Official Title: Data-Assisted Approach for High Intensity Weight Loss for Diabetes Remission
NCT04663061
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Data-Assisted Approach for High Intensity Medical Weight Loss for Diabetes Remission

National Clinical Trial (NCT) Identified Number: NCT04663061

Principal Investigator: Jamy Ard

Sponsor: Wake Forest School of Medicine

Funded by: Savvy Sherpa, LLC

Version Number: v.1.1

12 October 2020

Table of Contents

STATEMENT OF COMPLIANCE

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

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

    National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.
    OR
2. The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the [specify NIH Institute or Center (IC) [Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.
    For either option above, the following paragraph would be included:
    The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

Principal Investigator or Clinical Site Investigator:

Signed: Date:

Name*: Jamy D. Ard, MD

Title*: Principal Investigator

Investigator Contact Information:

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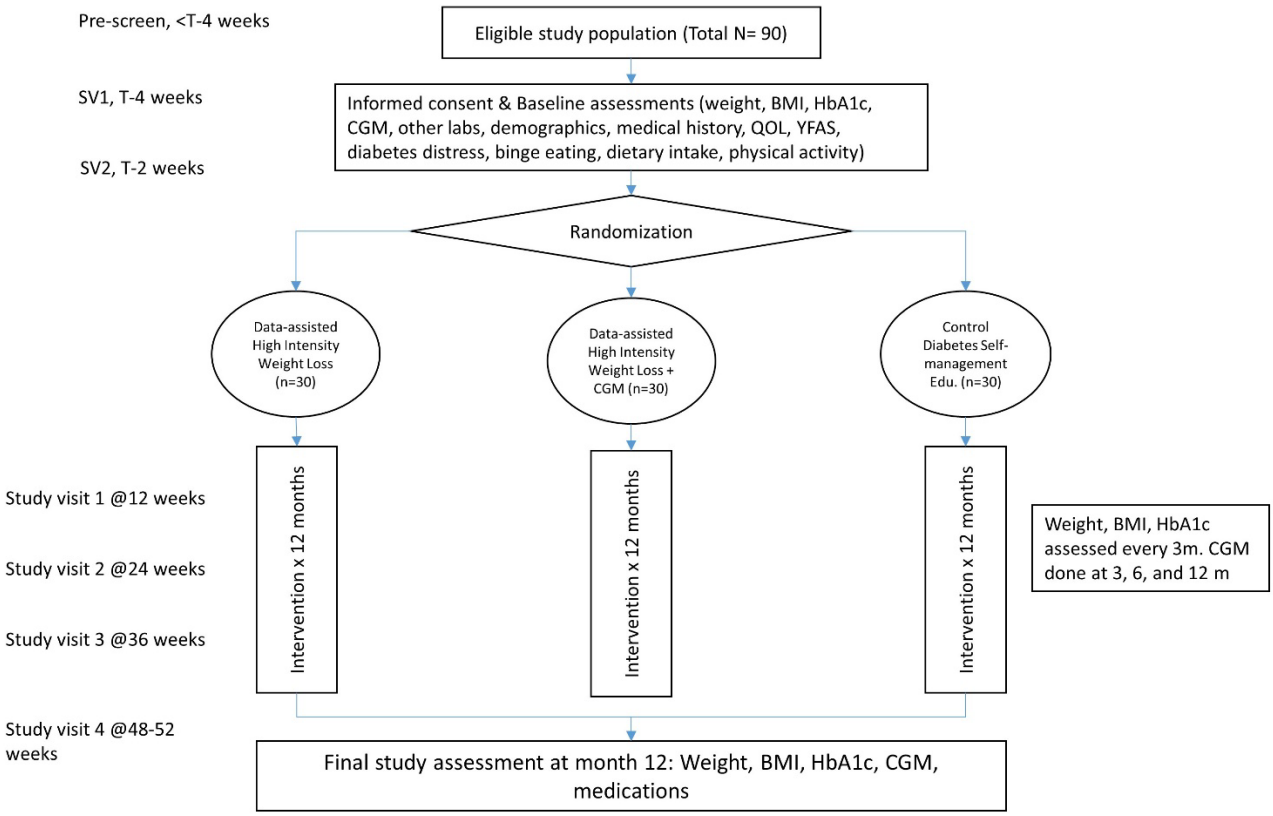
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Data-Assisted Approach for High Intensity Medical Weight Loss for Diabetes Remission	
Grant Number:	IRB00067950	
	We will study the efficacy of a high intensity medical weight loss intervention paired with a digital platform to create weight loss and induce remission of T2DM compared to a diabetes self-management education intervention. The digital platform provides the capability to tailor the treatment plan, provide automated support, and alert providers when a participant may need more support from the clinical team. If shown to be efficacious, this research could be highly impactful, causing us to rethink our approach to care for those with T2DM and shift the paradigm for millions of individuals in the US. Furthermore, this approach will demonstrate the feasibility of helping people engage in metabolic treatment strategies in a way that is scalable leveraging digital and mobile solutions that extend the patient-provider relationship, shift care from episodic approaches to more of an on-going model that extends into the life of the patient, while also integrated within the healthcare system workflows.	
Objectives*:	Primary Objective:	Test the effectiveness of the combined interventions (data-assisted approach for high intensity medical weight loss) for weight loss in a group of adults with recently diagnosed type 2 diabetes compared to standard of care diabetes self-management education.
	Secondary Objectives:	Demonstrate the feasibility of pairing a high intensity medical weight loss treatment for diabetes remission with a digital platform that integrates remote monitoring, patient self-report, and care pathways into a data-assisted and personalized treatment program.
Endpoints*:	Primary Endpoint:	Change in body weight (kg) from baseline to 12 months
	Secondary Endpoints:	Hemoglobin A1c (%) change from baseline at 3, 6, 9, 12 months
		Diabetes remission at 12 months, including partial remission (HbA1c of 5.7-6.4% without the use of anti-diabetes

	medications) and complete remission (HbA1c of 5.7-6.4% without the use of anti-diabetes medications) Continuous glucose monitoring outcomes. CGM related outcomes that we will assess at baseline and 12 months include time in range, episodes of hypoglycemia, glucose variability, and average glucose.
Study Population:	Participants will be individuals 18 and older who have T2DM diagnosed within the past 6 years with a BMI of 27-50 kg/m^2. Participants must have an HbA1c between 6.5-11.9%. Sample size will be 30 participants per treatment group.
Phase* or Stage:	Phase 4
Description of Sites/Facilities Enrolling Participants:	Wake Forest Baptist Health Weight Management Center (WMC) Wake Forest Baptist Health Diabetes Center (DC)
Description of Study Intervention/Experimental Manipulation:	Participants randomized to the HIWL treatment group will be placed on a meal replacement-based weight loss protocol. Our active intervention will be delivered with the aid of a technology platform that will automate portions of the intervention and assist clinicians in tailoring treatment and responding to participant needs in a “just-in-time” manner that we frame as a “data-assisted approach.”
Study Duration*:	15 months
Participant Duration:	12 months

1.2 SCHEMA


Pre-screen, <T-4 weeks
Eligible study population (Total N= 90)
SV1, T-4 weeks
Informed consent & Baseline assessments (weight, BMI, HbA1c, CGM, other labs, demographics, medical history, QOL, YFAS, diabetes distress, binge eating, dietary intake, physical activity)
SV2, T-2 weeks
Randomization
Data-assisted High Intensity Weight Loss (n=30)
Data-assisted High Intensity Weight Loss + CGM (n=30)
Control Diabetes Self-management Edu. (n=30)
Intervention x 12 months
Intervention x 12 months
Intervention x 12 months
Study visit 1 @12 weeks
Study visit 2 @24 weeks
Study visit 3 @36 weeks
Study visit 4 @48-52 weeks
Weight, BMI, HbA1c assessed every 3m. CGM done at 3, 6, and 12 m
Final study assessment at month 12: Weight, BMI, HbA1c, CGM, medications

1.3 SCHEDULE OF ACTIVITIES

Study activity	T<-4	T -4	T -2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	28	32	36	40	44	48	52
Phone screen	x																																		
Consent		x																																	
Screen visit (SV) 1		x																																	
History and physical exam		x																																	
Medication review		x																																	
Past medical history		x																																	
Electrocardiogram		x																																	
Center for Epidemiologic Studies Depression Revised Scale		x																																	
SV2			x																																
EuroQOL-5D			x																									x							x
Diabetes Distress Scale			x																									x							x
Binge Eating Scale			x																									x							x
Yale Food Addiction Scale			x																																
Dietary intake assessment[1]			x													x												x							x
Physical activity assessment[2]			x													x												x							x
Adverse events			x													x												x							x
Randomization				x																															
Treatment orientation				x																															
Lifestyle counseling (Experimental groups)				x	x	x	x	x	After this point, lifestyle counseling will be based on treatment response and guided by data-assisted intervention strategy.																												
Continuous glucose monitoring			x													x												x							x
Body weight		x	x	x												x												x			x				x
Height		x																																	
Blood pressure		x	x	x												x												x			x				x
Pulse		x	x	x												x												x			x				x
Waist circumference		x	x													x												x			x				x
Clinical labs (CMP)						x		x		x		x		x		x												x				x			x
HbA1c			x													x												x			x				x
Insulin, lipids, C-peptide			x																									x							x
CBC, CMP			x																																
Study closeout visit																																			x

1- ASA24 self-administered 24 hour dietary recall

2- Pedometer-https://www.yamax.co.uk/yamax-pedometers/

2 Introduction

2.1 STUDY RATIONALE

We will study the efficacy of a high intensity medical weight loss intervention paired with a digital platform to create weight loss and induce remission of T2DM compared to a diabetes self-management education intervention. The digital platform provides the capability to tailor the treatment plan, provide automated support, and alert providers when a participant may need more support from the clinical team. If shown to be efficacious, this research could be highly impactful, causing us to rethink our approach to care for those with T2DM and shift the paradigm for millions of individuals in the US. Furthermore, this approach will demonstrate the feasibility of helping people engage in metabolic treatment strategies in a way that is scalable leveraging digital and mobile solutions that extend the patient-provider relationship, shift care from episodic approaches to more of an on-going model that extends into the life of the patient, while also integrated within the healthcare system workflows.

2.2 BACKGROUND

Largely as a consequence of increasing obesity rates, diabetes prevalence is growing and is predicted to continue to grow in the US. Obesity rates in the U.S. have increased dramatically in the past 3 decades.[1] The increasing rates of obesity have been linked with a higher rate of diseases, including type 2 diabetes mellitus (T2DM).[2] The association between excessive weight gain and T2DM has been well established, and it is suspected that much of the increased prevalence of T2DM is being driven largely by excessive weight gain. [3] It is expected that the prevalence of T2DM could increase from most recent levels in 2015 of 12.2% of US adults aged 18 and older to 25-33% by 2050.[4]

The consequence of a high burden of diabetes is costly for our society. T2DM affects a number of organ systems, which results in significant morbidity and mortality and increased health care costs. The American Diabetes Association estimates that approximately 16% of CVD deaths are attributable to diabetes. [5,6] It is estimated that approximately 55% of deaths due to renal failure are attributable to diabetes.[7] As a result of the effect of diabetes on CVD risk, renal function, and other organ systems, diabetes accounted for approximately 246,000 deaths in the U.S.[7] In 2012, the estimated cost of diabetes was $245 billion in the US, where an individual with diabetes had an average medical expenditure of $13,700 annually—2.3 times higher than those without diabetes.[7]

Prevention of T2DM is an important strategy to combat the growing threat that T2DM poses; however, once someone develops T2DM, our options are limited. Our current strategies to deal with diabetes primarily include prevention strategies or, once developed, glycemic and risk factor control. The well-known Diabetes Prevention Program has shown that weight losses of 7% of body weight can lead to over 50% reduction in the incidence of T2DM in people with known impaired fasting glucose or glucose intolerance. [8-10] While prevention is important, some will develop diabetes despite lifestyle changes, and many others may not have access to or do not avail themselves of preventive treatments. Once a person develops T2DM in our current health care system, the focus is primarily on learning how to live with and manage the disease using education, diabetes medications, and lifestyle changes. [11,12]

Even when T2DM is well controlled, significant risks and negative impacts associated with living with T2DM still remain. A recent systematic review showed that there was a 30% relative risk increase for severe hypoglycemia when attempting to achieve intensive glycemic control without any significant improvements in risk for all-cause and cardiovascular mortality. [13] In 5 years, the ACCORD trial reported 19% more deaths in the intensive glucose-management group than in the standard glucose-management group. [14] Recent reports have identified increased risk of all-cause mortality with intensification of T2DM treatment when adding insulin to metformin, raising questions about risks associated with insulin therapy. [15] Additionally, the impact of T2DM on quality of life can be significant. Norris et al pooled data from 118 studies that assessed health related quality of life in persons with T2DM, finding that all 8 component scores of the Short Form-36 were lower than comparable U.S. population norms. [16]

We know that diabetes remission can be achieved with significant weight loss in the right patient populations. The landmark DiRECT trial demonstrated that long-term remission of T2DM can be achieved with the use of a total meal replacement diet and achievement of >10% weight loss.[17] After 1 year of treatment, those in the intervention group had a mean weight loss of 10% compared to no weight loss for the control group. The rate of diabetes remission, defined as an hemoglobin A1c of <6.4% was 46% in the treatment group compared to 4% in the control arm. Remission was achieved in 86% of participants who lost at least 15 kg. At 2 years of follow up, the intervention group maintained a lower body weight (-5.4 kg [95% CI, -6.9 to -4]) and HbA1c (-0.44% [-0.76 to -0.13]); the rate of diabetes remission at 2 years was 36% for the intervention group compared to 3% for the control group (aOR 25·82, 8·25 to 80·84; p<0·0001).[18] Participants in this trial were 20-65 years old, had T2DM for <6 years, BMI 27-45 kg/m^2, and were not on insulin.[17]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There is some minor discomfort and risk of mild bruising during venipuncture.

A breech of participant confidentiality is an additional risk for each participant.

The participants in this study may also be subject to fluctuations in their blood glucose levels as a result of restricting calories and modifying the types of foods they are consuming. This could lead to symptomatic hypoglycemia.

Discomfort associated with venipuncture is rapidly reversible. Bruises from venipuncture will heal in several days. Hypoglycemia is reversible with appropriate therapy.

The continuous glucose monitor will be worn throughout the study for those in the High Intensity Weight Loss Group plus Continuous Glucose Monitoring group and by everyone else during study visits at baseline and weeks 12, 24, and end of study. Use of the continuous glucose monitor could be associated with some skin irritation from the adhesive or the filament that is under the skin. Some people will notice some discomfort with use of the monitor.

2.3.2 KNOWN POTENTIAL BENEFITS

The benefits to participants of participating in the study are that persons may lose weight or changes in body composition may occur. Additionally, many may see improvements in the control of their blood glucose values and lower overall risk of heart disease, heart attacks or stroke. If the study hypotheses are correct, the treatments could make a difference for a lot of people living with diabetes.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks to participants in this study are not largely different from what might be experienced in the course of diabetes care and weight loss treatment in the general community, but the potential benefits may be significant especially if persons are able lower their blood glucose levels to the point that they normalize and do not require medication to control their blood glucose.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
Test the effectiveness of the combined interventions (data-assisted approach for high intensity medical weight loss) for weight loss in a group of adults with recently diagnosed type 2 diabetes compared to standard of care diabetes self-management education.	Change in body weight (kg) from baseline to 12 months	Body weight is primary target for medical weight loss interventions	
Secondary			
Demonstrate the feasibility of pairing a high intensity medical weight loss treatment for diabetes remission with a digital platform that integrates remote monitoring, patient self-report, and care pathways into a data-assisted and personalized treatment program.	Hemoglobin A1c (%) change from baseline at 3, 6, 9, 12 months; Diabetes remission at 12 months, including partial remission (HbA1c of 5.7-6.4% without the use of anti-diabetes medications) and complete remission (HbA1c of 5.7-6.4% without the use of anti-diabetes medications);	As a result of weight change, we expect to see changes in glycemic control.	Reductions in fat mass due to energy restriction, leading to less insulin requirements and greater use of fat stores to make up the energy deficit.
Tertiary/Exploratory			
Demonstrate the impact of including CGM as part of the remote monitoring system with the data-assisted approach for high intensity medical weight loss treatment.	Patient satisfaction with CGM; length of time to achieve A1c goals; study retention	CGM provides immediate feedback to patients about glycemic control. We expect this to improve behavioral reactions and future choices in a shorter term.	Feedback loops with relevant data and clear actions leading to more decisive improvements in biomarkers.
Compare estimated healthcare expenditures and	EuroQOL-5; healthcare utilization from self-report	Intensive weight loss intervention involves cost and time. However,	Weight reduction could decrease healthcare utilization by resolving

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
utilization between the active treatment groups and the control intervention	and review of medical records	we might expect cost savings due to reduction in weight and improved glycemic control.	obesity related complications and decreasing need for medications and other healthcare.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This project will determine if a data-assisted, high intensity medical weight loss intervention (HIWL) will lead to significant weight loss and diabetes remission in individuals with a BMI 27-50 kg/m^2 with T2DM of less than 6 years as compared to a diabetes self-management education intervention (DSME). Complete diabetes remission is considered to be achieved when the patient is not taking any anti-diabetes medication for at least 12 months, and the HbA1c is < 5.7%. Partial remission is achieved when the patient is not taking any anti-diabetes medication and has an HbA1c of 5.7-6.4% for at least 12 months. Using a randomized controlled study design, we will randomly assign 90 participants to HIWL, HIWL + CGM, or DSME. Participants assigned to HIWL will receive a high intensity behavioral weight loss intervention delivered using a digital patient engagement platform. Participants will be prescribed a low calorie dietary plan and a recommended physical activity program designed to produce 15-20% weight loss over 12 months. Those assigned to HIWL + CGM will receive the same intervention as HIWL; in addition we will provide them with CGM to use as part of their remote monitoring on a daily basis. Those assigned to DSME will participate in a comprehensive diabetes education program designed to provide education and skills for optimal diabetes management plus lifestyle modification counseling to produce 5% weight loss over the same timeframe. The primary outcome of weight loss will be assessed at 12 months.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We will use a randomized controlled trial design to compare the two interventions. This provides the best study design to assign causality and a direct link to our secondary objectives of improved glycemic control.

4.3 JUSTIFICATION FOR INTERVENTION

From a patient-centered perspective, reducing the burden of disease (e.g., medication dosage, diabetes self-monitoring, and diabetes distress) has a direct impact on the individual. From a health system perspective, if those with T2DM cost approximately $7,700 more annually to care for than those without T2DM [7], inducing remission saves $23,100 over 3 years. Based on data from the DiRECT trial, the absolute risk reduction (ARR) at 2 years is 33%; therefore, the number needed to treat (NNT) to achieve one remission is 3 (1 ÷ ARR). Comparatively, the well-accepted Diabetes Prevention Program had an overall absolute risk reduction of 14.3% compared to placebo, with a NNT of 7.[19] Even if the ARR is adjusted based on modifying the population of patients included in such an intervention (e.g., including people on insulin), an ARR of 20% is still superior to the Diabetes Prevention Program.

To make this type of intervention accessible, we need to demonstrate a model of delivery that is scalable and sustainable. Our application addresses this specific challenge. The Wake Forest Baptist Health Weight Management Center (WMC) has the expertise and infrastructure to deliver total meal replacement diets designed to achieve higher percentages of weight loss. We have demonstrated previously that our mean weight loss achieved in all-comers is higher than that reported in the DiRECT trial. We have also reported improvements in glycemic control and diabetes remission rates. Our intent with this proposal is to pair our proven treatment programs with a digital platform designed to provide a tailored treatment experience that is scalable and sustainable.

Our proposed strategy is to use a combination of software applications, remote monitoring, patient self-reporting tools, and defined care algorithms to create a data-assisted high intensity medical weight loss treatment strategy for diabetes remission. We believe this approach can be effective in engaging patients with the lifestyle and behavior change needed to achieve the treatment goals. By using the digital platform, we can leverage computer automation to expand the reach of individual providers, tailor and personalize treatment immediately based on real-time data flows, and provide assistance in a "just-in-time" fashion that creates efficiency that allows for greater scale of implementation. The shorter latency time between patient need and provider support means that patients will likely stay engaged longer and more consistently to achieve better outcomes. We can also integrate this system with the electronic health record (EHR) providing the patient's care team a clear view of the actions and resulting impacts of the intervention.

4.4 END-OF-STUDY DEFINITION

This study will be carried out to completion, defined as 12 months of follow up for all enrolled participants.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Age 18+	Phone
Type 2 diabetes mellitus by A1c +/- medication ≤ 6 years	Phone
BMI 27-50 kg/m^2	Phone; SV 1
Able to participate in intervention	Phone
Has a mobile phone with text messaging	Phone

5.2 EXCLUSION CRITERIA

Poorly controlled depression (CES-D >16)	Phone; SV 1
Recent hospitalization for psychosis or bipolar disorder	Phone
Poorly controlled blood pressure (>159/99)	SV 1
Prior surgical procedure for weight control	Phone
Unable to make changes to their diet	Phone
Unable to exercise (walk for at least 6 minutes and perform simple strength and stretch exercise tests)	Phone
Use of weight loss medications in previous 3 months	Phone
Recent self-reported weight change (+/- 15lbs)	Phone
Current use of oral corticosteroids more than 5days/month	Phone
Cardiovascular disease event within the past 6 months	Phone
Severe pulmonary disease requiring supplemental oxygen	Phone
Renal failure (end stage renal disease)	Phone
History of non-skin cancer in the past 5 years	Phone
Major liver dysfunction within the last 2 years	Phone
Recently quit smoking less than 6 months prior	Phone
Inability to attend visits and adhere to study protocols	Phone
Pregnancy or currently lactating	Phone

5.3 LIFESTYLE CONSIDERATIONS

During the study, participants will be asked to:

- Refrain from receiving outside treatment for obesity, including other treatment plans, medications, or pursuing surgery
- Avoid pregnancy

Anyone who engages in either will have their study participation closed out.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include the successful treatment of a previous affective disorder, and the lifting of physical activity restrictions previously in place. Rescreened participants will be assigned the same participant number as for the initial screening.

In the case that a participant fails screening due to indications of suicidal ideation (as noted on the CESD-R), the research team will implement an Immediate Action Protocol to address the safety of the participant and ensure appropriate care. The study clinician will be notified and assess the immediate safety of the participant. If the participant is thought to be at high risk for self-harm, an immediate referral to psychiatric care will be initiated. Transportation to the appropriate facility will be arranged. If the participant is not suspected to be high risk and can contract for safety, follow up with psychiatric care will be arranged.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential volunteers for this study will be recruited from the greater Winston-Salem, NC metro area. This is a primary catchment area for Wake Forest Baptist Health, and remains a reliable source of participants for clinical trials conducted by members of this research team. Both Drs. Ard (obesity medicine) and Aloi (endocrinology) have clinical programs in the WFBH system that can serve as a source of patients. Patients in these clinics who meet potential eligibility criteria to enroll will be invited to screen for the study. We will also screen medical records using i2b2 and the CTSI to identify potential participants who meet eligibility criteria. Individuals who are identified in the medical record screen will be invited to screen for the study via direct mail. In the direct mail invitation, participants will be able to complete a brief survey to indicate interest in screening for the study. One of the study team members will follow up with the potential volunteer by phone to complete a phone screen. If the potential participant passes the phone screen and is interested in proceeding, he/she will be invited to an in-person screening.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

ACTIVE INTERVENTION

High intensity medical weight loss: Participants randomized to the HIWL treatment group will be placed on a meal replacement-based weight loss protocol. Dr. Ard will oversee the medical management team and implementation of this protocol at the Weight Management Center. He serves as the medical director for medical weight management and has over 13 years of experience treating a wide range of patients with a low calorie meal replacement protocol. Participants will consume a minimum of 80 grams of protein daily in 4-5 servings of meal replacement. Minimum caloric intake will be 960 kcal/day with adjustments to intake made based on BMI and activity levels, holding the percent of calories from protein constant at 35%. The meal plan provides 100% of daily recommended needs for micronutrients. Meal replacements will be supplied at no cost to the participant at weekly clinic visits. Meal replacements are in the form of shakes, soups, and meal bars. Participants will begin to incorporate food into their routine beginning at week 13 with guidance from a dietitian. From weeks 13-24, caloric prescriptions will be between 1100 to 1600 kcal/day, using a combination of meal replacements and food, for continued weight loss. Beyond week 25, caloric intake will be individually tailored to achieve continued gradual weight loss or maintenance of body weight based on individual weight loss goals. Minimum caloric intake during this third treatment segment will be 1200 kcal/day. Participants will be seen by a study team clinician weekly for the first 4 weeks of the treatment plan. This weekly follow up will allow the medical weight loss team the opportunity to assess early treatment response, assess for side effects, and adjust medications to avoid hypoglycemia, hypotension, and/or dehydration. The first month of treatment is also critical to identify potential non-responders and alter their treatment plan early on. Research suggests that treatment non-response in the first 4-12 weeks is associated with poor weight loss outcomes. [20,21] Beyond this first month of scripted intervention, the team will use information from the digital platform (described below) to dictate the type and intensity of follow up. Key factors that will influence the treatment plan are treatment response including pace of weight loss and changes in glycemic control; engagement in key behaviors including self-monitoring and physical activity; and complexity of the participant's medical regimen including use of insulin, anti-hypertensives, or other medications that we adjust during weight loss.

Digital platform: Our active intervention will be delivered with the aid of a technology platform that will automate portions of the intervention and assist clinicians in tailoring treatment and responding to participant needs in a "just-in-time" manner that we frame as a "data-assisted approach." Consumer-centric healthcare models enabled by technology are a new frontier in healthcare. Rising healthcare costs, consumer adoption of smart-phones, and a shift toward value-based payment models designed to produce better health outcomes all contribute to this trend. Our partner technology provider is Carium. Carium's software product is a HIPAA compliant, cloud-based, flexible platform, accessible via mobile and web applications, that allows patients and providers to co-create personalized care plans that are

informed by data and enable continuous collaboration during the course of everyday life. Through just-in-time encouragement and information, automatic medication reminders, and secure communication with care providers, the application supports patients in achieving their health goals, maximizing medication adherence, and achieving optimal health outcomes. This approach moves our current treatment pathways from generalized protocols that try to anticipate patient needs based on average responses to customized treatment plans that amplify the reach and impact of the current provider team. This makes the proposed intervention highly scalable and sustainable in a value-based care world. The platform has been deployed in a variety of healthcare settings, including primary care practices, care management programs, and community centers. In addition to the software component, the Carium team provides expertise in clinical practice transformation, patient engagement, behavior change science, and the latest technology. Core capabilities of Carium's offer include integration with remote monitoring devices such as activity trackers (Apple HealthKit, FitBit, Google Fit, etc.), glucometers (Omron, Dexcomm, Contour, etc.), blood pressure cuffs (Omron, etc.), scales (FitBit, Omron, BodyTrace, etc.); surveys, interviews, and self-assessments; secure messaging (one-to-one and groups) (Figure 2); photo and text journaling; content management and sharing; data-driven reminders, rules, and alerts to enable habit-engineering and behavior change; automation for patient experience and care team efficiency; dashboards and reports on engagement, patient progress, outcomes, population health; and seamless integration into clinical EMR workflows.

Body weight: To further enhance intervention engagement and self-monitoring, participants in the HIWL group will also receive a **Bluetooth-connected body weight scale**. The scale and Carium digital intervention will link electronically; the scales will transmit weight data automatically in a secure fashion to participants' accounts, allowing the participant and his or her providers to view the weight data in real time. We will instruct participants to weigh themselves daily throughout the course of the study.

Continuous glucose monitoring: Thirty participants will receive the HIWL intervention as outlined above and also receive a supply of continuous glucose monitors to use throughout the trial. The CMG we provide will give the patient instant feedback on blood glucose levels and be readable using a mobile phone device or an associated CGM reader (For details of the CGM device, see 8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS) . The data from the CGM will be integrated into the Carium app and used to help guide the patient's actions based on defined care pathways.

Development and refinement of care pathways: We will work with the Carium development team to expand and tailor the standard care pathway for the treatment objectives of this proposal—weight reduction and improved glycemic control. The focus of the care pathway will be on supporting lifestyle change, minimizing risk of adverse events, and providing actionable data to predict higher risk of disengagement. We will build key modules that enable automated guidance based on stage of treatment and anticipated difficulties/challenges that are most likely at a given stage. This process will use participant response to brief surveys and queries to determine which content needs to be delivered and when clinical support (i.e., someone from the clinic team) should be engaged. This will result in provision of content and support when it is most appropriate and in an efficient manner. For example, through this process we can develop content that anticipates GI related side effects of a MR-based diet (e.g., constipation) and provide participants with educational content on how to prevent it in the first 1-2 weeks of treatment. Surveys would be timed to go out when our clinical experience suggests symptoms of constipation might develop. If a survey response indicates that current constipation

prevention measures are ineffective, a team member can engage the participant in a chat session to provide support to resolve the issue before it becomes more distressing and resource intensive (e.g., requiring a call to the center with multiple workflows and provider types engaged to deal with a preventable/predictable side effect). Content can be programmed based on participant characteristics (e.g., on insulin versus only on metformin) so that information can be targeted and highly relevant to the individual user. The pathway will also have key outcome indicators that will roll up into a clinical dashboard shared by the provider team. The indicators will help providers allocate time and attention to those who would benefit most based on pre-set cut points. Over time, we will adjust the cut points based on treatment outcomes to improve the sensitivity and specificity of each indicator.

CONTROL INTERVENTION:

Diabetes self-management education (DSME): The DSME intervention will be administered and delivered at the WFBH Diabetes Center, located next to the Weight Management Center. The diabetes education program is accredited by the American Diabetes Association in recognition of meeting national standards for diabetes self-management education. The goal of the program is to provide participants with information to make informed decisions about how to best integrate diabetes management strategies into their daily lives. Assessment, planning, implementation, and evaluation are the basic components of the diabetes education process. The DSME will be delivered by qualified personnel in group and individual settings. The DSME will be provided over the course of 12 months. Participants will have a variety of learning objectives that are part of the core Comprehensive Diabetes Education Program provided by the WFBH Diabetes and Endocrinology Center. Participants will attend an initial group class or individual appointment in the first month, followed by at least quarterly individual appointments through the next 11 months. Additional appointments may be recommended by the diabetes educator. Participants will be prescribed a weight reducing diet that is 500-750 kcal below estimated total energy expenditure using the Mifflin-St. Jeor equation.[22] The dietary plan will focus on carb counting and healthy diet quality, allowing up to 45 g carbs per meal for women and 60 g carbs per meal for men. Similar to the HIWL intervention, the physical activity prescription will be a goal of 180 minutes of moderate intensity activity per week, using a combination of resistance training and aerobic exercise. However, the DSME group will not have exercise training sessions, but we will provide written and oral instructions on strategies in the group and individual counseling sessions to meet the exercise goals.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Fidelity to treatment impacts reliability and validity of study findings. To ensure consistency of intervention content and delivery, we will use standardized treatment protocols and procedures. A

comprehensive Manual of Operations and Procedures will be developed in the start-up period and distributed to all personnel. Written procedures will exist for assessments, treatment delivery, and monitoring of treatment delivery. Study personnel will be thoroughly trained in the interventions and given corrective feedback in practice sessions. Even among highly trained interventionists, there is a potential for slight deviations from treatment protocol to occur over time, commonly referred to as "intervention drift." In order to protect against this, regular "booster" training sessions will be conducted. Treatment fidelity will be monitored also by live supervision. The Interventionist will be observed regularly by one of the investigators during group and individual sessions. Live supervision corrects for procedural and intervention drift and enhances adherence to the protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be randomized using a web-based protocol for treatment assignment. Once participants are screened as eligible to participate, the study coordinator will submit the participant's study number for treatment assignment via the study web portal. Randomization will be done in blocks of 10, stratified by sex.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

For participants in the HIWL or HIWL + CGM interventions, participation and engagement will be monitored through the Carium platform on a regular basis. At the end of each week of participation, a summary assessment of participant engagement levels will be generated from the platform. Individuals who show unexplained drop offs in participation levels will have follow up outreach to assess key factors that might be affecting engagement.

For participants in the control intervention, participation and engagement will be monitored during participation in the group-based DSME. There will be a regular review of food diaries and tailored information provided to the participants to help guide plan implementation. Participants who are showing signs of lower or decreased engagement will be engaged by the study team to see what can be done to maintain/improve engagement.

6.5 CONCOMITANT THERAPY

6.5.1 RESCUE THERAPY

Medication adjustment: For participants in the data-assisted HIWL arms, the medical weight loss team will make medication adjustments at the beginning of the intervention, at any subsequent clinic visit or

encounter where the participant reports symptoms of hypoglycemia with corresponding low blood glucose readings, or at quarterly assessments of HbA1c. For participants in the DSME intervention, Dr. Aloi with meet weekly with the diabetes education interventionist to review participant blood glucose logs and make adjustments in medication dosing. Participants will be asked to self-monitor BG values at least twice daily (fasting and pre-dinner meal), not including additional measures if they are experiencing signs/symptoms of hypoglycemia. At each clinic visit, we will review the average values and ascertain episodes of hypoglycemia, defined as glucose levels less than 70 mg/dL. If the participant reports an episode of severe hypoglycemia (hypoglycemia resulting in a loss of consciousness or inability to self-treat) or symptomatic hypoglycemia on multiple occasions to a non-clinical staff member, one of the study clinicians will be notified to make adjustments in medications within 24 hours per the protocol (Table 4).Medication can be discontinued if the lowest dose available is being prescribed and the average BG ≤ 140 or HbA1c < 6.5%. Once total insulin dose is below 20 units daily with adequate control, the participant will be transitioned to an oral medication regimen (i.e., non-insulin).

Table 4. Medication Dose Adjustment Plan			
Event	Action	Follow up	Desired outcome
Initiating weight loss intervention	Reduce meds by up to 50% and/or discontinue all oral hypoglycemic	1 week	No hypoglycemic events and average BG less than or equal to baseline A1c
One episode of severe hypoglycemia or symptomatic hypoglycemia 2 times or more per week	Reduce meds by 50-100%	1 week	No hypoglycemic events
14-day average BG < 126	Reduce meds by 25-50%	2 weeks	Average BG ≤ 140
14-day average BG > 140 in absence of hypoglycemia	Increase meds by 25%	2 weeks	Average BG ≤ 140 and no hypoglycemia
HbA1c > 7% at quarterly assessment	Increase meds by 25% or add new class	2 weeks	Average BG ≤ 154 and no hypoglycemia

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from HIWL, HIWL + CGM, or Control groups, but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).
The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Initiation of a disqualifying weight loss treatment (e.g., bariatric surgery)
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation (e.g., becomes pregnant)

The reason for participant discontinuation or withdrawal from the study will be recorded on the Study Discontinuation Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits and study staff are unable to contact the participant after at least 3 attempts.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit within 5 business days, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

All measures will be assessed at baseline and every 3 months thereafter (unless a different schedule is specified below). The primary outcome (change in body weight) will be assessed as weight at 12 months – weight at baseline.

Weight: Weight and height will be measured in light indoor clothes without shoes using standard procedures. Weight measurements will be taken to the nearest 0.1kg by a high-quality digital scale. Scales will be calibrated annually by the Bureau of Weights and Standards and quarterly by trained study personnel using standard weights. Height will be measured using a standard wall-mounted stadiometer. Study personnel will be trained and certified to follow measurement procedures according to study protocol. Percent weight loss will be calculated based on baseline weight obtained at the first in-person screening visit.

Glycemic control: Serum HbA1c measurements will be drawn quarterly on all participants. Assessment of glycemic control will be done in the context of anti-diabetes medication usage. Documentation of medications will be obtained electronically from all available sources (e.g., EHR, pharmacy) and by physical review of medicines using the "brown bag" method. Participants will be requested to bring all of their medication to the clinic for review. Research assistants will reconcile medication regimens from the electronic record and those presented by the patient. Medicines will be described as any prescription or non-prescription substance they take on a regular basis including tablets, liquids, inhalers, creams and ointments. Continuous glucose monitoring (CGM) with sub-dermal sensors will be used as a secondary measure of glycemic control for all participants. CGM provides information beyond what traditional finger stick blood glucose testing affords. CGM provides measurements of interstitial blood glucose (BG) at 1- 15 minute intervals and correlates well with capillary blood glucose measurements. Collection of continuous glucose values allows immediate recognition of current BG and prediction of trajectory of BG; preventing hypoglycemia. We will utilize the FreeStyle Libre, which is one of the most frequently used CGM in the world as a result of both its accuracy and simplicity of use. Sensors are placed on the upper arm using a painless spring loaded injector. BG recordings are available within an hour and the device will record BG every 15 minute minutes without a need for calibrations for 2 weeks. CGM related outcomes that we will assess at baseline and 12 months include time in range, episodes of hypoglycemia, glucose variability, and average glucose. For individuals in the HIWL + CGM arm of the trial, data from the CGM they are using in the intervention will be used for these outcomes.

Diabetes remission: Diabetes remission status will be assessed at 12 months as a secondary outcome for this study. At the time of assessment, if the participant has achieved an HbA1c of 5.7-6.4% without the use of anti-diabetes medications, the participant will be classified as being in partial remission. If the participant has achieved an HbA1c of <5.7% without any medications, the participant will be classified as being in complete remission. The sum of these two outcomes will comprise the outcome of any remission (partial + complete).

Demographics: Demographic information including sex, race/ethnicity, and date of birth (age) will be captured at the first screening visit during verification of eligibility. Medical history including date of

diabetes diagnosis (duration of diabetes) and co-morbid conditions will be captured by interview and verification from the medical record when available.

Dietary intake: To assess **dietary intake**, we will use NCI's automated, self-administered 24-hour dietary recall, the Automated Self-Administered 24-hour (**ASA24 ®**) dietary assessment tool (version: ASA24-2018). The ASA24-2018 will be completed on three, non-consecutive days (including one weekend day) at baseline (pre-randomization), and again at months 3, 6, and 12. The ASA24-2018 is available for use on computers and mobile devices. At the baseline visit, participants will complete one ASA24 assisted by a research staff member. They will then be asked to complete a second and third ASA24 during run-in, on their own, as a part of the baseline assessment. During office visits at each relevant follow-up time point (3, 6 and 12 months), participants will again complete the ASA24. Following each of these visits, a staff member will contact participants within six days (on a randomly selected day) to inform them to complete 2 additional dietary recalls and will offer to conduct the recall over the phone if needed (the ASA24 performs equally well as a self- or interviewer- administered questionnaire).[23,24] Follow-up reminder calls will be made to encourage completion of the recalls if not completed within 24-hours following a contact. Using the ASA24 data from each time point (baseline, 3, 6, and 12 months), specific outcomes of interest will include: **total daily energy intake** (kcal; averaged across 3 days), **macronutrient composition** of diet (%Carbohydrate/Fat/Protein; averaged across 3 days), **number of eating episodes** per day, and **Healthy Eating Index (HEI)-2015** score (a validated summary measure of dietary quality, rated on a 100-point scale, [25,26] which is sensitive to change with dietary intervention[26,27], and can be calculated using publicly-available SAS code from the ASA24 website).

Physical activity: We will use pedometers to assess objective physical activity (PA) – operationalized as **daily step counts** – at baseline, 3, 6, and 12 months. Although accelerometry is the gold standard for objective PA measurement,[28] pedometers have 99.8% step count accuracy, particularly when worn at the hip.[29,30] For our study, participants will be fitted with a pedometer and asked to wear it for all waking hours (except while bathing or water activities) over their right hip for 7 consecutive days at each relevant time point in follow-up. At the end of the 7th day, participants will open the unit, record the final step count, and return the pedometer to WFSOM via a pre-stamped mail envelope. Self-report: In order to compare our results with the extant literature that has used self-reported PA outcomes, we will also include the short form of the IPAC, a self-report instrument with good reliability (Spearman's rho=0.8) and criterion validity comparable to other self-report instruments.[31]

Diabetes medication class/dose: All medications will be assessed quarterly as previously described. Variables of interest include medication name, total dose, and class of medication at baseline and longitudinal changes during the trial follow up.

Healthcare utilization and quality of life: To capture differences in quality of life associated with the intervention arm, we will use EuroQol's EQ-5D-5L instrument as the quality measure [32]. This instrument takes responses to five questions on mobility, self-care, ability to perform usual activities, pain, and anxiety/depression to produce a validated quality score (0 to 1). This instrument will be administered at baseline and at the end of the study (12 months). We anticipate no patient deaths during the study period; as such, we will treat the difference in the quality score at the end of the study period and at baseline as the change in the quality of life year (QALY). For instance, if the quality score is 0.4 at baseline and 0.6 at the study-end, the change in the quality of life will be 0.2 QALYs.

Cost data: There will be two cost categories: *intervention costs* and *healthcare utilization costs*. Intervention costs will cover the costs incurred in the implementation of the intervention. This will include, for the HIWL arm, the provider visits (in-person and telemedicine) associated with the intervention will be assessed in terms of the insurance reimbursement ($). For intervention services and resources not reimbursed by insurance (meals, software installation, staff time), we will use the micro-costing approach to aggregate the costs. As insurance reimbursement for the same service may vary by insurer, we will use Medicare fee-for-service reimbursement as the standardized rate so as to limit confounding arising from differences in insurer composition across intervention arms (ResDAC 2020). Patient out-of-pocket costs will also be included (e.g., insurance co-payments and deductibles). We will not include any costs relating to the research administration (e.g., staff time for data collection and analysis). For the HIWL+ CGM arm, we will include the cost of continuous glucose monitoring. Healthcare utilization costs will include healthcare services used during the study period but are not part of the interventions: hospitalizations, emergency department visits, outpatient visits, and prescription medications. Costs of these services will be assessed at Medicare rates. We will refer to the sum of the intervention and healthcare utilization costs as the *total costs.* Note that an intervention may lead to higher intervention costs compared to the control arm; however, If an intervention results in higher rates of diabetes remission, then healthcare utilization may be lower for the intervention cohort, compared to the control arm. The total cost captures the net change of the higher intervention and lower utilization costs.

Cost-effectiveness Outcomes: Our main outcome for cost-effectiveness analysis will be diabetes remission. We will compare the relative costs of achieving one additional remission using alternative interventions. As secondary outcomes, we will also examine the cost-effectiveness of (a) one percentage unit reduction in A1c and (b) one additional QALY.

8.2 SAFETY ASSESSMENTS

The primary safety assessment will be monitoring of blood glucose and frequency of hypoglycemia. All participants in the HIWL only and the control group will receive a blue tooth-connected digital glucometer. The participants will be instructed to monitor blood glucose at least twice daily, including once fasting and once 4-hours postprandial. Participants will also be instructed to monitor blood glucose if they feel symptoms of hypoglycemia. The study physicians will adjust medications as noted previously based on self-monitored blood glucose and reported episodes of hypoglycemia. For individuals in the HIWL + CGM arms, the monitoring of blood glucose will be continuous.

Participants in the active intervention arm will also have safety monitoring as part of their treatment protocol while initiating weight loss with the HIWL dietary strategy. Dr. Ard will be responsible for reviewing the chemistry panels that will be obtained at weeks 2, 4, 6, 8, 12, and 16. He will adjust the treatment plan including making adjustments in the dietary prescription or concomitant medications to resolve any abnormalities.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Participants will be queried for side effects and specific adverse events (AE) at each in-person study visit using a standardized questionnaire. Blinded staff will enter data directly into our centralized study database. Should an AE be detected using this process, or by spontaneous report between visits, or if an AE is detected using physical or laboratory examination, a determination of relatedness to study intervention will be made by the study physician. Serious adverse events (SAE) will be reviewed by the study physician and reported to the IRB per local policy. We will examine the **total number of AEs and SAEs at 12 months** by study group, as well as several subcategories of events.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor/funding agency within 10 days of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the study sponsor/funding agency within 15 days of the investigator becoming aware of the problem

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

1. Test the effectiveness of the combined interventions (data-assisted approach for high intensity medical weight loss) for weight loss in a group of adults with recently diagnosed type 2 diabetes compared to standard of care diabetes self-management education.

H1- The data-assisted approach for HIWL (with or without CGM) will lead to 12% greater weight loss compared to the standard of care DSME.

2. Assess the impact of the data-assisted approach for high intensity medical weight loss on glycemic control outcomes including hemoglobin A1c and diabetes remission rates compared to diabetes self-management education.

H2a- The data-assisted approach for HIWL (with or without CGM) will lead to greater reduction in HbA1c compared to DSME.

H2b- The data-assisted approach for HIWL (with or without CGM) will lead to a greater proportion of participants achieving diabetes remission (HbA1c < 6.5%) compared to DSME.

3. Explore impacts of adding CGM to the HIWL intervention on time to achieve A1c goals and participant satisfaction.

H3a- The HIWL + CGM approach will achieve A1c goals in a shorter timeframe than HIWL alone.

H3b- Participant satisfaction will be equivalent between the HIWL and HIWL + CGM approaches.

4. Explore differences in healthcare utilization between the treatment groups.

H4- The HIWL groups will have lower healthcare utilization compared to standard of care DSME.

9.2 SAMPLE SIZE DETERMINATION

Power Considerations: Power was estimated assuming a longitudinal framework based on linear mixed models allowing for attrition. The estimated change in weight for the active intervention is 15% at 12 months. The estimated change in weight for the DSME intervention is 3% at 12 months. We anticipate 10% of the study population will be lost to follow up; however, we estimated power based on lost to follow up rates of up to 20%. Using a pooled standard deviation of 6.8% for percent weight loss, we will have > 95% power to detect our hypothesized difference at 12 months with 30 participants per arm.

9.3 POPULATIONS FOR ANALYSES

All participants who are randomized and receive the intervention will be included in the analysis population (intent to treat).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Analyses: In general, two types of analyses will be performed: 1) those aimed at estimation of the difference between intervention groups for outcomes like percent change in body weight and HbA1c, and 2) those aimed at estimating differences in the proportion of participants achieving remission by treatment arm. We will analyze the data based on intention to treat principles. Analysis of covariance will be used to estimate the effect of the intervention on 12-month continuous measures including body weight percent change and HbA1c. The model to be used will include the following covariates: the baseline value of the outcome, gender, and age (to control for possible imbalance due to the small number of participants randomized). 95% confidence intervals will be generated for the intervention effect on these and other outcomes. The proportion of remission between two groups will be compared using a two-sided chi-square test and summarized using an odds ratio (OR) and confidence intervals (CI). The primary outcome will be percent change in initial body weight. Secondary outcomes include change in HbA1c and diabetes status (remission will be indicated by a dichotomous yes or no).

Cost-Effectiveness Analysis: The most commonly used measure of cost-effectiveness is the incremental cost-effectiveness ratio (ICER), defined as the ratio of between incremental costs (difference in total costs between intervention and control arms) and incremental diabetes remission (difference in the number of patients with remission in the intervention and control arms) [33]. This measure is meaningful in contexts where an intervention increases total costs (since the denominator is expected to be positive, with higher diabetes remission in the intervention arm relative to the control arm). However, in our context where total costs include both intervention and non-intervention healthcare utilization, total costs for the intervention arm may be lower (e.g., if diabetes remission is accompanied by fewer emergency department visits or fewer medications). In this situation, we will report two measures: a) the average additional intervention cost for each additional diabetes remission achieved; and b) the average reduction in healthcare utilization cost for each additional diabetes remission achieved. For the secondary outcome of A1c reduction, we will similarly estimate the average cost of achieving one percentage point reduction in A1c and one additional QALY for each arm (Laiteerapong et al. . We will obtain 95% confidence interval of each estimate based on bootstrap resampling (Briggs et al. 1999). We will perform a variety of sensitivity analyses, including alternative healthcare reimbursement rates (e.g., 10 percent higher than Medicare rates).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Written informed consent will be obtained from all participants during the baseline study visit.

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

A trained staff member or investigator will give an overview of the study, describe the intervention components and data collection requirements, and encourage potential participants to ask questions. All potential participants will be informed of the study design and interventions, the risks and benefits of participation, their rights and responsibilities as research participants, and alternatives to participation. They will also be informed that participation is voluntary and that they can withdraw from the study if their initial or on-going experience makes it oppressive, burdensome, or otherwise uncomfortable. Potential participants will be asked to read the informed consent form and to ask questions. The form will be written in simple, easy-to-understand language. As a part of the consent process, study staff will be required to review all key aspects of the study verbally and will be provided with a structured checklist for this purpose. A copy of the signed and dated consent form will be given to participants, and the original document will be placed in the participants' individual study files, which will be stored in a secure location at the clinical site.

10.1.2 CONFIDENTIALITY AND PRIVACY

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed by deleting any data files three years after study closure, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Participants who provide consent for storage of blood samples will have a sample of blood stored with a unique identifier that will not include any identifiable information. The unique identifier will be a randomly assigned number and only the principal investigator will have access to the code that links the unique identifier to the study participant. In the case that future researchers need to know more details

about the study participants' health, only those participants who consented to being contacted in the future for inclusion in additional research will be contacted.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Study coordinator	Maintenance of regulatory documents; reporting to IRB
Investigator team	Review of data, outcomes, and safety events
Biostatistician	Analysis

10.1.5 SAFETY OVERSIGHT

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

10.1.6 CLINICAL MONITORING

The clinical care teams for each treatment group will be responsible for monitoring the clinical health of the participants as it pertains to the conduct of this protocol.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event

EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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