Official Title: Continuous Glucose Monitoring Versus Blood Glucose Monitoring to Optimize Glycemic Outcomes in People With Type 2 Diabetes Following the Virta Treatment Program" (IGNITE: Impact of Glucose moNitoring and nutrItion on Time in rangE Study)

Brief Title: IGNITE (Impact of Glucose moNitoring and nutrItion on Time in rangE)

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Continuous Glucose Monitoring versus Blood Glucose Monitoring to Optimize Glycemic Outcomes in People with Type 2 Diabetes Following the Virta Treatment Program

Study Name: IGNITE (Impact of Glucose moNitoring and nutrItion on Time in rangE)
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Revision	Date	Summary of Change
Ver 1.0	20Jun2022	Original Protocol
Ver 2.0	06Dec2022	• Inclusion criteria changed to include: HbA1c between 7.0%- 11.5% documented within 180 days prior to consent, Stable diabetes medication regimen and lifestyle patterns (eating and activity) within approximately 30 days prior to consent, and Confirmed download of FreeStyle Libre

		2 app on smartphone with regular WiFi or cellular data access ● ASA24 version 2020 updated to indicate version 2020 or later ● Additional language to describe repeat sensor wear scenarios at baseline, month 3, and 6 ● Clarification for when IDC may contact participants; the updated protocol language clarified to match the consent Minor clarifying and formatting edits

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1 List of Abbreviations

Abbreviation	Abbreviation definition
AE	Adverse event
ADA	American Diabetes Association
ASA24	Automated Self-Administered 24-Hour Dietary Assessment Tool
BGM	Blood glucose monitoring
BHB	Beta-hydroxybutyrate
BMI	Body mass index
CGM	Continuous glucose monitoring
CI	Confidence interval
CIRBI	Center for IRB Intelligence
CLIA	Clinical Laboratory Improvement Amendments
DKA	Diabetic ketoacidosis

EMR	Electronic medical record
HbA1c	Glycated hemoglobin
HCP	Healthcare provider
HHS	Hyperosmolar hyperglycemic syndrome
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
ICF	Informed consent form
ID	Identification
IDC	International Diabetes Center
IGNITE	Impact of Glucose moNitoring and nutrItion on Time in rangE
MES	Medication effect score
NGSP	National Glycohemoglobin Standardization Program
PRO	Patient reported outcome
PWD	People with diabetes
SAE	Serious adverse event
SOC	Standards of Medical Care
SOP	Standard operating procedure
T2D	Type 2 diabetes
TIR	Time in range
TITR	Time in tight range
UAE	Unanticipated event
UPIRTSO	Unanticipated Problems Involving Risks to Subjects or Others
WFKD	Well-formulated ketogenic diet

2 Protocol Summary

Title:	**Continuous Glucose Monitoring versus Blood Glucose Monitoring to Optimize Glycemic Outcomes in People with Type 2 Diabetes Following the Virta Carbohydrate-Restricted Treatment Program (IGNITE Study)**
Population:	N=150; Adults ≥18 years with T2D who are enrolled in the Virta Treatment
Intervention:	Use of CGM during participation in the Virta Treatment
Objectives:	*Primary:* Difference in change in 14-day CGM-derived TIR (% time with glucose 70-180 mg/dL) from Baseline to 3-month Post-Dietary Change period between participants with T2D who are randomized to use either BGM or CGM as part of Virta Treatment. *Secondary:* ● Difference in 90-day mean blood ketone levels between BGM and CGM arms ● Difference in changes in other CGM-derived metrics from Baseline to 3-month Post-Dietary Change period between BGM and CGM arms

	● Difference in percent of participants reaching CGM-derived consensus targets at the end of the 3-month Post-Dietary Change period between BGM and CGM arms ● Difference in Change in HbA1c from Baseline to the end of the 3-month Post-Dietary Change period between BGM and CGM arms
Design/Methodology:	Non-pivotal, randomized, parallel group, two-arm, prospective study. 1:1 randomization to either BGM or CGM during Baseline assessment period. See Appendix A for a study schematic and Appendix B for a table of study periods and assessments.
Total Study Duration:	Approximately 24 months
Subject Participation Duration:	Approximately 7-8 months

3 Background/Rationale and Purpose

3.1 Background Information

More than 37 million people in the United States have diabetes, and type 2 diabetes (T2D) accounts for 90-95% of all diagnosed cases. The number of adults diagnosed with diabetes has more than doubled in the last 20 years, which creates significant burdens for the economy, healthcare system, and families affected by the disease. Options to help manage T2D are more important than ever before.[1]

Nutrition-related interventions have long been recognized as a critical component of diabetes care and management. Current guidance from the American Diabetes Association (ADA) Standards of Medical Care (SOC) states there is no "one-size-fits-all" eating pattern, or ideal macronutrient distribution, that works for all people with diabetes.[2] A variety of eating patterns (e.g., Mediterranean, very-low-carbohydrate, vegetarian) have demonstrated good efficacy for people with diabetes (PWD). However, evidence suggests all healthy eating patterns should emphasize non-starchy vegetables, minimal added sugars and refined grains, and whole foods over highly processed foods whenever possible. Reducing overall carbohydrate intake has demonstrated the most evidence for improving glycemia in people with T2D and should be considered with emphasis on the aforementioned components of healthy eating pattern.[2]

People with T2D often learn about how their food choices impact their glucose by performing intermittent fingersticks, which is also called blood glucose monitoring (BGM). Continuous glucose monitoring (CGM), which tracks glucose continually over time is also an option. However, as of 2022, CGM is only recommended in the ADA SOC for PWD who require insulin.

Several studies in PWD who use insulin suggest that CGM may lead to greater improvements in glycated hemoglobin (HbA1c) compared to usual care, which is often BGM.[3,4] CGM studies in PWD who do not use insulin are sparse; however, Jackson et al conducted a review of the available data and reported CGM may improve glycemic outcomes in PWD not using insulin and may have the potential to improve lifestyle changes and adherence to diabetes treatments.[5] Wright and Subramanian, also suggest there is evidence that CGM provides benefits to PWD who are treated with less-intensive therapies; they present data showing that behavioral interventions that use CGM improve dietary habits, physical activity, bodyweight, and problem-solving skills.[6]

One of the key benefits of CGM is the ability to see granular changes in glycemia over time. While HbA1c has long been the gold-standard for assessing glycemia, the HbA1c does not provide a clear picture of glucose variability or the patterns of hyper- and/or hypo-glycemia. The 2022 ADA SOC recognizes that CGM can provide better insights into more personalized diabetes care, and they call out ten core metrics that should be considered when evaluating CGM data. There is specific emphasis on time in range (TIR), the goal of which for most PWD is 70% of time in the target glucose range of 70-180mg/dL.[7] A 14-day TIR has been shown to correlate well with HbA1c[8] and emerging data suggest TIR is also correlated with risk of diabetes-related complications.[9]

Two recent randomized controlled trials in PWD who were treated with basal insulin[10] or less intensive therapies[11] showed that use of CGM improves TIR by about 15%, which is noteworthy when considering a 5% improvement in TIR is considered clinically meaningful.[12] CGM's immediate feedback on current glucose levels and the retrospective review of glucose patterns from CGM reports may help optimize diabetes therapy, including dietary changes. The value of CGM for making nutrition and lifestyle modifications has strong potential, but it needs further research, which could lead to expanded indications for CGM for people with T2D.

Very few nutrition intervention studies have used CGM technology to guide the intervention in people with T2D. Griauzde et al provided intermittent access to CGM as part of a low-carbohydrate intervention (< 100 g carbohydrate per day) and found that HbA1c decreased by 0.4% more than a comparison group who received usual care without CGM; they also showed that TIR increased by almost 18% over 12 months in the group that was using CGM.[13] Similarly, Oser et al showed that CGM was an effective educational and motivational tool in a study of 17 people with newly diagnosed T2D who used CGM as part of a nutrition-focused lifestyle intervention that emphasized carbohydrate restriction to minimize glycemic excursions.[14] In this study, 67% of participants achieved HbA1c < 6.5% without diabetes medications and 80% of the participants showed an HbA1c reduction of 2.3% $\pm$ 1.3%. While both studies appear promising, neither are randomized controlled trials with an adequate comparison group and neither of these studies evaluated TIR as a primary outcome.

All people with T2D are encouraged to adopt lifestyle modifications focusing on eating patterns, physical activity, and weight management to improve their health. Treatment for people with T2D at Virta Health includes an individualized, remotely delivered, lifestyle-based intervention emphasizing a carbohydrate-restricted diet to induce nutritional ketosis.

Enrollment in the Virta Treatment is contingent on medical approval from the Virta HCP. Upon enrollment, participants receive introductory educational resources and an appointment with a health coach. Treatment at Virta includes guidance on the use of a well-formulated, ketogenic diet (WFKD), biometric feedback, behavior change support, optional peer support, and medication management

(referred to as the "Virta Treatment"). The WFKD is a carbohydrate-restricted, moderate-protein, nutrient-dense eating pattern that emphasizes whole foods, including a variety of low-carbohydrate vegetables. Health coaches provide frequent nutritional guidance and troubleshooting while healthcare providers (HCPs), physicians and nurse practitioners, provide medication management and medical oversight. As participants begin dietary changes, blood glucose declines and diabetes medications are titrated to match emerging glycemic patterns; this typically occurs within the first three months.

In response to carbohydrate restriction with moderate protein intake, blood ketones rise, and a state of nutritional ketosis can be achieved. Blood ketones, therefore, serve as a marker of carbohydrate and protein intake and can be utilized as a marker of adherence to a carbohydrate-restricted, ketogenic diet.[15] Blood ketones can be utilized by most tissues as a source of energy and can serve as a metabolite with recognized signaling properties.[16] Further, greater blood ketone concentrations as a result of a ketogenic diet have been associated with better health outcomes such as greater weight loss.[17]

The impact of Virta Treatment has been evaluated in a non-randomized, controlled intervention trial. In brief, 262 adults with a mean age of 54 years, a mean time with T2D of 8.4 years, and a mean baseline A1c of 7.5% underwent Virta's nutrition intervention and continuous care plan. The comparison group received usual diabetes care, including standard dietary advice, outside of Virta. The trial showed that the impact of Virta's intervention on diabetes-related health parameters is rapid, with an average of 1% reduction in HbA1c, a reduction in or elimination of diabetes medications, and a clinically meaningful weight loss for most participants at 10 weeks.[18] Importantly, HCP oversight allowed for diabetes medication changes to reduce the risk of hypoglycemia in patients taking medications that are prone to hypoglycemia. Of those taking insulin or sulfonylureas at baseline, 87% and 93%, respectively, had medications either stopped or doses reduced by 10-weeks. Similar or improved results persisted after one[19] and two[20] years of trial participation. Notably, the retention rate throughout the trial was high: 91% at 10-weeks, 83% at 1-year, and 74% at 2-years.

Similar to most lifestyle modification programs for PWD, the Virta Treatment relies on BGM by fingerstick; however, dietary adoption and adherence to the Virta Treatment may be enhanced by the timely feedback of CGM data. Therefore, the following protocol describes a randomized, controlled trial intended to assess whether the addition of CGM into Virta's clinical care plan improves TIR, glycemia, and adherence to nutrition therapy as evidenced by blood ketone monitoring.

3.2 Rationale and Purpose

The purpose of this three-month, randomized, controlled trial is to compare the difference in change in 14-day CGM-derived TIR (% time with glucose 70-180 mg/dL) from Baseline to 3-months Post-Dietary Change in participants with T2D who are assigned to use either BGM or CGM. The difference in mean blood ketone levels and additional glycemic endpoints will also be compared, and several exploratory endpoints, including medication changes, dietary intake, and body weight will be described.

The study also includes a three-month Follow-Up period (months three to six), where participants will remain using their randomly assigned glucose monitoring modality (e.g., BGM or CGM); this period will help assess durability of the results found during the intervention.

This study will provide insights into how continuous feedback from CGM affects glycemic outcomes, such as TIR and HbA1c, compared to the standard method of BGM. It is important to understand if the

methods of glucose monitoring differ, because greater TIR and lower HbA1c are associated with reduced risk of diabetes complications.

While many studies have compared the differences in glycemic outcomes between BGM and CGM, this study would be one of the first-of-its kind to compare differences between the two glucose monitoring methods as part of a randomized, controlled nutrition intervention in people with T2D. It would also be one of the first-of-its kind to use TIR as a primary endpoint in a nutrition-focused program. Further, it is possible that this study will help demonstrate whether the continuous feedback provided by CGM influences adherence to dietary guidance.

4 Objectives

4.1 Study Objectives

The primary objective of this study is to compare the difference in change in 14-day CGM-derived TIR (% time with glucose 70-180 mg/dL) during Baseline and 3-month Post-Dietary Change periods between participants with T2D who are randomized to use either BGM or CGM to guide dietary and diabetes medication adjustments as part of the Virta Treatment.

The secondary objectives of this study are to compare:

1. Difference in 90-day mean blood ketone levels between BGM and CGM arms
2. Difference in changes in other CGM-derived metrics from Baseline to 3-month Post-Dietary Change period between BGM and CGM arms
3. Difference in percent of participants reaching CGM-derived consensus targets at the end of the 3-month Post-Dietary Change period between BGM and CGM arms
4. Difference in Change in HbA1c from Baseline to the end of the 3-month Post-Dietary Change period between BGM and CGM arms

The exploratory objectives of this study are to describe:

1. Change in CGM-derived TIR during Baseline and 6-month Follow-Up period
2. Change in other CGM-derived metrics during Baseline and 6-month Follow-Up period
3. Percent reaching CGM-derived consensus targets during 6-month Follow-Up period
4. Change in A1c from Baseline to 6-month Follow-Up period
5. Change in diabetes medication use
6. Change in dietary intake
7. Change in body mass index (BMI) and body weight
8. Percent reaching blood ketone targets $\geq$ 0.5mM
9. Mean blood ketone levels
10. Change in CGM-derived 'time in tight range' (TITR; glucose 70-140 mg/dL)
11. Absolute values in CGM-derived metrics
12. Number of contacts between participants and Virta care team
13. Change in mean scores on patient-reported outcome (PRO) surveys

4.2 Study Outcome Measures

For all CGM-related outcome measures, data will be assessed in the following ways:

- Baseline CGM data for both study arms will come from the 14-day, blinded, FreeStyle Libre Pro sensors and readers using the Libre 2 algorithm
- 3-month Post-Dietary Change CGM data (end of month three data) will come from:
    - CGM Arm: 14-day, FreeStyle Libre 2 data download from LibreView
    - BGM Arm: 14-day, blinded, FreeStyle Libre Pro sensors and readers using the Libre 2 algorithm
- 6-month Follow-Up period CGM data (end of month six data) will come from:
    - CGM Arm: 14-day, FreeStyle Libre 2 data download from LibreView
    - BGM Arm: 14-day, blinded, FreeStyle Libre Pro sensors and readers using the Libre 2 algorithm

The blinded FreeStyle Libre Pro reader used for collecting outcome measures data will use the Libre 2 algorithm to keep outcome measure data comparable between study arms.

4.2.1 Primary Outcome Measures

Outcome	Assessment Method
Change in 14-day CGM-derived TIR (% of time with glucose 70-180 mg/dL) from Baseline to 3-month Post-Dietary Change period	See CGM-related outcome measures described above

4.2.2 Secondary Outcome Measures

Outcome	Assessment Method
1. Mean of all blood ketone levels from day 0 to day 90	BHB levels as tested by Precision Xtra Blood Glucose & Ketone Monitoring System; ketones requested twice daily throughout study
2. Change in other CGM-derived metrics from Baseline to 3-month Post-Dietary Change period: a. Time above range >180 mg/dL b. Time above range >250 mg/dL c. Time below range <70 mg/dL d. Time below range <54 mg/dL e. Mean sensor glucose f. % Coefficient of variation g. Mean amplitude of glucose excursion	See CGM-related outcome measures described above
3. Reaching CGM-derived consensus targets in the 3-month Post-Dietary Change period (yes/no): ● Time >250 mg/dL <5% ● Time >180 mg/dL <25% ● Time 70-180 mg/dL >70% ● Time <70 mg/dL <4% ● Time range <54 mg/dL <1% ● Time 70-180 mg/dL >70% AND Time <70 mg/dL <4%	See CGM-related outcome measures described above

● Time 70-180 mg/dL >70% AND Time <54 mg/dL <1%	
4. Change in HbA1c from Baseline to 3-month Post-Dietary Change period	HbA1c assessed at Virta-approved, CLIA-certified laboratory using NGSP HbA1c method

4.2.3 Exploratory Outcome Measures

Outcome	Assessment Method
1. Change in CGM-derived TIR (glucose 70-180 mg/dL) from Baseline to 6-month Follow-Up period	See CGM-related outcome measures described above
2. Change in other CGM-derived metrics from Baseline to 6-month Follow-Up period: ● Time above range >180 mg/dL ● Time above range >250 mg/dL ● Time below range <70 mg/dL ● Time below range <54 mg/dL ● Mean sensor glucose ● % Coefficient of variation ● Mean amplitude of glucose excursion	See CGM-related outcome measures described above
3. Reaching CGM-derived consensus targets in the 6-month Follow-Up period (yes/no): ● Time >250 mg/dL <5% ● Time >180 mg/dL <25% ● Time 70-180 mg/dL >70% ● Time <70 mg/dL <4% ● Time range <54 mg/dL <1% ● Time 70-180 mg/dL >70% AND Time <70 mg/dL <4% ● Time 70-180 mg/dL >70% AND Time <54 mg/dL <1%	See CGM-related outcome measures described above
4. Change in HbA1c from Baseline to 6-month Follow-Up period	HbA1c assessed at Virta-approved, CLIA-certified, laboratory using NGSP HbA1c method
5. Change in medication use, as described by class, dose, and medication effect score (MES),[21] from Baseline to end of Month 1, 2, 3, and 6	Medication name, class, dose, and frequency will be extracted from the participant's medical record; MES will be calculated for each period
6. Change in dietary intake from Baseline to end of month 1, 2, 3, and 6 ● Total energy intake ● Total macronutrients and fiber (including type of fats) ● Select micronutrients ● Healthy Eating Index score ● Food group equivalents	Dietary intake based on a single Automated Self-Administered 24-hour (ASA24®) diet recall (Version 2020 or later) collected via web-based survey

7. Change in BMI and body weight from Baseline to month 1, 2, 3, and 6	Cellular-connected BodyTrace body weight scale (BodyTrace, New York, New York, USA); Self-reported height; BMI calculated from measured weight and self-reported height
8. Reaching blood ketone targets $\geq$ 0.5mM based on the mean of all blood ketone levels in month 1 (0-30 days), 2 (31-60 days), 3 (61-90 days), and 6 (150-180 days and 0-180 days) (yes/no)	BHB levels as tested by Precision Xtra Blood Glucose & Ketone Monitoring System; ketones requested twice daily throughout study
9. Mean blood ketone levels during month 1 (0-30 days), 2 (31-60 days), 3 (61-90 days), and 6 (150-180 days and 0-180 days)	BHB levels as tested by Precision Xtra Blood Glucose & Ketone Monitoring System; ketones requested twice daily throughout study
10. Change in CGM-derived 'time in tight range' TITR (glucose 70-140 mg/dL) during Baseline, 3-month Post-Dietary Change period, and 6-month Follow-Up period	See CGM-related outcome measures described above
11. Absolute values in CGM-derived metrics during 3-month Post-Dietary Change period and 6-month Follow-Up period ● Time >250 mg/dL ● Time >180 mg/dL ● Time 70-180 mg/dL ● Time 70-140 mg/dL ● Time <70 mg/dL ● Time range <54 mg/dL ● Mean sensor glucose ● % coefficient of variation ● Mean amplitude of glucose excursion	See CGM-related outcome measures described above
12. Number of contacts between participants and Virta care team during month 1 (0-30 days), 2 (31-60 days), 3 (61-90 days), and 6 (150-180 days and 0-180 days)	Absolute count of non-automated messages exchanged between participants and Virta care team
13. Patient-reported outcomes (PROs) ● Diabetes Distress Scale-17[22] at Baseline, end of month 3, and end of month 6 ● Lifestyle change survey (study-specific) end of month 3 and end of month 6 ● CGM arm only: CGM Satisfaction Survey[23] at end of month 3	All surveys administered via REDCap

5 Study Design

This is a non-pivotal, randomized, parallel group, two-arm, prospective study. This 3-month intervention with a 3-month follow-up at 6 months will evaluate the impact of BGM and CGM as tools to guide

dietary and diabetes medication adjustments during Virta Treatment. Participants will be randomized 1:1 to either a BGM or CGM arm, with approximately seventy-five participants per arm.

The intervention phase is defined as the "Post-Dietary Change" period and it occurs Day 0 through the end of the Month 3 assessments, approximately Day 90 to 104. The "Follow-Up" period begins immediately following the Month 3 assessments and runs through the end of the Month 6 assessments, approximately Day 180 to 194.

Appendix A provides an overview of the study design and Appendix B provides an overview of study periods and assessments.

6 Study Partcipant Selection

6.1 Participant Inclusion Criteria

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

1. Age $\geq$ 18 years
2. U.S. residence with plans to remain in the U.S. for study duration (for shipping purposes)
3. Diagnosis of T2D
4. HbA1c between 7.0-11.5% documented within 180 days prior to consent
5. Stable diabetes medication regimen and lifestyle patterns (eating and activity) within approximately 30 days prior to consent
6. Using at least one glucose-lowering medication (oral or injectable) for diabetes management at the time of consent; if using insulin, this may include up to a total of three or fewer insulin injections per day (e.g., once or twice daily basal insulin, once or twice daily basal insulin plus one prandial insulin dose, once or twice daily pre-mix insulin, or another combination etc.)
7. English language comprehension
8. Confirmed download of FreeStyle Libre 2 app on personal smartphone with regular WiFi or cellular data access
9. Willing and able to record study data using smartphone, tablet, and/or computer
10. Willing to wear and use study-provided CGM devices for up to 7 months
11. Willing to perform fingersticks to test blood glucose
12. Willing to perform fingersticks to test blood ketones twice daily
13. Eligible to initiate and intention to participate in the dietary changes required as part of the Virta Treatment for at least 7 months

6.2 Participant Exclusion Criteria

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

1. Type 1 diabetes
2. Currently using an insulin pump or multiple daily injection insulin therapy with >3 insulin injections per day or using bolus injections to cover every meal
3. Currently following a self-reported, very low-carbohydrate eating pattern
4. Currently using a personal CGM or plans to use a personal CGM during the study period
5. Advanced-stage renal, cardiac, hepatic, or other chronic disease
6. History of ketoacidosis
7. Pregnant, lactating, or planned pregnancy

8. Allergy to medical grade adhesive or isopropyl alcohol used to disinfect skin
9. Participation in another interventional trial at the time of enrollment or during the study period
10. Participant is unsuitable for participation due to any cause as determined by Investigators

7 Study Procedures and Intervention

7.1 Pre-Study Staff Training

The site may include up to 10 total IGNITE study staff, from Virta and IDC, for a FreeStyle Libre 2 training experience. This training will provide the opportunity for study staff to participate in hands-on, experiential learning using the commercially approved, 14-day FreeStyle Libre 2 system. This experience is for educational purposes only and provides study staff with the opportunity to practice using the Libre 2 and to troubleshoot potential device issues prior to the enrollment of participants in the study. This training will occur after IRB protocol approval, but prior to the enrollment of any participants in the study described by this protocol.

Training participants will have the opportunity for a group-training session lasting approximately 60 minutes or have the option to independently read the FreeStyle Libre 2 product instructions and complete a product experience on their own. Participants from IDC and Virta will sign a participant training waiver, and they will be able to participate in training if they meet the self-assessed eligibility criteria. The self-assessed inclusion/exclusion criteria will be included in the training waiver.

7.2 Recruitment, Screening, and Randomization Procedure

Prospective study participants include any person with T2D who seeks treatment in the Virta Treatment program. Prospective participants will be identified through screening during a Virta pre-enrollment period. As part of the normal Virta enrollment process, all people complete an online health assessment with a medical provider. People who meet initial study criteria will be approached by a Virta HCP during the routine new-patient visit and further screened for exclusions, such as currently eating a self-reported very-low carbohydrate diet or currently using a personal CGM. Those who continue to meet inclusion/exclusion criteria and who express interest in study participation will be contacted by members of the Virta research team who will explain the study in further detail, complete additional screening questions, answer questions, and obtain informed consent as appropriate.

Up to 2,000 free-living adults with T2D may be invited to participate in this study, and approximately 200 participants will be consented; this is based on the following assumptions 1) approximately 10% of people choose to volunteer to participate in research 2) some participants (estimate up to 50 people) will consent, but may withdraw before being randomized and therefore will need to be replaced and 3) approximately 15% attrition is expected for the randomized participants within the 3-month study intervention period. Therefore, to meet the sample size calculation requirements, 150 qualifying participants need to be randomized to obtain 126 participants with evaluable data. Evaluable data is defined as participants with at least five days of blinded Libre Pro CGM data at baseline.

All participants must obtain Virta's standard medical approval from a Virta HCP and meet all eligibility criteria, as defined in Section 6, to participate in the study. Once the informed consent form (ICF) has been signed, the participant is formally enrolled in the study and a participant ID number will be assigned and recorded in the shared Virta and IDC study database (REDCap). Participants will be randomized 1:1 to either the BGM or CGM arm (Table 1) once a minimum of five days of blinded Libre Pro CGM data is confirmed by the participant. Of note, the blinded Libre Pro CGM system provides a way for the participant to see the number of days of data recording while the sensor is in use. If a participant wears a blinded Libre Pro CGM at baseline that does not capture at least 5 days of data, the participant will be provided the option to wear a repeat blinded CGM or choose to exit the study. Participants who capture five or six days of blinded CGM data may also be provided an option to wear a repeat blinded CGM to collect additional blinded CGM data.

Blinding procedures are not described since blinding is not possible in a study comparing two different methods of glucose monitoring (BGM versus CGM); the participants will know which arm they are assigned to in order to conduct the appropriate monitoring.

Given that enrolling participants takes several months to complete, a block randomization scheme will be used to ensure that participants are assigned to BGM and CGM arms in approximately equal proportions each month. The participant randomization schedule will be generated by the study statistician using the random number generator in SAS. Participants will remain in their assigned study arm throughout the intervention and follow-up period (day 0 to day 194).

Table 1. Randomization arms and associated study-arm devices

Study Arm	**Devices Used**
Blood Glucose Monitoring (BGM) Arm	Commercially approved FreeStyle Libre Pro Sensor and Reader (blinded CGM) Commercially approved Precision Xtra Blood Glucose & Ketone Monitoring System for glucose and ketone monitoring; used in accordance with package inserts.
Continuous Glucose Monitoring (CGM) Arm	Commercially approved FreeStyle Libre Pro Sensor and Reader (blinded CGM for baseline assessment only) Commercially approved 14-day, personal FreeStyle Libre 2 system and associated phone-based app; used in accordance with package inserts.

	Commercially approved Precision Xtra Blood Glucose & Ketone Monitoring System used for fingerstick ketone monitoring and as indicated for glucose monitoring; used in accordance with package inserts.

8 Study Intervention

The intervention will compare the impact of two glucose monitoring methods, BGM or CGM, as part of Virta Health's diabetes care program. All care and education are provided via telemedicine (i.e., virtually) and with the use of web-based software applications for biomarker reporting, monitoring, and communication with Virta's care team.

As part of standard Virta Treatment, participants will receive continuous coaching from the Virta care team that focuses on modifying daily nutrition choices to achieve and sustain nutritional ketosis as measured by blood BHB 0.5-3.0 mmol/L. The care team includes health coaches for day-to-day program guidance and HCPs for medication management and clinical oversight. Virta HCPs review glucose values reported by participants in the Virta app. HCPs make proactive and reactive medication dose adjustments to prevent hypoglycemia while participants are experiencing metabolic improvements. Care for Virta participants is provided continuously and is not limited by specific time milestones (e.g., appointments are not at scheduled timepoints).

The current Virta Treatment relies on BGM for glucose assessment and does not supply CGMs as part of routine care. **Thus, the intervention under study is use of CGM compared to BGM (Virta's current standard care) for glucose monitoring.**

In the BGM arm, participants, health coaches, and Virta HCPs will use BGM and ketone data to guide medication management decisions and to encourage program adherence, per their usual practices. The blinded Libre Pro CGM data collected at baseline and during the intervention and follow-up periods will not be available to participants or the Virta care team; however, data from the blinded Libre Pro CGM assessments can be made available to BGM arm participants after study completion, upon request from the participant. BGM and ketone data will be used to help determine which foods, behaviors, and medications sustain nutritional ketosis. Typical BGM assessment in the Virta Treatment includes one to two fingerstick glucose tests per day depending on the participant's medication regimen. Fingerstick data is reported in the Virta app by the participant.

In the CGM arm, participants receive Virta's usual care except instead of using BGM, participants, health coaches, and Virta HCPs will use real-time and retrospective CGM and ketone data to guide medication management decisions and to encourage program adherence. Emphasis will be placed on guiding participants to use the CGM device and its associated data to determine which foods, behaviors, and medications help them achieve CGM glucose targets and sustain nutritional ketosis. Glucose target ranges will be individualized for each participant and use of CGM alarms to alert participants of high or low glucose will be individualized based on a shared decision-making approach that aligns with current guidance on providing technology-enabled diabetes care. Virta Health coaches will consider CGM data during participant contact as needed, and HCPs will systematically assess CGM data during the defined Contact Periods and at any point throughout the study as indicated by clinical care. IDC will provide minimal participant support for technical CGM-related issues.

8.1 Ongoing Study Procedures

Study duration is expected to be approximately 215 days, an approximately 21-day baseline assessment period plus a 194-day Post-Dietary Change intervention and Follow-Up period. Throughout the study, participant communication with Virta staff will occur via phone, secured email, and chat messages within the Virta app, which feed into the Virta electronic medical record (EMR).

8.2 Baseline Assessments

After signing the ICF, demographic and anthropometric information will be assessed to describe the participants. Age at enrollment, race, ethnicity, income, education, marital status, year of type 2 diagnosis, gender identity, biological sex, weight, height, etc. will be collected at baseline.

Baseline assessments also include a 14-day, blinded CGM assessment using the FreeStyle Libre Pro system. The FreeStyle Libre Pro system (sensor and reader) is commercially available and will be used according to user manual instructions; however, the system will be started at home by the participant instead of in a clinic with an HCP. The sensor will be returned to the clinical site for data download. A minimum of five days of blinded Libre Pro CGM sensor data must be obtained for randomization. Participants will use the provided reader to confirm adequate days of data recording during the Baseline assessment period.

All 14-day, blinded, FreeStyle Libre Pro sensors will be returned via mail. Data will be uploaded with a FreeStyle Libre Pro reader using the Libre 2 algorithm and then downloaded to secure study computer. Blinded FreeStyle Libre Pro sensors will be tracked by linking sensor serial numbers with study participant ID numbers.

Once baseline assessments are complete, the study intervention (use of CGM vs. BGM) begins concurrently with the initiation of the WFKD (Day 0).

8.3 Outcome Assessments

Outcome-related measures will be assessed at Baseline, Month 1, Month 2, Month 3, and Month 6. Primary and secondary outcome assessments will occur after the intervention, the “Post-Dietary Change” period, which is approximately Day 90 to 104. Additional secondary and exploratory outcome assessments will occur after “Follow-Up” period, which is approximately Day 180 to 194.

The study will include five defined Contact Periods between study staff (Virta and IDC) and study participants (“Baseline”, “Month 1”, “Month 2”, “Month 3”, and “Month 6”). Each Contact Period will last approximately two to three weeks, to accommodate the 14-day sensor wear. Required assessments can take place anytime during the Contact Period. Each Contact Period includes a plus or minus 10 or 14 day window, depending on the period; however, this should minimally impact the length of study participation since assessment windows are set according to initiation of the WFKD at Day 0. For example, assessment activities during Contact Period Two could start as early as day 20 or end as late as Day 54 and be in-window; and the target start date for Contact Period Three would remain at Day 90 regardless of when Contact Period Two was completed.

Outcome measures will be assessed using study-specific glucose and ketone testing supplies, which will be provided by Abbott Diabetes Care, the manufacturer of these products. Supplies will be mailed to each participant from the IDC after consent is signed and throughout the study as needed. All application and start-up of the FreeStyle Libre Pro and FreeStyle Libre 2 systems will be done independently by the participant with manufacturer- and study-provided resources for support.

Participant supplies include:

- Blinded 14-day FreeStyle Libre Pro system with sensors and reader
- Personal 14-day FreeStyle Libre 2 system with the associated phone-based Libre 2 app
- Precision Xtra Blood Glucose & Ketone Monitoring System with glucose and ketone test strips
- Lancing devices with lancets
- Supply return kits

Personal 14-day Libre 2 data will be collected at multiple assessment points throughout the study for CGM arm participants. The 14-day Libre 2 data are retrieved electronically from the FreeStyle Libre2 app, which is sent to the LibreView website. Data is automatically uploaded to LibreView when the subject's smartphone is connected to the internet. Data will be downloaded from LibreView by staff at the specified intervals for outcome assessment purposes.

Participants will be instructed to contact the Virta care team for study-related questions, healthcare-related questions, and any adverse events. Care related to the treatment of adverse events associated with study-supplied devices may be recommended. Medical care that does not pertain to diabetes management will not be provided to study participants as a part of this protocol. Participants will be instructed to contact IDC for problems related to study-provided monitoring supplies. IDC may contact participants directly for device-related issues and for questions/issues related to outcome assessments (e.g. survey data, blinded sensor data, etc.). IDC will maintain accountability records for study-specific glucose and ketone monitoring supplies including dates and quantity of product issued to participants.

8.4 Contact Schedule

Contact period	Key tasks
#1: Baseline Assessments: Day -21 to -1	● Eligibility confirmed and consent conducted and documented ● Participant receives baseline study supplies and instructions for completing baseline assessments, including HbA1c, in the mail ● Participant is randomized once they confirm that the minimum of five days of Libre Pro CGM data has been recorded. If a participant is not able to obtain a minimum of five days of blinded CGM data, they will be provided an option to repeat the blinded sensor wear period or choose to withdraw. ● Participants who capture five or six days of blinded CGM data on the first sensor may be provided an option to wear a repeat blinded CGM sensor to collect additional blinded CGM data. Wearing a repeat sensor, if 5 or 6 days of blinded sensor data was obtained on first sensor, is not required for randomization. ● Participant continues wearing 14-day blinded CGM sensor and promptly mails sensor(s) back for data capture

	○ Note: Participants randomized to the CGM arm will be instructed to return the blinded CGM sensor(s) and the associated reader. ● Plan initiation of the WFKD ● Participant receives study supplies according to randomization assignment in preparation for initiation of study intervention ● Baseline assessments are documented Note: There may be several days between Day -1 and Day 0 to account for participant readiness to begin the program; final clearance by the Virta care team (i.e. standard process); supply shipping issues; or personal factors for the participant (e.g. scheduling, medication adjustment, CGM wear issues). In other words, Day –21 to Day -1 will include initiation of baseline assessments, and Day 0 will mark the actual start of the program. All baseline assessments must be completed before Day 0. The difference between Day -1 and Day 0 will be as short as possible; Investigator discretion will be used to determine an inappropriate delay between study Day -1 and Day 0.
#2: Month 1 Assessment: Day 30 to 44 with up to +/- 10 days **Intervention Period**	● Participants complete month 1 assessments ● BGM group: ○ Prompted to apply and start Libre Pro CGM for 14-day wear ○ Participant confirms five days of blinded CGM data has been recorded. If a participant is not able to obtain a minimum of five days of blinded CGM data, they will be provided an option to repeat the blinded sensor wear period. ○ Participant promptly mails blinded CGM sensor back for data capture ● CGM group: ○ Maintains consistent personal Libre 2 use for 14 days ○ HCP documents CGM data review and shares learnings with participant asynchronously ● Additional glucose and ketone monitoring supplies sent as needed ● Month 1 assessments are documented
#3: Month 2 Assessment: Day 60 to 74 with up to +/- 10 days **Intervention Period**	● Participants complete month 2 assessments ● BGM group: ○ Prompted to apply and start Libre Pro CGM for 14-day wear ○ Participant confirms five days of blinded CGM data has been recorded. If a participant is not able to obtain a minimum of five days of blinded CGM data, they will be provided an option to repeat the blinded sensor wear period. ○ Participant promptly mails blinded CGM sensor back for data capture

	● CGM group:
	  ○ Maintains consistent personal Libre 2 use for 14 days
	  ○ HCP documents CGM data review and shares learnings with participant asynchronously
	● Additional glucose and ketone monitoring supplies sent as needed
	● Month 2 assessments are documented

#4: Month 3 Assessment: Day 90 to 104 with up to +/- 10 days
 	
Intervention Period
	● Participants complete month 3 assessments, including HbA1c
	● BGM group:
	  ○ Prompted to apply and start Libre Pro CGM for 14-day wear
	  ○ Participant confirms five days of blinded CGM data has been recorded.
	  ○ If a participant captures less than 7 days of blinded CGM data, they will be provided an option to wear a repeat blinded CGM to collect additional blinded CGM data.
	  ○ Participant promptly mails blinded CGM sensor(s) back for data capture
	● CGM group:
	  ○ Maintains consistent personal Libre 2 use for 14 days
	  ○ HCP documents CGM data review and shares learnings with participant asynchronously
	● Additional glucose and ketone monitoring supplies sent as needed
	● Month 3 assessments are documented

#5: Month 6 Assessment: Day 180 to 194 with up to +/- 14 days
 	
Follow-Up Period
	● Participants complete month 6 assessments, including HbA1c
	● BGM group:
	  ○ Prompted to apply and start Libre Pro CGM for 14-day wear
	  ○ Participant confirms five days of blinded CGM data has been recorded.
	  ○ If a participant captures less than 7 days of blinded CGM data, they will be provided an option to wear a repeat blinded CGM to collect additional blinded CGM data.
	  ○ Participant promptly mails blinded CGM sensor(s) back for data capture
	● CGM group:
	  ○ Maintains consistent personal Libre 2 use for 14 days
	  ○ HCP documents CGM data review and shares learnings with participant asynchronously
	● Month 6 assessments are documented
	
	Note: The month 6 assessment is the final study contact. Participants in the BGM arm will be required to return all blinded Libre Pro CGM sensors and the associated reader promptly after study completion. Participants will not be required to return any other study-provided glucose or ketone monitoring supplies at the end of the study.

9 Early Termination and Participant Withdrawal

A participant can choose to terminate study participation and exit the study at any time and for any reason. A participant can be withdrawn from the study without their consent if deemed necessary based on adverse event(s) or for any other reason deemed appropriate by Investigators, such as non-compliance with study instructions. If a participant chooses early termination or is withdrawn, the Investigators will decide whether the participant could be eligible to complete a final assessment.

Participants will be asked their reason for early withdrawal and reason for CGM discontinuation if applicable. Participants who terminate or are withdrawn early will be required to return used blinded Libre Pro CGM sensors and the associated Libre Pro reader promptly after study exit; they will not be required to return any other study-provided glucose or ketone monitoring supplies. Early termination or participant withdrawal will not impact participation in the Virta Treatment.

10 Lost to Follow-Up

Multiple attempts will be made to contact participants who become lost to follow-up. Investigator discretion will determine whether a participant should be withdrawn if reasonable attempts for contact are unsuccessful.

11 Protocol Deviation

A protocol deviation occurs when the study is not conducted according to this protocol. All deviations will be documented in study deviation log. Investigators will not knowingly deviate from this protocol except in the cases of protecting participant safety. The delegated Investigator will notify the IRB of protocol deviations in accordance with IRB policies and procedures.

12 Potential Risks and Benefits

12.1 Risks

Blood draws

Blood draw by venipuncture for HbA1c at Baseline, month 3, and month 6 is a standard care procedure which would occur regardless of participation in this study. Blood draws may cause discomfort and bruising at the puncture site. Participants may also experience lightheadedness or fainting during the blood draw and there is a slight risk of infection. The total blood volume needed for each HbA1c test is less than 5 mL.

Capillary (fingerstick) blood glucose and ketone testing

BGM by fingerstick is a standard care procedure for PWD. Participants will follow Virta's usual frequency recommendations for BGM. Fingerstick ketone monitoring is a routine procedure for Virta participants and uses the same technique as BGM. Study subjects will be asked to monitor and log fingerstick ketones twice daily; this is more than Virta's usual recommendation of once daily. Risks arising from

fingerstick testing are minimal and may include pain, bruising, or the infrequent occurrence of skin infection.

CGM use

CGM use is a routine part of the care for many PWD. CGM users usually report less pain or discomfort with CGM than with capillary blood glucose testing. Mild pain on insertion of CGM may be experienced by subjects at low frequency. Known allergies to medical grade adhesives is an exclusion from participation. Cutaneous complications of CGM use are typically wear-related erythema, itching, and induration. The incidence of these complications is expected to be low, 0.13 to 0.15 events per week of wear-time, with the majority (79%) being mild. Study discontinuation rate due to skin reactions is expected to be very low.[24]

Privacy

The study requires use of web-based applications, which include providing personal information and personal health information. There is always some risk that data will be compromised, and that personal information will become available to unexpected parties. Several mechanisms are in place to protect personal information, including use of de-identified participant identification (ID) numbers whenever possible.

Surveys

Surveys will be used to collect information on food intake and other PROs. Sometimes survey questions can trigger uncomfortable feelings. Participants will be informed that they are not required to respond to questions that make them uncomfortable for whatever reason.

12.2 Potential Benefits

Participants in both arms of the study may benefit from the additional monitoring they are requested to complete as part of the study. For example, this study requests two blood ketone tests per day for 6-7 months, which is more than what participants are requested to do in the usual Virta Treatment. The additional monitoring information collected may be useful for helping participants and providers manage diabetes care.

Participants assigned to the CGM arm may benefit from access to continuous glucose data and the use of the FreeStyle Libre 2 app. Use of FreeStyle Libre 2 and the associated app may aid in a better understanding of which foods and behaviors keep glucose and ketones in target ranges.

Additionally, information from this study could lead to new and more effective methods for helping people with T2D manage their glucose and diabetes or adhere to nutrition therapies.

12.3 Analysis of Risks in Relation to Benefits

In this study, risks posed beyond standard care are minimal. The rationale for exposing study participants to the minor risks associated with blood draws, capillary glucose and blood ketone testing, and CGM use, is that these components of usual diabetes care are outweighed by the potential benefit

to patients if this study can help define whether method of glucose testing may impact health-outcomes.

13 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

13.1 Definitions

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the intervention, regardless of whether it is considered related to the intervention.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Life-threatening means the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Event (UAE) is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol, the ICF, and/or other relevant sources of information, such as product labeling and package inserts
- the expected natural progression of any underlying disease, disorder, or condition for the participant experiencing the adverse event, and/or the participant's predisposing risk factor profile for the adverse event.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) means:

- any problem or event which in the opinion of the Investigator was unanticipated, serious; AND
- at least possibly related to the research procedures

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.

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Severity of events will be defined as:

- **Mild** requires minimal or no treatment and does not interfere with the participant's daily activities.
- **Moderate** results in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with the participant's functioning.
- **Severe** interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment.

13.2 Safety Review

Risks described in section 12.1, AEs, SAEs, and UAEs will be monitored continuously throughout the study by study staff.

13.3 Reporting Plans

The delegated Investigator will report all reportable AEs, SAEs, UAEs, and UPIRTSOs to Advarra in accordance with IRB policies.

AE's are considered reportable if they meet any of the following:

- Severe sensor-related reactions or infections requiring in-person medical care
- Severe hypoglycemia defined as requiring assistance of another person due to altered consciousness, and requiring another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- Severe hyperglycemia if the event involves diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS), as defined in Kitabchi et al.[25]

Reportable AEs and all SAEs will be recorded within an adverse event log with a description including the nature of the event, the date and time of onset and/or frequency, determination of non-serious versus serious, intensity (mild, moderate, severe), duration of the event, relationship to the intervention, the expectedness, and outcome of the event.

This study does not include an independent monitoring committee (e.g., no Data Safety Monitoring Board). Since the study procedures are of minimal risk, SAEs are not expected. If any UAEs related to the research and involving risks to subjects or others happen during this study (including SAEs), they will be reported to the IRB in accordance with Advarra IRB standard operating procedure (SOP).

13.4 Stopping Rules and Study Suspension or Termination

This study will be stopped prior to completion if information becomes available during the study that indicates a stop, which may include information related to adverse events or the potential for adverse

events. The study may also be stopped prior to completion if recruitment challenges or retention issues will impact the ability to properly analyze defined endpoints or for other reasons determined by the Investigator.

14 Data Management and Record Keeping

Data for the study will be collected and documented: 1) verbally and electronically from participants by Virta and IDC staff, 2) in Virta's HIPAA compliant EMR and patient-facing app (the mobile interface where patients interact with the care team), 3) from the Libre Pro reader and LibreView website , 4) in REDCap, 5) via the web-based ASA24 and 6) in electronic files on secured, password protected institutional computers.

CGM-related data will either be uploaded directly from the blinded Libre Pro reader and then downloaded to an institutional computer or downloaded from the LibreView website (for participants assigned to the CGM arm). CGM data will be saved on password-protected computers, which are backed up to a secure server. Participants assigned to the CGM arm will need to create a personal account in order to access the phone-based app associated with the FreeStyle Libre 2 system. Data in the app is secure to the extent provided by the manufacturer.

Participant and study-related data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system that is licensed to IDC. REDCap includes password protection and internal quality checks, including field validation to help identify inconsistent, incomplete, or inaccurate data. Data entered into REDCap will come directly from the original source data; or in some cases REDCap will serve as the source data (e.g. protocol deviations; tracking participant phone calls between participants and IDC staff; when participants respond to surveys directly in REDCap; etc.). REDCap maintains a built-in audit trail that logs all user activity and all pages viewed by every user, this includes entering data, exporting data, modifying a field, running a report, or add/modifying a user, etc.

Participants will complete surveys directly in REDCap and directly in ASA24. ASA24 is a free, web-based dietary assessment tool that is run by the National Institutes of Health. ASA24 data is associated with study ID and does not capture any personally identifiable information from participants. All completed surveys will be retained in the web-based server as a source document and will also be downloaded from the servers and stored as .CSV or similar files throughout the study.

This trial will be registered at ClinicalTrials.gov once the protocol has been approved by the IRB; trial results will be added to the ClinicalTrials.gov after study completion.

14.1 Data Monitoring

Investigators and study staff will periodically monitor data for completeness and quality as specified in data-sharing contracts and to provide the opportunity to address any concerns.

14.2 Confidentiality

Participants will be assigned a unique ID number at the time of enrollment. Whenever possible, participant records and datasets will contain the unique ID only. The participant will be informed during

the study screening process and via the ICF that their personal study-related data will be accessible by both Virta and the IDC throughout the duration of the study. Participant data and any related records may also be made accessible to regulatory authorities or as required by law.

The confidentiality of all participant information and data are protected to the extent allowed by law. Records will be kept confidential in accordance with HIPAA privacy regulations. Investigators and personnel will not use data or records for any purpose other than conducting the study; however, deidentified participant data may be used for educational purposes and shared in medical journals, at scientific meetings, or in similar settings. No identifiable data will be used for future study without first obtaining IRB approval. In the case a limited data set is needed for future study, a data use agreement will be utilized.

14.3 Records Retention

Clinical research records, including IRB records and records related to the study will be stored in a manner that ensures privacy, confidentiality, security, and accessibility when the clinical research is being conducted and after the study is completed. Based on regulatory requirements, Advarra will retain study records for at least 3 years after the last site reviewed by the IRB has terminated. Any hardcopy documents will be moved to the Advarra archive files at termination. After the record retention period has been met, all study-related materials are destroyed. Once a study is terminated in CIRBI (Center for IRB Intelligence), the study is automatically archived in the system for the retention period noted above. Prior to purging study documentation/information from CIRBI (i.e., studies that have met the retention period), CIRBI sends out an automated notification to the study contacts. The notification instructs the study contacts to log in to CIRBI and retrieve any documentation/information needed within 30 days of the notification. After the 30-day period, all documentation/information is purged from CIRBI.

All HIPAA-related documents containing PHI collected by the IDC, will be retained for at least six years after completion of the study. Physical documents will be consolidated and stored in boxes in a secure location after study completion and electronic documents will be maintained in designated research study folders on the institutional drive in accordance with the HealthPartners data retention guidelines.

15 Statistical Plan

15.1 Analysis of Primary Endpoint

Summary statistics (including number, mean, median, standard deviation, minimum and maximum) for percentage (%) of TIR (glucose 70 - 180 mg/dL), based on 14-day CGM assessments, will be calculated by treatment and period.

The primary endpoint will be analyzed using a linear mixed model with treatment (BGM or CGM), period (Baseline (period A) and Post-Dietary Change (period B)), and interaction between treatment and period as fixed effects, and patient as random effect. The model will be fitted to all the data simultaneously and from this model the relevant treatment differences will be estimated. Adjusted mean estimates for each treatment with standard errors, the adjusted estimate of treatment mean difference with standard error and a 95 % confidence interval for the treatment mean difference will be provided. The statistical test will be two-sided tests at a nominal 5% significance level.

Enrolled participants without adequate Baseline blinded Libre Pro CGM data will not be included in the analysis. Adequate Baseline blinded CGM data is defined as a minimum of 5 days of sensor data. In cases where two blinded sensors are worn in the same contact period, sensor data may be combined.

15.2 Analysis of Secondary Endpoints

Summary statistics (including number, mean, median, standard deviation, minimum and maximum for a continuous variable, or % at each level for a categorical variable) of each secondary endpoint, will be calculated by treatment and period.

Mean blood ketone levels at month 3: Mean blood ketone levels at month 3 will be calculated as average of all fingerstick BHB levels from day 0 to 90. Mean blood ketones levels will be analyzed using a linear regression model with treatment (BGM or CGM) as the effect variable.

Change in other CGM-derived metrics and A1c: These metrics include percent (%) of time with glucose above 180 mg/dL, above 250 mg/dL, below 70 mg/dL, and below 54 mg/dL based on 14-day CGM during Baseline (period A) and Post-Dietary Change (period B). These metrics also include measures of mean and variation in glucose profiles: mean glucose, % coefficient of variation, mean amplitude of glucose excursion (MAGE) based on 14-day CGM during Baseline (period A) and Post-Dietary Change (period B). Change in A1c during Baseline and Post-Dietary Change period is also included and evaluated here.

All secondary endpoints will be analyzed using linear mixed models with treatment (BGM or CGM), period (Baseline (period A) and Post-Dietary Change (period B)), and interaction between treatment and period as fixed effects, and patient as random effect. Analyses of such models are similar to the analysis for the primary endpoint.

Reaching CGM-derived consensus targets at month 3: This includes percent (%) of time with glucose >250 mg/dL <5% (yes/no); percent (%) of time in glucose >180 mg/dL <25% (yes/no); percent (%) of time in glucose 70-180 >70% (yes/no); percent (%) of time in glucose <70 mg/dL <4% (yes/no); percent (%) of time in glucose <54 mg/dL <1% (yes/no); percent (%) of time in glucose 70-180 AND percent (%) of time in glucose <70 mg/dL <4% (yes/no); percent (%) of time in glucose 70-180 AND percent (%) of time in glucose <54 mg/dL <1% (yes/no) based on 14-day at Post-Dietary Change (period B).

Since each endpoint is a dichotomous variable indicating if a patient reaches the consensus target goal at month 3 (yes/no), they will be analyzed using logistic regression models with treatment (BGM or CGM) as the effect variable.

15.3 Analysis of Exploratory Endpoints

Analysis of exploratory endpoints is descriptive (including number, mean, median, standard deviation, minimum and maximum for a continuous variable, or % at each level for a categorical variable). A 95% confidence interval (CI) will be calculated for each endpoint, but no hypothesis testing or inferential analysis will be conducted due to the exploratory nature of these variables.

15.4 Study Hypotheses

Alternative primary hypothesis: CGM will lead to greater improvements in TIR at month three compared to BGM in people with T2D who participate in the Virta Treatment.

Alternative secondary hypotheses:

- CGM will lead to greater blood ketone levels at month three (a presumed marker of adherence to the Virta dietary plan) compared to BGM in people with T2D who participate in the Virta Treatment.
- CGM will lead to greater improvements in other glycemic markers at month three compared to BGM in people with T2D who participate in the Virta Treatment.

15.5 Sample Size Determination

The sample size estimation is based on the following assumptions:

- 80% power (at 0.05 significance level) to test the primary hypothesis, which is the difference in TIR between BGM and CGM arms
- anticipated mean difference in TIR between CGM and BGM = 10%
- anticipated standard deviation of TIR in each arm = 20%

The two-sided t-test suggests N=63 for each arm. Assuming an 85% retention rate at the end of the 3-month Post-Dietary Change period brings the required sample size to approximately N=75 per arm; or N=150 randomized participants with adequate Baseline data.

Consented participants who are not randomized do not count toward the 150 total participants; these participants may be replaced.

16 Ethics/Protection of Human Subjects

This protocol and any amendments will be submitted to Advarra for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the Investigator. A copy of the initial IRB approval letter will be provided to the study funder (Abbott Diabetes Care) before commencement of this study.

This study will be conducted in full accordance with all applicable Federal and state laws and regulations including 45 CFR, and the HIPAA Privacy Rule. Any episodes of non-compliance will be documented. The Investigators will perform the study in accordance with this protocol, will obtain consent, and will report unexpected problems in accordance with IRB policies and procedures. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research participants during and after the study.

16.1 Informed Consent and HIPAA Authorization

Interested participants will be asked to electronically sign a combined ICF and HIPAA authorization form that will be sent to participants from Virta staff via DocuSign. Participants will be enrolled in the study after signing the ICF. The ICF will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the informed consent and HIPAA authorization will be emailed to each participant.

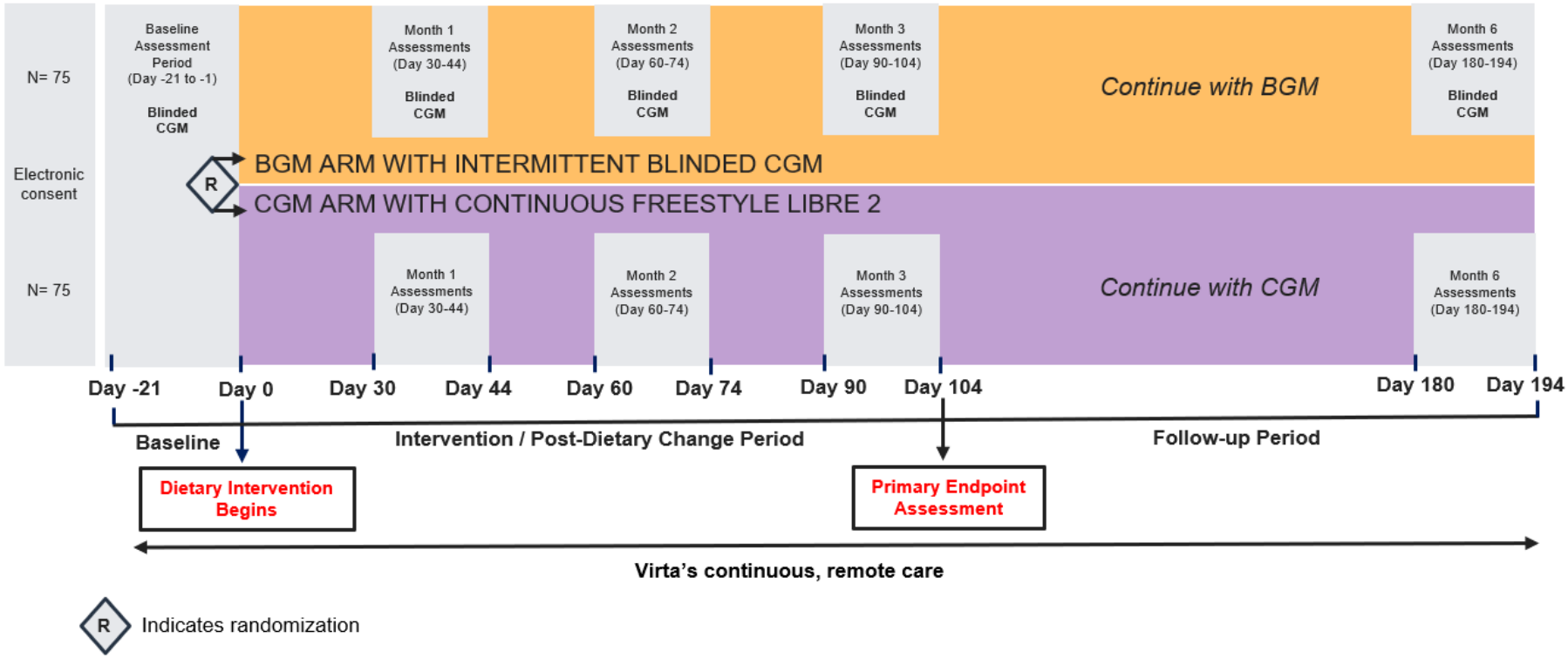
16.2 Conflict of Interest

Study personnel from Virta Health have been offered stock options in Virta Health and therefore have the potential for a significant financial interest in the company. The intervention being tested in the present investigation, however, is the utilization of a commercially available continuous glucose monitor from Abbott Diabetes Care, to which Virta Health study personnel have no conflict. The ICF and any publications resulting from this study will reflect these potential perceived conflicts of interest.

17 Appendices

Appendix A. Study Schematic
Appendix B. Study Periods and Assessments
Appendix C. Participant-Facing Materials

17.1 Appendix A. Study Schematic



17.2 Appendix B. Study Periods and Assessments

Study Period	**Baseline**	**Diet Change**	**Post-Dietary Change / Intervention**			**Follow-Up**
Study Day	-21 to -1	0	30 to 44 +/-10	60 to 74 +/-10	90 to 104 +/-10	180 to 194 +/-14
Assessment (Contact #)	**Baseline Assessment (Contact 1)**		**Month 1 Assessment (Contact 2)**	**Month 2 Assessment (Contact 3)**	**Month 3 Assessment (Contact 4)**	**Month 6 Assessment (Contact 5)**
Demographic Data	X					
14-Day Baseline Blinded CGM	X					
Personal Libre 2 CGM Use (CGM arm only)		←	←	X	→	→
14-Day CGM Data Download (CGM arm only)			X	X	X	X
14-Day Blinded CGM Wear & Data Download (BGM arm only)			X	X	X	X
Ketones 2x/Day		←	←	X	→	→
HbA1c	X				X	X
Medication Use	X		X	X	X	X
ASA-24 (single recall)	X		X	X	X	X
Height	X					
Weight/BMI	X		X	X	X	X
Diabetes Distress Survey	X				X	X
Lifestyle Change Survey					X	X
CGM Satisfaction Survey (CGM arm only)					X	
Participant Contacts with Virta			X	X	X	X
Adverse Events	←	←	←	X	→	→

17.3 Appendix C. Participant-Facing Materials – See attached document

- Questionaries to be administered via REDCap
  - Demographic Survey – REDCap Distribution
  - Diabetes Distress Scale-17 (DDS-17) – REDCap Distribution
  - CGM Satisfaction Survey – REDCap Distribution
  - Lifestyle change survey – CGM Arm (study-specific) – REDCap Distribution
  - Lifestyle change survey – BGM Arm (study-specific) – REDCap Distribution
  - Reasons for CGM Discontinuation (CGM ARM if applicable) – REDCap Distribution
- Materials to be distributed by postal mail and e-mail
  - IGNITE Study Overview and Instructions
  - FreeStyle Libre Pro Blinded CGM Instructions
  - IGNITE Study CGM Group Instructions
  - IGNITE Study BGM Group Instructions
  - Returning your FreeStyle Libre Pro Blinded Reader

18 References

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