phone. As is the case with all behavior intervention utilizing current technology, we will explain to participants that transmission of such information is not secure.

Data will be obtained and stored based on structured interviewing of intervention acceptability, and audio-tapes of session delivery. All aspects of data collection and data storage will be carefully monitored to ensure rapid detection of errors, inconsistencies or other problems. The data collectors will follow a strict written protocol that describes study measures for protecting data privacy, explain to each participant that s/he has the right to refuse to participate or to refuse to answer any individual question that s/he finds objectionable, and emphasize the importance of telling the truth. All institutions associated with this study are experienced in training data collection fieldwork personnel how to handle, store, and process sensitive and confidential data. Certain routine administrative, personnel, physical security, information management, and computer system or network security practices are always in place. These practices include building an audio-tape vault security, non-disclosure pledges, and account/keyword security on computer networks.

In addition, we take multiple project-specific steps to protect subjects from the risk of a breach in confidentiality. All data will be collected using study ID numbers. Thus, no questionnaire will contain identifying information, and the roster containing the unique identifying number and direct participant identifiers will be kept in a local password-protected database on a secure network drive at the clinical sites. Finally, only aggregate data that cannot be used to identify individuals will be included in any reports released to other agencies or for publication.

## 16. Study Timeline

The study timeline for Phase 2 (SMART Trial) and Phase 3 (Efficacy Trial Development) is included below.



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## Appendix 1.

## PHYSICAL ACTIVITY STUDY PROTOCOL

### Background

This protocol is designed specifically for the collection of physical activity data provided by participants enrolled in the ACT1ON DP3 SMART Pilot.

Physical activity is an essential part of type 1 diabetes (T1D) management. Regular exercise has been shown to help individuals with T1D reduce HbA1c and improve lipid blood lipid profiles, body composition, and endothelial function[1,2]. People with T1D who exercise more frequently also tend to have lower total daily insulin needs and experience fewer diabetes related complications such as retinopathy, microalbuminuria, and diabetic ketoacidosis (DKA)[3,4].

It is currently recommended for individuals with T1D to participate in at least 150 minutes of accumulated physical activity per week, with no more than two consecutive days without physical activity[5,6]. There are, however, distinct barriers to meeting physical activity guidelines among people with T1D, including exercise-related dysglycemia. Exercise, especially vigorous aerobic activity, increases the risk of hypoglycemia for at least 24 hours after[7]. Having to ingest additional carbohydrates (and thus calories) in response to hypoglycemia may create a feeling of futility around exercise that may prevent individuals with T1D from meeting recommended physical activity guidelines[8].

Research exploring the role of exercise in the management of T1D is needed. Specifically, the effects of varying exercise intensities and modalities on glycemic outcomes and weight management for people with T1D remains under-researched. The inclusion of additional physical activity data within the ACT1ON DP3 SMART Pilot study would allow for the elucidation of the effects of varying amounts and intensities of physical activity on its primary outcomes of weight management and glycemic control.

## Site Descriptions

The two clinical sites include the 1) University of North Carolina at Chapel Hill (UNC-CH) and 2) Division of Pediatric Endocrinology and Diabetes at Stanford University.

## Selection & Recruitment of Subjects

**Eligibility:**

Any participant in the SMART pilot willing to provide data regarding their physical activity will be invited to participate.

Of the 42 participants at each site (84 total) that will be recruited, we expect that up to 80 (40 at each site) will participate in the physical activity portion of the protocol.

## Process of Obtaining Consent

Participants will indicate whether or not they are willing to participate in the physical activity component of the study, including willingness to wear a Garmin Vivosmart 4 Fitness Tracker and provide a session rate of perceived exertion (sRPE) rating with each bout of structured exercise during each 14-day data collection period. Consent to participate will be obtained remotely via phone at the time of the participant's next regularly scheduled measurement visit following approval of this protocol. All participants currently enrolled are eligible to participate in this part of the study at each of their remaining measurement visits.

## Study Outcome Variables

The Garmin Vivosmart 4 fitness tracker utilizes a built in Garmin Elevate™ Heart Rate monitor, altimeter, accelerometer, and Bluetooth® Smart and ANT+® technology to measure outcomes of interest, including heart rate (HR), step count, floors climbed, and energy expenditure (EE). The wearable device automatically syncs to the GarminConnect application.

**Session Rate of Perceived Exertion (sRPE)** will be assessed by participants utilizing a validated sRPE scale. The scale will be made accessible to participants through a QR code printed on labels attached to a water bottle and keychain provided to the participants by the study site. If participants do not have access to a smartphone capable of utilizing a QR code, the link to the sRPE form will be provided through email. Session RPE has been shown to be a valid, reliable, and practical tool for monitoring training load. This method asks participants to assess the intensity of their workout with a single number rating between 0 – 10, with 0 being equivalent to complete rest and 10 being a maximal bout of exercise. Through incorporating both RPE and duration of exercise, this method can provide insight to the physical and psychological effort of exercise over the course of 14 days, as well as the total strain and monotony of training experienced by participants. It is recommended that participants wait at least 30 minutes following exercise to record their session RPE in order to prevent intensity of the end of their workout from affecting the overall rating of perceived exertion for the session.

## Objective Measures of Physical Activity Procedures

Heart rate, step count, floors climbed and energy expenditure data will be gathered through the use of a wearable fitness tracker during a 14-day wear time consistent with the 14-day CGM wear time that is part of the current study protocol.

a.) Research staff will provide participants with a Garmin Vivosmart 4 at each measurement visit and instruct participants on its use. For visits done remotely, the wearable device will be shipped to the participants.
    a. Research staff will:
        i. Instruct participants on how to use the Garmin Vivosmart 4 fitness tracker.

ii. Instruct participants on how to connect to the GarminConnect app and create a user profile.
iii. Although the Garmin watch itself does not have GPS, the watch can use an antenna in a smartphone that can record GPS data for a walk, run, or bike activities. Participants will be informed in the information sheet and verbally by staff that they should not turn this feature on. We are not using GPS for any portion of this study.
iv. Emphasize the importance of charging the Garmin Vivosmart 4 each night to prevent data loss due to inadequate battery life.
v. Instruct participants how to return the Garmin Vivosmart 4 fitness tracker following the completion of the 14-day data collection period.

b.) Participants will ship the Garmin Vivosmart 4 fitness tracker back to the study site following the completion of the 14-day data collection period using prepaid materials provided to them by the study site.

## Session Rate of Perceived Exertion (sRPE) Data Collection Procedures

a.) Following consent to participate, research staff will create an sRPE chart and corresponding QR Code for each participant. These will be stored in a secure folder in the ACT1ON Study staff site on Microsoft OneDrive.
b.) The corresponding QR code will be printed on weatherproof labels which will then be applied to a water bottle and key chain to be shipped to participants along with the wearable device ahead of the timing of their next measurement visit. Participants will keep the water bottle and keychain as an additional incentive for participation in this part of the study. Additional QR-coded stickers will be provided to participants in case of loss or damage.
c.) During the remote measurement visit, research staff will:
    a. Assist participants in the setup of the wearable device
    b. participants their preferred time of day for exercise.
    c. Schedule regular email or phone messages to remind participants to record their exercise session and perceived exertion.
    d. Instruct participants in how to use the QR code to access their sRPE chart.
    e. Instruct participants in how to use the sRPE scale to measure their exercise intensity utilizing the script provided in the appendix.
    f. Detail the information to be provided following each bout of structured exercise and to record their sRPE at least 30 minutes following exercise, but within 24 hours.

Following a bout of structured exercise during the 14-day wear time, participants will scan the QR code to access their sRPE chart and record the time of day, duration, exercise modality, and their rate of perceived exertion for

the session (sRPE). These values should be recorded at least 30 minutes after exercise, but within 24 hours.

## Insulin Dosing

For participants who are using insulin pumps, insulin use data will be downloaded from the participant's insulin pump remotely.

## Materials and Technology

The Garmin Vivosmart 4 is a waterproof fitness tracker worn around the wrist with built in accelerometer, altimeter and Garmin Elevate™ heart rate monitor. This fitness tracker has a touch interface and a battery life of up to seven days. It can automatically sync with the GarminConnect application through the use of Bluetooth® Smart and ANT+® technology. We will have 10 Garmin Vivosmart 4 fitness trackers at each study site, for a total of 20. The Garmin Vivosmart 4 will be provided to participants by mail prior to their next scheduled visit and returned following the 14-day wear time by mail to the study site with a prepaid shipping envelope.

The GarminConnect application allows for the wireless syncing and storage of physical activity data and also provides participants with real-time feedback on their physical activity stats.

Each participant will also be given a water bottle and a keychain, each with weatherproof labels attached containing the QR code corresponding to their sRPE chart to allow for quick and easy access to their assessment form.

The website, www.qr-code-generator.com will be used to generate individual QR Codes needed to allow participants to access their sRPE assessment form.

A secure platform, such as Microsoft OneDrive or REDCap, will be utilized for the secure storage of sRPE data from participants.

# Study Timeline

| | Participant Timeline | Measurement Visits | RD Session (Longer session) | RD Check-In (Phone) |
|---|---|---|---|---|
| Initialize CGM, Provide Garmin, and Familiarize Participants with instructions for Garmin & sRPE | -14 Days | Baseline Visit | | |
| | -7 Days | | **RD 1:** Healthy Diet & Problem Solving Strategies (60-90 min) | |
| Return CGM & Garmin Randomization 1 → | Day 0 | | **RD 2:** Intervention Diet (60-90 min) | |
| | 1 Wk | | | **RD 3** (10-15 min) |
| | 2 Wks | | | **RD 4** (10-15 min) |
| | 1 Mo | Online Form | **RD 5** (30-60 min) | |
| | 1.5 Mo | | | **RD 6** (10-15 min) |
| | 2 Mo | | | **RD 7** (10-15 min) |
| | 2.5 Mo | | | **RD 8** (10-15 min) |
| Initialize CGM, Provide Garmin, Refresh Participants on Instructions for Garmin and sRPE | 3 Mo | Measurement Visit 2 | | |
| Return CGM & Garmin Randomization 2 → | 3.5 Mo | | **RD 9:** Intervention Diet (Same or New) (30-90 min) | |
| | 3 Mo + 3 Wks | | | **RD 10** (10-15 min) |
| | 4 Mo | | | **RD 11** (10-15 min) |
| | 4.5 Mo | Online Form | **RD 12** (30-60 min) | |
| | 5 Mo | | | **RD 13** (10-15 min) |
| | 5.5 Mo | | | **RD 14** (10-15 min) |
| | 6 Mo | | | **RD 15** (10-15 min) |
| Initialize CGM, Provide Garmin, Refresh Participants on Instructions for Garmin and sRPE | 6.5 Mo | Measurement Visit 3 | | |
| Return CGM & Garmin Randomization 3 → | 7 Mo | | **RD 16:** Intervention Diet (Same or New) (30-90 min) | |
| | 7 Mo + 1 Wk | | | **RD 17** (10-15 min) |
| | 7.5 Mo | | | **RD 18** (10-15 min) |
| | 8 Mo | Online Form | **RD 19** (30-60 min) | |
| | 8.5 Mo | | | **RD 20** (10-15 min) |
| | 9 Mo | | | **RD 21** (10-15 min) |
| | 9.5 Mo | | | **RD 22** (10-15 min) |
| Initialize CGM, Provide Garmin, Refresh Participants on Instructions for Garmin and sRPE | 10 Mo | Measurement Visit 4 | | |
| Return CGM & Garmin | 10.5 Mo | | **RD 23:** Study Closeout (30 min) | |

## Appendix 2.

### sRPE Familiarization Script

Thank you for agreeing to participate in the physical activity component of our study! In addition to wearing a Garmin Vivosmart 4 activity tracker during this two-week period, if you decide to participate in structured exercise, we ask that you take the time to fill out a quick assessment form to provide us with a measure of the intensity of your workout.

**Assessment Form Details**

The assessment form asks you to record four things. These are the **time of day** you exercised, **how long** you exercised for, the **type of exercise** you participated in and then your **rate of perceived exertion**. For the rate of perceived exertion, we want you to answer the question "How hard was your workout?" To do this you will provide a rating of the intensity of your workout from 0 to 10, with 0 being equal to resting at home on your couch and ten being equal to the hardest workout you have ever done.

Do you have any questions so far? (**If yes:** Go back over the assessment form)

**Accessing Assessment Form**

**If no:** Great! We ask that you fill out this form at least 30 minutes after your workout, but within 24 hours. You can access the assessment form through a QR code that we have printed on a sticker on your water bottle or keychain. You can use a QR code scanner or your smartphone camera to utilize the QR code. If you are unfamiliar with or unable to use QR codes, we are also happy to send you a link to the form over email or text.

Do you have any questions about how to access the assessment form? (**If yes:** Review how to use QR codes or establish if the participant would prefer an email/text link).

**Email Reminders**

**If no:** Great! We will also send you a daily email reminder to fill out this form during this time. If you haven't exercised that day, however, you do not need to worry about filling out the form for that day. Is there a time of day that you prefer to receive this reminder email? You might think about a time that would be within 24 hours of your favorite time to exercise.

**If They Have a Preferred Time:** Ok, great! We can set up the email reminders to remind you around that time of day.

**If They Do Not Have a Preferred Time:** Ok, we will just plan to remind you at about the same time every day.

# Garmin Vivosmart 4 Physical Activity Tracker

One physical activity device should be assigned per participant. Each physical activity device will be labeled and recorded in an excel document to track inventory.

## Charging the Garmin Device

Site staff should charge the Garmin Vivosmart 4 **prior to shipping.**

- Pinch sides of charging clip (1) to open arms on clip
- Align clip with magnetic charging contacts (2) and release arms of clip
- Plug USB cable into a power source to turn on device
- Ensure fit is correct on magnetic charging contacts and watch is charging

The device will turn on and say, “Hello!” (see photo below).


- After initial charge, usually, best time to charge device is overnight (when participant is sleeping, can leave charger on night stand or next to bed)

## App and Device Setup

Participant device accounts that require email address to complete sign up will use study-generated email accounts:

Format: ACT1ON-(3-digit site number)-(3-digit participant number at site)@gmail.com

Example: ACT1ON-000-001@gmail.com

## Setting up Study ID:

After informed consent form and all other applicable consenting documents have been signed, a participant ID number will need to be created by study team prior to performing any testing procedures for the study.

The ACT1ON protocol uses the following format when assigning participant ID numbers:

- Protocol designation prefix – ‘ACT1ON’ for this study
- Site number (###) – site number (same for each protocol) – always 3 numbers
    - Stanford site number = 000
    - UNC site number = 111
- Patient number at site (###) – always 3 numbers
    - Example (for Stanford): ACT1ON-000-001

- Example (for UNC): ACT1ON-000-001

Each site will have prepared login credentials for 10 subjects.

## Garmin Connect App Download

- The Garmin Vivosmart 4 uses the Garmin Connect app. The app is available for iOS on the App Store and Android on Google Play. See below for Garmin Connect App setup.

## Create Account for Garmin Connect

- Each participant will have a Garmin Connect account to record his or her activity
  - Open Garmin Connect App
  - Press “Create account”
  - Allow participant to review legal terms and conditions
  - Enter participant ID in “name” field
  - Enter study email address in “email address” field
  - Enter assigned study password in “password” field
  - Bring physical activity watch in close range to participant’s smartphone so device can connect
  - Allow participant to follow on-screen tutorial on physical activity watch and app
  - When prompted, select preferred display orientation (portrait or landscape)
  - Select watch face that shows heart rate


Watch face (above) shows:

1) Current heart rate
2) Resting heart rate zone

## Garmin Use

- Double tap touchscreen to wake the device up
- Note: screen turns off when not in use
  - Device is still active and recording data when screen is off
- The device should be secured above the wrist bone and not move while running or exercising
- Watch should be worn on non-dominant wrist

## Log an Exercise

The participant should log exercise through the Garmin physical activity wearable.

Participant can record a timed activity, which can be saved and sent to their Garmin Connect account.

Press to view the menu.
Select .
Swipe to scroll through the activity list, and select an option:

- Select for walking.
- Select for running.
- Select for strength training.
- Select for a cardio activity.
- Select for a bike activity.
- Select for an elliptical trainer activity.
- Select for a Toe-to-Toe™ step challenge.
- Select for pool swimming.
- Select for a yoga activity.
- Select for a stair stepper activity.
- Select for other activity types.

- Double tap touchscreen to stop and resume activity timer
- Tap to view additional screens which appear at top of touchscreen
- After participant completes activity, double tap touch screen to stop timer
- Select an option:
    - Select to save the activity.
    - Select to delete the activity.
    - Select to resume the activity.

## Syncing Your Data with Garmin Connect Mobile App

- Garmin device automatically syncs data with Garmin Connect Mobile app each time the app is opened
- Garmin device periodically syncs data with Garmin Connect Mobile app automatically
- Can also manually sync data at any time
    - Bring device near smartphone
    - Open Garmin Connect app
    - Press to view the menu
    - Select >
    - Wait for data to sync
    - View current data in Garmin Connect app

## Preparing Garmin for Re-Assignment

- Garmin watch will be mailed back to clinic after every 2-week data collection period is complete (refer to timeline above)
- Previous personal data on the Garmin device should be erased prior to assignment of the next participant
    - Press to view Menu
    - Select > > **Reset**.
    - Select the following option:
        - To reset all of device settings to factory default values and delete all user-entered information and activity history, select **Delete Data and Reset Settings**
    - Press
    - Select
- Garmin Connect app should also be deleted from participant's smartphone at the end of final study visit

## Other Notes

- Garmin Vivosmart 4 should be worn on the same wrist at all times
- Suggestions for optimal charge time include overnight since we are not collecting sleep data
- Keep device on flat surface like a countertop when not in use
- If patient prefers, can charge device ~30 mins daily when sitting (not preferred)
- The device withstands pressure equivalent to a depth of 50 m and is waterproof
- Can be worn for swimming and showering, but preferably not scuba diving or highspeed watersports
- Clean device with a cloth dampened with mild detergent solution and wipe dry after watch is returned
- Make sure device is completely dry before placing on wrist. Avoid chemical cleaners, solvents, and insect repellents that can damage the plastic components and finishes
- Thoroughly rinse device with fresh water after exposure to chlorine, salt water, sunscreen, cosmetics, alcohol, or other harsh chemicals
- Full manual for Garmin Vivosmart 4 provided here: https://www8.garmin.com/manuals/webhelp/vivosmart4/EN-US/vivosmart_4_OM_EN-US.pdf