T1D Exchange

Wireless Innovation for Seniors with Diabetes Mellitus (WISDM)

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CHAPTER 1: INTRODUCTION

1.1 Introduction and Rationale

Older adults with type 1 diabetes (T1D), a growing but under-evaluated population (1-4), are prone to hypoglycemia and hypoglycemia unawareness, particularly when diabetes is longstanding. Hypoglycemia, which in addition to producing altered mental status and sometimes seizure or loss of consciousness, can be associated with falls leading to fractures, and cardiac arrhythmias resulting in sudden death (5-7). Hypoglycemia must always be considered a possible contributing factor in older adults with T1D in whom these events occur, especially when a glucose measurement is not available from the time of the event (8). In Medicare beneficiaries with diabetes, hospitalizations related to hypoglycemia are now more frequent than those for hyperglycemia and are associated with high 1-year mortality (6). Emergency room visits due to hypoglycemia also are common (5). These reports likely underestimate the risk of hypoglycemia in older adults with T1D since they include individuals with the more prevalent type 2 diabetes in whom severe hypoglycemic events are likely considerably less frequent than they are in individuals with T1D.

Unlike treatment guidelines in younger individuals with T1D which focus on optimizing glycated hemoglobin (HbA1c) levels, treatment approaches for older adults with T1D often focus on minimizing hypoglycemia rather than attempting to achieve low HbA1c levels (9, 10). Despite these efforts, biochemical hypoglycemia occurs frequently and severe hypoglycemia (SH) occurs more often in older than younger adults with T1D. Data from the T1D Exchange registry has shown a remarkably high frequency of SH in older adults with longstanding T1D: 18% of registry participants $\geq$60 years old reported seizure or loss of consciousness due to hypoglycemia in the prior 12 months (11). In addition, although there may be less of a push towards tight control in older adults, T1D Exchange registry data indicate that SH is just as common with HbA1c levels >8.0% as it is for HbA1c levels <7.0% (11). A T1D Exchange study (12) of 201 adults $\geq$60 years old with T1D duration $\geq$20 years (101 with SH in the prior year and 100 without SH in the prior 3 years) found that glucose concentrations measured with blinded continuous glucose monitoring (CGM) were <70 mg/dL for a median of 91 minutes per day and <50 mg/dL for 31 minutes per day. Furthermore, mean HbA1c was similar in the individuals who had experienced SH in the prior year compared with those who had not experienced SH in the prior 3 years (7.8% versus 7.7%). These data do not support the strategy of "raising the HbA1c" an effective approach for hypoglycemia prevention in older adults with T1D.

Hypoglycemia unawareness, or the loss of physiological symptoms associated with a low blood glucose level, is associated with duration of diabetes, making it particularly prevalent in older adults. The presence of hypoglycemia unawareness is associated with a 20-fold increased risk for experiencing SH (13). The prevalence of hypoglycemia unawareness was remarkably high in the T1D Exchange of older adults (12), with 58% of those with SH within the prior year having hypoglycemic unawareness compared with 25% in those with no SH in the prior 3 years. Furthermore, glycemic variability was significantly greater for those having experienced SH within the prior year, supporting mechanisms beyond awareness of hypoglycemia contributing to risk for SH in older adults with T1D.

The occurrence of hypoglycemia and fear of hypoglycemia have adverse effects on quality of life of both the individuals with T1D (14) and their families (15). Hypoglycemia fear and associated behaviors impact participation in activities that are beneficial to emotional and physical well-being (e.g., exercise, socializing, and travelling), and may lead to intentional hyperglycemia. Diabetes-related distress (i.e., the emotions, stresses and worries associated with diabetes) is also an important component of QOL for people with T1D and is associated with poor glycemic control, longer duration of diabetes, higher rates of depression, and prior SH (16).

Aging is associated with normative decline in cognitive functioning independent of any disease process. Thus, older adults often have more difficulty learning and adopting new technologies and following complex medication regimens. Older adults with T1D have additional risk for more substantial cognitive impairment given increased rates of microvascular and macrovascular complications from longstanding diabetes. We previously found that mild cognitive impairment is common in community dwelling older adults with T1D (see preliminary data) and that it is related to activities of daily living and everyday diabetes related tasks (17). Further, those with SH perform poorer in some areas of cognitive function than those without SH (12) making it possible that cognitive impairment increases the risk of a SH event. While it is possible that SH results in greater cognitive impairment, this has not been supported in a younger T1D cohort in DCCT/EDIC followed for over 18 years (18). The combination of cognitive difficulties and blunting of the alerting symptoms of hypoglycemia may put older adults at high risk for hypoglycemia (19).

1.2 Continuous Glucose Monitoring

CGM measures interstitial glucose concentrations and provides for real-time observation of glucose levels, trend direction and alarms for when glucose drops to low levels. The components or CGM include a receiver, a transmitter and a sensor. In December 2016, the FDA expanded the indications for the Dexcom G5 sensor to allow for replacement of fingerstick blood glucose testing for diabetes treatment decisions.

Several randomized trials have demonstrated the efficacy of CGM when it is used on a regular basis by individuals with T1D, particularly adults (20-23). Among individuals with HbA1c levels above target, improvement has been demonstrated in HbA1c levels and in a reduction in biochemical hypoglycemia. Among individuals with HbA1c levels at or below target, CGM has been demonstrated to reduce biochemical hypoglycemia while at the same time maintaining excellent HbA1c levels better than a control group (24). While these trials have found consistent glycemic benefit with CGM use, it is clear that the amount of benefit is related to the amount of CGM use (22, 23).

In addition, regular CGM users have reported substantial satisfaction with use of the device and improved QOL (25). The JDRF funded RCT of CGM in children and adults showed a modest improvement in hypoglycemia fear associated with CGM use in the adult cohort, but no changes in other more general measures of QOL (23). Langendam et al. found no benefit of continuous glucose monitoring on QOL in their Cochrane Review, although only 5 of 22 studies included QOL outcomes (26). However, all of these studies used earlier generation CGM devices. Based on the extremely high compliance with daily CGM use in recently completed trials coordinated by the Jaeb Center for Health Research using the Dexcom G4 or G5 sensor, substantially higher patient satisfaction and improvement in QOL is likely with the current generation Dexcom device.

CGM can alert when blood glucose is low or trending downward and this information can be automatically shared with others; features that may be particularly helpful for those at risk for SH. Polonsky and Hessler surveyed existing CGM users and found that older age was associated with a greater perceived benefit in hypoglycemia safety and interpersonal support, although the mean age of this sample was 41 years (25). Despite its potential benefits to reduce hypoglycemia and hypoglycemia fear, CGM is used by only a small proportion of older adults with T1D. In the T1D Exchange registry, only 19% of adults over the age of 60 are using CGM, a percentage that likely over-represents CGM use in this age group since all of the registry participants, by selection, are seen by an endocrinologist who has a practice focused on T1D.

None of the CGM randomized trials have included a substantial number of participants 60 years or older (21-23, 27): For instance, in the JDRF CGM RCT, only 19 of 451 participants were 60 years or older

(23). Since these trials involved a small number of older adults, used older generation sensors, and aimed to lower HbA1c rather than reduce hypoglycemia, the benefits of CGM found in the prior studies cannot be generalized to diabetes management in the older adult T1D population. Furthermore, most studies of CGM have excluded patients experiencing recent SH or hypoglycemia unawareness, whereas in clinical practice these are just the patients for whom CGM might have the greatest benefit. In a retrospective clinic-based analysis, implementation of CGM for one year in patients with problematic hypoglycemia at baseline was associated with a reduction, but not elimination, of severe hypoglycemic events (28).

1.3 Preliminary Studies

The T1D Exchange Clinic Network and the Jaeb Center for Health Research (JCHR) Coordinating Center have experience in conducting CGM and hypoglycemia studies in older adults with T1D. The Exchange conducted a case-control study of 201 individuals ≥60 years old with T1D for ≥20 years at 18 clinical sites (14 of which are participating in the proposed study), coordinated by JCHR (12). The objective of the study was to assess potential contributory factors for the occurrence of severe hypoglycemia, including cognitive functioning, social support, depression, hypoglycemia unawareness, various aspects of diabetes management, residual insulin secretion (as measured by C-peptide levels), frequency of biochemical hypoglycemia, and glycemic control and variability. Cases (N=101) had at least one severe hypoglycemic event in the prior 12 months while controls (N=100), frequency-matched to cases on age, had no severe hypoglycemia in the prior 3 years. HbA1c levels (mean 7.8% versus 7.7%) and CGM-measured mean glucose (175 mg/dL versus 175 mg/dL) were similar between cases and controls. More cases than controls had hypoglycemia unawareness; only 11% of cases compared with 43% of controls reported always having symptoms associated with low blood glucose levels ($p<0.001$). Cases had greater glucose variability than controls ($p=0.008$) and experienced CGM glucose levels <60 mg/dL more often than in controls ($p=0.04$). Cases scored worse than controls on measures of general mental status, processing speed and executive functioning. As expected, hypoglycemia fear was higher in cases compared with controls.

In this sample of non-demented, community dwelling and functionally independent older adults with T1D, 55% of the combined sample was at least mildly impaired (compared to demographically corrected normative data) on a brief neuropsychological test battery, with 35% in the moderate to severely impaired range. This was clinically relevant, as cognitive performance was associated with simulated diabetes task performance (e.g., calculating an insulin dose based on a nutritional label) and instrumental activities of daily living (17). Due to the cross-sectional nature of this work, however, it is not known if cognitive impairment is a cause or consequence (or both) of hypoglycemia. In those with mild or moderate cognitive impairment, falling glucose alert and threshold alarm features of CGM may be particularly useful to "remind" patients to check their blood glucose when the glucose level is decreasing and approaching the hypoglycemic range.

1.4 Summary of Study Rationale

Reducing hypoglycemia is an important aspect of management of T1D in older adults, many of whom have hypoglycemic unawareness, cognitive impairment, or both. CGM offers the opportunity to reduce hypoglycemia and its related complications such as fractures from falls and hospitalizations and improve QOL including reducing hypoglycemic fear and diabetes distress. Despite these potential benefits, CGM is used by only a small proportion of older adults with T1D (19% in the T1D Exchange registry). Previous studies assessing CGM efficacy have included only a small number of adults ≥ 60 years of age, excluded patients most prone to SH, focused on improving HbA1c rather than hypoglycemia, and used older generation CGM sensors. These studies are not generalizable to the population of older adults with T1D. The potential benefit of CGM in reducing hypoglycemia in the older adult population has not been well studied. A randomized trial is needed to assess the benefits and risks of CGM in older adults with T1D.

1.5 Protocol Synopsis

1.5.1 Study Objective

The primary objective of the study is to determine if CGM can reduce hypoglycemia and improve quality of life in older adults with T1D.

- A secondary objective is to evaluate the cost-effectiveness of the continuous glucose monitoring device, relative to care as usual

1.5.2 Study Design

6-month parallel group randomized clinical trial (RCT) comparing an intervention group using CGM with a control group following usual care (without CGM).

- The RCT will be preceded by a screening period in which blinded CGM will be used to assess compliance, safety and collect baseline data.

The RCT will be followed by an extension study

- Participants in the CGM group will continue to be followed for an additional 6 months. Participants in the control group will be given the opportunity to use CGM for 6 months.

1.5.3 Major Eligibility Criteria

- Clinical diagnosis of T1D
- Age ≥60.0 years
- Insulin regimen involves either use of an insulin pump or multiple daily injections of insulin.
- No use of real-time CGM for diabetes management in past 3 months
- HbA1c ≤10.0%
- Individual does not have a diagnosis of dementia

1.5.4 Sample Size and Treatment Groups

The randomized trial is planned to include 200 participants, with a minimum of 40% of participants using an insulin pump and minimum of 40% of participants using multiple daily injections of insulin.

Following the run-in period, eligible participants will be randomly assigned with equal probability to the following 2 groups:

- CGM
- BGM

1.5.5 Visit and Phone Contact Schedule During RCT

Following randomization, the CGM Group will have a study visit at 10 days, while the BGM group will have a phone call for the 10 day contact. In-clinic study visits for both groups will occur at 4, 8, 16 and 26 weeks. In addition to the in-clinic study visits, the BGM group will have blinded sensor placement visits one week prior to each of the 8, 16, and 26 week visits.

1.5.6 Main RCT Outcome Measures

Primary outcome at 6 months: Percent of time with glucose level <70 mg/dL

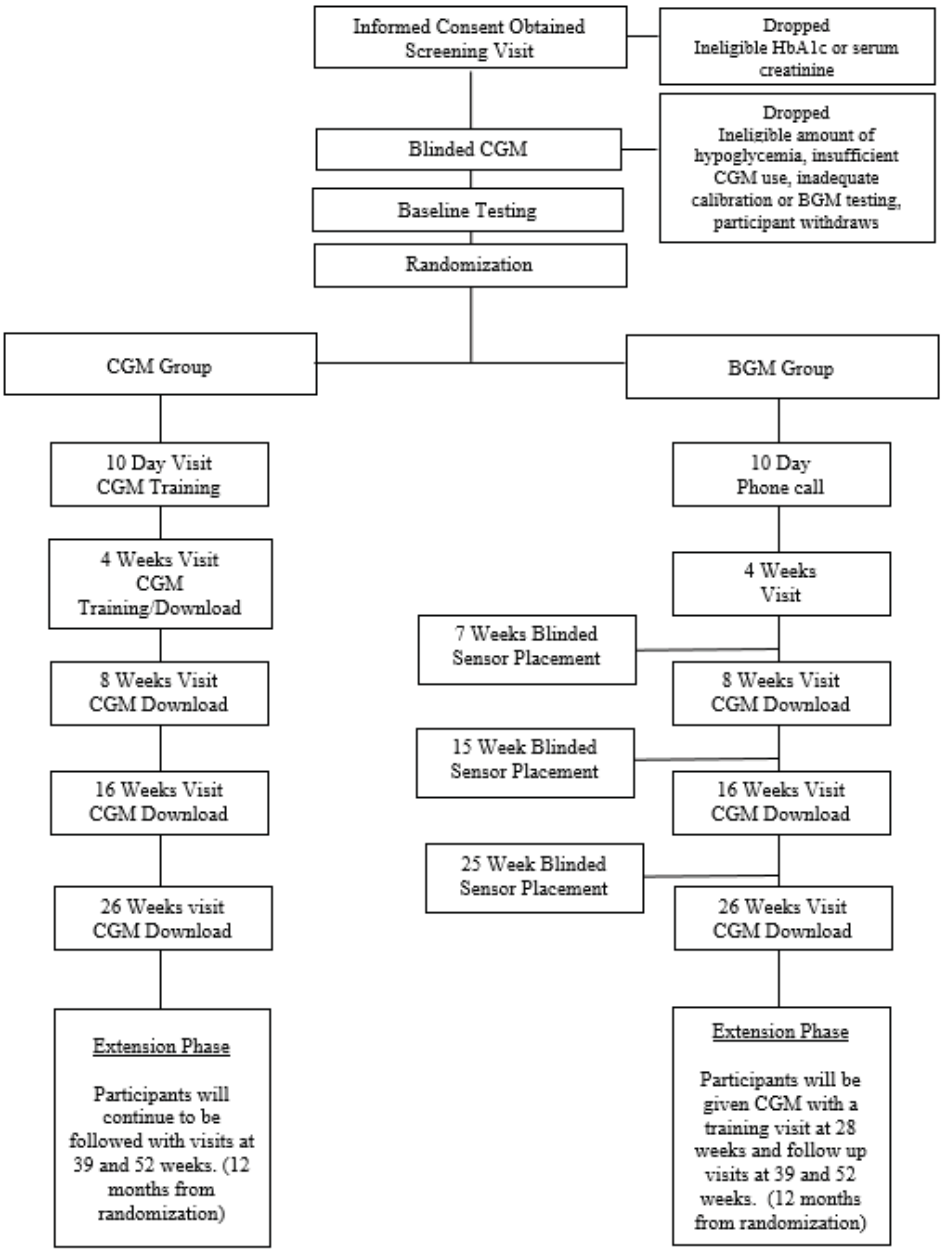
Secondary outcomes:

- Patient Reported Outcome measures: fear of hypoglycemia, attitudes towards hypoglycemia and hyperglycemia, diabetes distress, glucose monitoring satisfaction, general quality of life, emotional well-being
- HbA1c
- Episodes of severe hypoglycemia and diabetic ketoacidosis
- Falls, ER visits, hospitalizations, and device-related adverse events

- Additional CGM metrics for hypoglycemia, hyperglycemia, overall control
- Cost-utility assessment

1.6 Schedule of Study Visits and Procedures

Study Flow Chart



Pre-randomization Phase

Visit Time Point:	Screening	End of Blinded CGM Phase
Visit Window:	-	14 to 21 days after screening

Informed Consent	**X**	
HbA1c-point of care or local lab	**X[a]**	
Local lab Creatinine	**X[b]**	
Blinded CGM placement	**X**	
Physical Exam including assessment of vital signs and height/weight	**X**	
Medical History	**X**	
Hearing, Vision, and Frailty Assessment	**X**	
Functional Activities Questionnaire	**X[c]**	
Diabetes Management and lifestyle questions	**X**	
Patient Reported Outcome Questionnaires	**X[d]**	
Pre-randomization compliance assessment		**X**
Skin Assessment		**X**
CGM download (assess usage and amount of hypoglycemia)		**X**

[a]If not collected as usual care in the prior 30 days from the screening visit.

[b]obtained from local lab at study visit if not previously obtained as part of usual care within the prior 6 months of the screening visit.

[c] Completed in Redcap or on paper if Redcap not possible.

[d]Completed in Redcap or on paper if Redcap not possible. Includes hypoglycemic fear survey, PROMIS QOL, Diabetes Distress, Hypoglycemic Unawareness, Glucose Monitoring Satisfaction Survey, Preferring Hypoglycemia Scale, and Cost utility questionnaires including EQ-5D-5L and SF-12V2

Main Randomized Trial

Time Point	0	10d	4w	8w	16w	26w
Window		± 3 days	±7 days	±7 days	±7 days	±7 days
Contact Type (Phone or Visit)	V	V/P[a]	V	V	V	V
Blinded CGM[b]				X[c]	X[c]	X[c]
CGM Training	X[d]	X[d]	X[d]			
Review of insulin dosing and diabetes management	X	X[d]	X	X	X	X
Physical Exam including assessment of vital signs and height/weight					X	X
Skin Assessment[d]		X[d]	X[d]	X	X	X
Assessment of Adverse Events		X	X	X	X	X
Assess Device Issues		X	X	X	X	X
HbA1c-Point of Care or local lab				X	X	X
HbA1c - central lab	X				X	X
Central lab C-peptide (nonfasting) and glucose	X					
CGM download		X[d]	X[d]	X	X	X
NIH Toolbox Cognitive and Emotions Assessments	X					X
Questionnaires	X[e,f]					X[f]

[a]Study visit for CGM group. Phone call for BGM group

[b]For BGM group and for participants in CGM group who have discontinued real- time CGM use (if willing to continue study using a BGM)

[c]Blinded CGM placement will occur in clinic one week prior to each of the 8, 16 and 26 week study visits.

[d]For CGM group only

[e]Completed at randomization visit if not already completed at screening visit or from home prior to randomization visit.

[f]Completed in Redcap or on paper if Redcap not possible. Includes hypoglycemic fear survey, PROMIS QOL, Diabetes Distress, Hypoglycemic Unawareness, Glucose Monitoring Satisfaction Survey,

Preferring Hypoglycemia Scale, and Cost utility questionnaires including EQ-5D-5L and SF-12V2

Extension Phase

Extension Time Point	26w Visit from RCT	28w	39w	52w
Window	±7 days	±7 days	±7 days	±14 days
CGM Training	**X**	**X**		
Review of insulin dosing and diabetes management	**X**	**X**	**X**	**X**
Physical Exam	**X**		**X**	**X**
Skin Assessment	**X**	**X**	**X**	**X**
Assessment of Adverse Events	**X**	**X**	**X**	**X**
HbA1c-Point of Care or local lab	**X**		**X**	**X**
HbA1c-central lab	**X**		**X**	**X**
CGM download	**X**	**X**	**X**	**X**
NIH Toolbox Cognitive and Emotions Battery	**X**			**X**
Patient Reported Outcomes Questionnaires	**X[a]**			**X[a]**

[a]Completed in Redcap or on paper if Redcap not possible. Includes hypoglycemic fear survey, PROMIS QOL, Diabetes Distress, Hypoglycemic Unawareness, Glucose Monitoring Satisfaction Survey, Preferring Hypoglycemia Scale, and Cost utility questionnaires including EQ-5D-5L and SF-12V2

1.7 Summary of Protocol

1. Informed consent obtained
2. On the day of screening after consent is signed and eligibility is determined, patient reported outcome questionnaires will be completed and a blinded CGM sensor will be inserted. Training will be provided on calibration of the sensor (as needed per FDA labeling), its use in blinded mode, and sensor insertion.
3. Participants will be expected to insert a sensor at home after 7 days (or sooner if needed or per FDA labeling) and will be provided with a study blood glucose meter and test strips to be used for CGM calibrations and regular blood glucose monitoring.
4. The participant will return after 14 to 21 days to assess the blinded CGM data for eligibility to continue into the RCT. For eligibility:
   - CGM must be used for at least 240 hours (equivalent to 10 days out of 14 days) and self-monitoring of blood glucose (SMBG) testing must be performed at an average of 1.8 times each day for CGM calibrations or as needed per sensor requirements (if insufficient usage, blinded CGM may be repeated at investigator discretion)
   - Participants who spent more than 10% of time with sensor glucose levels < 54 mg/dl AND have had a severe hypoglycemic event in the past 6 months will be excluded from the study. In addition, the investigator will review CGM data for serious safety concerns that would prohibit participation in the RCT per investigator discretion.
5. Eligible participants will be randomly assigned to the CGM group or BGM group.
   - Participants in the CGM group will be instructed on how to utilize the CGM data for diabetes management. Participants will be encouraged to use CGM values for making diabetes management decisions and will be provided guidelines for when to confirm with a study BGM fingerstick.
   - Participants in the BGM group will receive instructions on how to optimally use SMBG in their diabetes management.
6. Following randomization, the CGM Group will have a study visit at 10 days, while the BGM group will have a phone call for the 10 day contact. In-clinic study visits for both groups will occur at 4, 8, 16 and 26 weeks.
   - In addition to the in-clinic study visits, the BGM group will have blinded sensor placement visits one week prior to each of the 8, 16, and 26 week visits.
7. Extension Phase, following the 26 week visit:
   - Participants randomized to the CGM group will continue to be followed for an additional 6 months with visits at 39 and 52 weeks to assess sustained use and determine if benefit over 12 months.
     Participants randomized to the BGM group will be given the opportunity to use CGM for 6 months with a CGM training visit approximately 2 weeks after initiating real-time CGM and study visits at 39 and 52 weeks.

1.8 General Considerations

The study is being conducted using the most currently approved version of the Dexcom CGM system for real-time use and sensors available at the time of study initiation. The sensor will be used according to FDA labeling. The CGM version may be upgraded to a newer version during the course of the study if one becomes available. The blinded CGM will use the currently approved Dexcom professional CGM according to FDA labeling.

The protocol risk assessment for this study has been categorized as no greater than minimal risk.

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Data will be directly collected in electronic case report forms, which will be considered the source data when applicable.

A risk-based monitoring approach will be followed, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013).

CHAPTER 2: ELIGIBILITY AND SCREENING VISIT

2.1 Study Population

Approximately 250-300 individuals ≥60 years old with T1D are expected to be enrolled in the study so that a minimum of 200 will enter the randomized trial. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Study participants who have signed an informed consent form prior to this notification can be randomized up until the end date, which means the recruitment goal might be exceeded. The maximum number of participants in the randomized trial will be 220.

The study will aim to enroll a minimum of 40% of participants using an insulin pump and a minimum of 40% of participants using injections of insulin with a goal of at least 80% of participants with at least 2% of time with sensor glucose levels < 70 mg/dl during the blinded CGM screening period (no more than 20% spending less than 2% of time < 70 mg/dl).

Enrollment may be restricted if necessary to achieve the above recruitment goals.

2.2 Informed Consent

Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. For potential study participants who are considered potentially eligible for the study, the study protocol will be discussed with the potential study participant by a study investigator and clinic coordinator. The potential study participant will be given the Informed Consent Form to read, ask questions, and will be provided a copy of the consent. Potential study participants will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review what study specific information will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

2.3 Eligibility and Exclusion Criteria

2.3.1 Inclusion

To be eligible for the study, all participants must meet the following criteria:

1) Clinical diagnosis of insulin dependent presumed autoimmune type 1 diabetes by the investigator and meeting at least one of the following criteria:
   i. Age > 6 months and < 10 years old at diagnosis OR
   ii. Positive pancreatic autoantibodies at any time (GAD-65, IA-2, ICA or ZnT8) or positive anti-insulin autoantibody at diagnosis only (within 10 days of starting insulin) OR
   iii. Presence of 2 or more of the following clinical indicators suggestive of type 1 diabetes:
      (a) Age at diagnosis < 40 years
      (b) Non-obese at diagnosis according to BMI (< 95th percentile pediatric and < 30 kg/m^2 adult)
      (c) Diabetic ketoacidosis (DKA) at any time,
      (d) Plasma C-peptide level < 0.8 ng/ml (with blood glucose > 80 mg/dL if available) at any time
      (e) Family history of type 1 diabetes in a first degree relative (parent, sibling, or child).
2) Age ≥60 years
3) HbA1c ≤10.0% at screening or within 30 days prior to screening visit *(the upper limit was selected as a surrogate measure of likelihood of adherence to the protocol with the belief that those with higher*

HbA1c levels are generally noncompliant with diabetes management and thus not good candidates for the trial)

4) Insulin regimen involves either use of an insulin pump (a minimum of 40% of study population) or multiple daily injections of insulin (minimum of 40% of study population).
5) Participant is able to manage his/her diabetes with respect to insulin administration and glucose monitoring *(which may include assistance from spouse or other caregiver)*
6) Participant understands the study protocol and agrees to comply with it
7) Participant comprehends written and spoken English
8) At least 240 hours (10 out of 14 days) of sensor glucose data with appropriate number of calibrations from the blinded CGM pre-randomization phase

2.3.2 Exclusion

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation.

1) Use of unblinded CGM, outside of a research study, as part of real-time diabetes management in the last 3 months
2) At least 10% of time spent with sensor glucose levels < 54 mg/dl during the blinded CGM screening period AND a severe hypoglycemic event in the past 6 months (a severe hypoglycemic event that required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions (see section 8.1).
3) Extreme visual or hearing impairment that would impair ability to use real-time CGM assessed at screening visit
4) Known adhesive allergy or skin reaction during the blinded CGM pre-randomization phase that would preclude participation in the randomized trial
5) Plans to begin non-insulin medication for blood glucose lowering during the course of the study
6) Stage 4 or 5 renal disease or most recent GFR < 30 ml/min/m^2 from local lab within the past 6 months
7) The presence of a significant medical or psychiatric condition or use of a medication that in the judgment of the investigator may affect completion of any aspect of the protocol, or is likely to be associated with life expectancy of <1 year.
8) Clinical diagnosis of dementia *(cognitive impairment that is mild and not considered sufficient for diagnosis of dementia is acceptable)*
9) Need for use of acetaminophen or acetaminophen-containing products on a regular basis during the 6 months of the trial (unless stipulation no longer required with use of newer generation sensors)
10) Inpatient psychiatric treatment in the past 6 months
11) Participation in an intervention study (including psychological studies) in past 6 weeks.
12) Expectation that participant will be moving out of the area of the clinical center during the next 6 months, unless the move will be to an area served by another study center.

2.4 Screening and Baseline Data Collection

Potential participants will be evaluated for study eligibility through the elicitation of a medical history and performance of a physical examination by a study investigator.

Information collected from the chart and solicited from the participant will include: medications, medical conditions, physical exam, diabetes management, demographics, socio-economic characteristics, insulin use, and other lifestyle factors.

A local HbA1c measurement will be obtained if not already obtained as part of usual care within the prior 30 days of the screening visit. A serum creatinine will be obtained as a local lab sample if not previously measured as part of usual care within the prior six months of the screening visit.

A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or his or her designee.

2.5 Testing and Assessments

Testing and Assessments will include the following:

1) Vision assessment with near vision reading card
2) Hearing assessment by self-report and recognition of alarms
3) Frailty assessment using 10-foot timed walk
4) Questionnaires completed online using RedCap (or paper if online not possible)
    a. Functional Activities Questionnaire
    b. Hypoglycemia Fear Survey
    c. Diabetes Distress Scale (DDS)
    d. Glucose Monitoring System Satisfaction Survey (GMSS)
    e. Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Short Form
    f. Hypoglycemia Unawareness Assessment –Clarke survey
    g. Preferring Hypoglycemia Scale
    h. Cost utility questionnaires including EQ-5D-5L and SF-12V2

The questionnaires are described in chapter 7. Instructions for testing administration will be detailed in a procedures manual.

If eligibility is confirmed at the screening visit, a blinded CGM sensor will be inserted and the participant will be instructed on its use and care.
Screening procedures will last approximately 2 hours.

CHAPTER 3: BLINDED CGM WEAR PHASE

3.1 Blinded Continuous Glucose Monitoring

If eligibility is confirmed at the screening visit, a CGM sensor will be inserted and the participant will be instructed on its use and care. The CGM receiver will be blinded so that the participant is not able to see the CGM glucose values. Additional sensors, a blood glucose meter and test strips will be provided. The participant will be instructed on sensor insertion and will need to insert a new sensor after 7 days or earlier if the initial sensor is no longer functioning.

Participants will be informed that to be eligible for the randomized trial, the blinded CGM must be used a minimum of 240 hours (equivalent to 10 days) and appropriately calibrated as needed according to FDA label.

3.2 Assessment of Blinded CGM Data and Blood Glucose Meter

The participant will return for a study visit 14-21 days after the Blinded CGM sensor was placed.

The CGM data will be downloaded to assess (1) whether the participant has used the CGM for at least 240 hours (10 of 14 days) and (2) whether the CGM was appropriately calibrated with an average of 1.8 calibrations per day and (3) the amount of time spent < 54 mg/dl and amount of time spent < 70 mg/dl.

Participants who spent at least 10% of time < 54 mg/dl AND have had a severe hypoglycemic event in the past 6 months will be excluded from the study due to safety concerns. Participants who spent less than 2% of time < 70 mg/dl may not be randomized if there are already too many participants in the study with little or no hypoglycemia during the baseline blinded CGM wear (see section 2.1).

- Participants not meeting the CGM usage requirement may be given a second opportunity to wear the blinded CGM sensor at investigator discretion.

Participants who are unable to meet the CGM requirements will be discontinued from the study and not enter the randomized trial.

Data from the blinded wear should be reviewed for safety and eligibility but should not be reviewed with the participant or used to adjust diabetes management if randomization to the study is going to occur. Once the participant is randomized the blinded data may be used for diabetes management for the CGM group but NOT the BGM group.

The skin where sensors were worn will be inspected to determine that there has not been a reaction that would preclude participation in the randomized trial.

CHAPTER 4: RANDOMIZATION VISIT

4.1 Timing of Visit

The randomization visit typically will coincide with the end of the blinded CGM phase visit, but if the participant is not prepared for starting the randomized trial (e.g., going out of town for a short period of time), initiation of the randomized trial can be deferred for up to 4 weeks.

The purpose of the visit will include the following:

- Completion of baseline cognitive and patient reported outcome questionnaires (if questionnaires not already completed)
- Collection of blood sample to send to the central laboratory for HbA1c, random C-peptide, and glucose
- Randomization to the CGM Group or the BGM Group
- For the CGM Group, initiation of unblinded CGM use and instructions on its use. For the BGM Group, instructions on optimally using SMBG for diabetes management.

4.2 Testing and Assessments

Testing and Assessments will include the following:

1) Cognitive Battery using NIH toolbox
2) Emotions Battery using NIH toolbox

Prior to the cognitive battery testing, a fingerstick will be performed to ensure the participant is not hypoglycemic. The cognitive testing should be delayed until hypoglycemia is resolved. Randomization may be delayed until cognitive testing is completed.

Questionnaires not completed at screening may be done at the randomization visit prior to randomization on the study website. The questionnaires are described in chapter 7. Instructions for testing administration will be detailed in a procedures manual.

4.3 Blood Samples

Blood will be drawn and sent to the central lab for:

- HbA1c
- C-peptide (nonfasting) + glucose

4.4 Randomization

Eligible participants will be randomized to one of two treatment groups in a 1:1 allocation:

1. CGM Group
2. BGM Group

The participant's randomization group assignment is determined by entering the Randomization Visit data on the study website.

- The Jaeb Center will construct a Master Randomization List using a permuted block design.
- Randomization will be stratified by clinical site

4.5 Study Supplies

The CGM group will be provided with the newest model of the CGM available at the time of study initiation (a newer model may be provided if one becomes available during the study), inclusive of a receiver, transmitter, and sensors.

One week prior to the 8, 16 and 26 week visits, the BGM group will have a sensor placed and will be provided with a professional CGM in blinded mode.

All study participants will be provided with a study blood glucose meter and test strips.

4.6 Initial Management Instructions

In both groups, adjustments in insulin management will be made as needed. Data from the blinded wear should not be used for adjustments in diabetes management for participants randomized to the BGM group. Blinded CGM data may only be reviewed following the 26 week outcome visit for the BGM group.

Both groups will be provided with instruction sheets regarding diabetes management pertinent to their treatment group.

The CGM group will be instructed on use and care of the CGM and how to use the CGM in real time to make management decisions.

The BGM group will be instructed on how to optimally use SMBG for diabetes management.

Further details on instructions to each group are provided in section 5.1.

CHAPTER 5: RANDOMIZED TRIAL PHASE

5.1 Home Procedures and Diabetes Management

5.1.1 CGM Group

Each participant will be asked to use a CGM sensor on a daily basis, inserting a new sensor as needed. Participants will be instructed to use the sensor according to FDA labeling. In addition, participants will be advised to check the blood glucose when symptoms or expectations do not match the CGM reading.

Participants in the CGM group will be encouraged to view retrospective CGM data weekly on a home computer or the smartphone application if it is being used.

5.1.2 BGM Group

A study blood glucose meter and test strips will be provided and will be used for a fingerstick blood glucose check with a recommendation of 4 times a day. Participants will be permitted to check a fingerstick glucose as many times a day as they choose.

5.2 Study Visits and Phone Contacts

CGM Group will have a study visit at 10 days, while the BGM Group will have a phone call for the 10-day contact. In-clinic study visits for both groups will occur at 4, 8, 16 and 26 weeks.

In addition to the in-clinic study visits, the BGM group will have blinded sensor placement visits one week prior to each of the 8, 16, and 26 week visits.

5.2.1 Study Visits

Study visits for both groups will occur at

- 10 days ($\pm$3 days)
- 4 weeks ($\pm$7 days)
- 8 weeks ($\pm$7 days)
- 16 weeks ($\pm$7 days)
- 26 weeks ($\pm$7 days)

Blinded sensor placement visits at: 7, 15 and 25 weeks for BGM group.

Additional office visits may occur as needed.

Procedures at Study Visits

The following procedures will be performed in both groups at each visit, unless otherwise specified:

- Assessment of compliance with CGM (CGM group) and fingersticks (BGM group)
- Solicitation of the occurrence of adverse events, including falls, hospitalizations, emergency department visits, severe hypoglycemia, and diabetic ketoacidosis
- Assessment of device issues
- Skin assessment for CGM group and following blinded sensor wear for BGM group
- Review of glucose data and insulin dosing and recommendations for changes in diabetes management
- HbA1c determination using a point of care device or local lab (8, 16, and 26 weeks)
- Collection of a blood sample to send to the central laboratory for HbA1c determination (16 and 26 weeks)
- Completion of questionnaires (26 weeks)

- Hypoglycemia Fear Survey
- Diabetes Distress Scale (DDS)
- Glucose Monitoring System Satisfaction Survey (GMSS)
- Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Short Form
- Hypoglycemia Unawareness Assessment –Clarke survey
- Preferring Hypoglycemia Scale
- Cost utility questionnaires including EQ-5D-5L and SF-12V2
- NIH Cognitive Toolbox
- NIH Emotions Toolbox

5.2.2 Phone Contacts

A phone contact will be scheduled at the following times:

- 10 days (±3 days) – BGM group only

The purpose of the phone contact will be:

- Solicitation of the occurrence of adverse events, including falls, hospitalizations, emergency department visits, severe hypoglycemia, and diabetic ketoacidosis
- Reminder about upcoming study visit

Additional phone contacts may be performed as needed.

5.3 Use of Blinded CGM by BGM Group

A blinded CGM sensor will be placed for the BGM group and worn for 7 days, with instructions to calibrate using the study provided BGM as indicated by the current sensor labeling.

The blinded sensor will be placed at a separate visit one week prior to each of the 8, 16, and 26-week study visits.

Participants will bring the CGM to the clinic at the next study visit.

The blinded sensor data will not be viewed by study staff involved in the care of the participant at the 8 and 16 week visits.

At the 26-week visit, sensor wear may be repeated for up to 7 additional days if there are fewer than 96 hours of glucose measurements for the blinded sensor wear between the 25 and 26 week visits. The 26-week visit will be deferred if blinded sensor wear is repeated.

CHAPTER 6: EXTENSION STUDY

6.1 CGM Group

Participants randomized to the CGM group will be given the opportunity to continue CGM and followed for 6 months. Site contact with the participant will be expected to approximate usual care.

- Visits will occur at 39 and 52 weeks. Procedures during these visits will reflect those completed at the 16 and 26 week RCT visits, respectively.

6.1 BGM Group

Participants in the BGM Group will be provided with a real-time CGM and sensors, unless the participant declines in which case the participant will be discontinued from the study.

- Participants will be instructed on use of the CGM and how to use CGM data to adjust diabetes management.
- Participants will receive CGM training during the 26 week visit of the RCT and will have an additional CGM training visit at approximately 28 weeks
- Additional study visits will occur at 39 and 52 weeks. Procedures during these visits will reflect those completed at the 16 and 26 week RCT visits, respectively.

Additional visits and phone contacts can be made as indicated.

CHAPTER 7: DATA COLLECTION AND TESTING PROCEDURES

Each questionnaire and testing procedure is described briefly below. The procedures for administration will be described in the study procedures manual.

1. Vision will be assessed using a near vision reading card binocularly. Participants will read the card and the smallest line the participant can read will be recorded. Administration time is approximately 5 minutes.
2. Hearing – assessed by self-report and recognition of CGM alarms.
3. Frailty 10-foot walk: This test will measure the time it takes for participant to walk 10 feet, to obtain an estimate of frailty. Administration time is approximately 10 minutes (30).
4. Hypoglycemic Awareness using the Clarke hypoglycemic unawareness scale (29): The Clark method of assessing Hypoglycemic Unawareness consists of 8 questions, which evaluate glycemic threshold for, and symptomatic responses to, hypoglycemia. Administration time is approximately 10 minutes.
5. Functional Activities Questionnaire (FAQ) (31). 10-item scale used as a measure of instrumental activities of daily living
6. Preferring Hypoglycemia Scale is a survey designed to measure attitudes toward hypoglycemia and hyperglycemia and fear of hyperglycemia (not yet published). Administration time is approximately 5 minutes.
7. Hypoglycemia Fear Survey (HFS-II) (32): The Hypoglycemia Fear Survey measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consists of a 10-item Behavior subscale that measured behaviors involved in avoidance and over-treatment of hypoglycemia and a 13-item Worry subscale that measures anxiety and fear surrounding hypoglycemia, each with a 5-choice Likert response format. Administration time is approximately 10 minutes.
8. Diabetes Distress Scale (DDS) (33): 28-item questionnaire used to measure diabetes-related concerns about powerlessness, management, hypoglycemia, social perceptions, eating, physician, and friends/family.
9. Glucose Monitoring System Satisfaction Survey (GMSS) (34): 15-item questionnaire used to assess glucose monitoring device-related treatment satisfaction and QOL that is appropriate for use with both CGM and SMBG (validated subscales in T1D include Openness, Emotional Burden, Behavioral Burden and Trust)
10. Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Short Form (35): 10-item measure of overall QOL that covers both physical and mental health (PROMIS; see www.nihpromis.org; can be used to generate an equivalent EQ-5D-5L score for use in utility analyses.)
11. NIH Toolbox Cognition Battery (NIHTB-CB, www.nihtoolbox.org) a ~30 minute computerized battery of neuropsychological tests with nationally representative normative data for ages 3-85. Cognitive domains assessed include executive functioning, attention, episodic memory, language, processing speed and working memory. In addition to individual measure scores, a Cognitive Function Composite Score, Fluid Cognition Composite Score and Crystallized Cognition Composite Score are also generated by the program.
12. NIH Toolbox Emotion Battery (NIHTB-EB, www.nihtoolbox.org) –a ~10 minute battery of computer adaptive measures of emotional function; the following selected measures within the following domains will be administered: Psychological Well Being (positive affect survey), Stress & Self-Efficacy (perceived stress survey and self-efficacy survey), Social Relationships (instrumental support survey and emotional support survey), and Negative Affect (fear-affect survey and sadness survey).
13. Cost Utility questionnaires – including the EuroQol EQ-5D-5L-5L and Optum SF-12V2v2 health utility instruments. Each are approximately 5-minute computer administered surveys assessing participants' current health status in specific dimensions such as mobility, pain, social functioning,

and ability to self-care. They are also validated as norm-based standard measures for conversion into a unidimensional preference measure of overall health status, for use in health utility assessments. Such preference-based health measures are required to support the calculation of health-related costs and benefits for the cost utility analysis.

CHAPTER 8: ADVERSE EVENTS AND RISKS

8.1 Definition

Reportable adverse events will include the following: severe hypoglycemia as defined below, hyperglycemia/diabetic ketoacidosis (DKA) as defined below, all device-related events with potential impact on participant safety, all falls or fractures, emergency room visits, and all events meeting criteria for a serious adverse event. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

Hypoglycemic events are recorded as Adverse Events only if the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Hyperglycemic events are recorded as Adverse Events if evaluation or treatment was obtained from a health care provider or if the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT), and had all of the following:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

In addition, hyperglycemia not meeting the definition of DKA will be reported as an adverse event if emergency evaluation or treatment was obtained at a health care facility; these events are considered Adverse Events and not Serious Adverse Events (SAE) unless one of the criteria for SAE is met.

8.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the study participant, and appropriate medical intervention will be made.

All reportable adverse events whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported on an adverse event form online. Each adverse event form is reviewed by the Medical Monitor at the Coordinating Center to verify the coding and the reporting that is required.

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study intervention. To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Yes

There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of

response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the adverse event has an etiology other than the study intervention (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events will be coded using the MedDRA dictionary.

Adverse events that continue after the study participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

8.3 Reporting Serious Adverse Events and Unexpected Adverse Device Events

A serious adverse event is any untoward occurrence that:

- Results in death.
- Is life-threatening (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

An *Unanticipated Adverse Device Event* is defined as an adverse event caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence.

Serious or unexpected device-related adverse events must be reported to the Coordinating Center within 24 hours via completion of the online serious adverse event form.

Other reportable adverse events and device malfunctions (with or without an adverse event) will be reported within 3 days of the investigator becoming aware of the event by completion of an electronic case report form.

Device complaints not associated with device malfunction or an adverse event must be reported within 7 days of the investigator becoming aware of the event.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to their institution.

8.4 Reportable Device Issues

All adverse device effects, device complaints, and device malfunctions will be reported irrespective of whether an adverse event occurred, except in the following circumstances.

The following device issues are anticipated and will not be reported on a Device Issue Form but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than 7 days
- CGM tape adherence issues
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement that don't meet criteria for AE reporting

8.5 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will provide independent monitoring of the study protocol including adverse events and device issues with potential impact on participant safety. Cumulative adverse event data will be semi-annually tabulated for review by the DSMB. Following each DSMB data review, a summary will be made available for submission to Institutional Review Boards. A list of specific adverse events to be reported to the DSMB expeditiously will be compiled and included as part of the DSMB Standard Operating Procedures.

8.6 Risks and Discomforts

8.6.1 CGM Sensor Inaccuracy

There is a small risk of using CGM for insulin dosing, without a confirmatory BGM measurement, due to the accuracy of the sensor and the possibility of an adverse event if the CGM glucose value substantially deviates from the true glucose level, particularly when an insulin bolus is given. This risk has been mitigated by advising participants to check the blood glucose when symptoms or expectations do not match the CGM reading.

8.6.2 Skin Reactions

There is a low risk for developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies. Sensors may fracture in situ on rare occasions. In the rare instances when this has occurred in the past, consulting physicians and surgeons have recommended not to remove the wire fragment from beneath the skin as long as there are no symptoms of infection or inflammation. In the event that signs and/or symptoms of infection or inflammation arise such as redness, swelling, and pain subjects should consult with the investigator or prescribing physician for the best course of action. If there is no portion of the broken sensor wire fragment visible above the skin, attempts to remove it without medical guidance are not advised.

During each follow-up visit, each site where a CGM sensor has been worn will be assessed by study personnel. Both acute and non-acute changes will be assessed (as described on the case report form and in the Procedures Manual). If a skin reaction is classified as severe (the observation is extremely noticeable and bothersome to participant and may indicate infection or risk of infection or potentially life-threatening allergic reaction) an Adverse Event Form will be completed.

8.6.3 Fingerstick Blood Glucose Measurements

Fingersticks may produce pain and/or ecchymosis at the site.

8.6.4 Psychosocial Questionnaires

As part of the study, participants and parents will complete psychosocial questionnaires which include questions about their private attitudes, feelings and behavior related to diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

The study may include other risks that are unknown at this time.

CHAPTER 9: MISCELLANEOUS CONSIDERATIONS

9.1 Benefits

It is expected that CGM devices will have an important role in the management of diabetes in older adults. Therefore, the results of this study are likely to be beneficial for patients with diabetes.

It is possible that participants will not directly benefit from being a part of this study. However, it is also possible that the blood glucose information from the monitor along with the information and instructions provided for management decisions will be useful for participants' diabetes self-management.

9.2 Participant Reimbursement

The study will provide the CGM and related supplies, for the randomized trial. Eligible study participant will also be provided a blood glucose meter and test strips. The study will provide the CGM and sensors for the extension study. Participants will be able to use the BGM from the RCT trial for the extension phase; however, test strips will not be provided for the extension portion of the study.

Participants will be provided with a reimbursement of $50 (which may be in the form of a gift card) for each completed protocol-required visit to help compensate for travel and other visit-related expenses. Participants randomized to the BGM Group will be provided a reimbursement of $25 for blinded sensor placement visits to help compensate for travel and other visit-related expenses. Additional travel expenses will be paid in select cases for participants with higher expenses. There will be no compensation for completing telephone calls or unscheduled visits.

Participants who complete the study will be able to keep the study BGM and CGM devices, assuming that commercially-available devices were used and the devices are functioning at the end of the study. Test strips for the BGM and sensors for the CGM to be used after the study will be the participant's responsibility.

9.3 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. Participants who discontinue using the study device should not be withdrawn and should continue study follow-up unless the participant requests to withdraw from the study.

9.4 Confidentiality

For security purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. During each visit, the study devices will be downloaded to a computer that is secured and password protected and the files will be uploaded to the Coordinating Center via the secure website for the study. Date of birth and email address will be required for creating an account in Dexcom Clarity. This information will be accessible to Dexcom. If participants do not want to provide their email or do not have an email address then an email account will be created for them. All files will include only the participant's identifier; no names or personal information will be included.

Laboratory specimens will be sent to the study central laboratory.

Data from the study may be provided to Dexcom, Inc., the company that makes the CGM.

9.5 Discontinuation of the Study

A study participant may be discontinued from the study if the investigator believes that it is not safe for the participant to continue.

The study may be discontinued if recommended by the DSMB for safety or other reasons or if funding for the study is lost.

CHAPTER 10: STATISTICAL CONSIDERATIONS

10.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

10.2 Statistical Hypothesis

- Null hypothesis: There is no difference in hypoglycemia (time spent <70 mg/dL) between those using CGM and those using BGM.
- Alternative hypothesis: There is a nonzero difference in hypoglycemia (time spent <70 mg/dL) between those using CGM and those using BGM.

10.3 Sample Size and Statistical Power

Among 138 BGM group participants in the JDRF CGM RCT who spent at least 2% of time <70 mg/dL during the baseline run-in, the estimated % of time < 70 mg/dL at baseline was 8% (115 minutes per day) and at 26 weeks was 7% (95% CI 6%, 8%) (100 minutes per day). The standard deviation of the 26-week time < 70 mg/dL adjusted for correlation with baseline was 4.5% (95% CI 4.0%, 5.0%) (65 minutes per day). For a conservative estimate the lower end of the BGM group estimate at 26-weeks (6%) and the upper end of the confidence interval for the standard deviation (5%) was used for sample size selection.

Table 1. Sample Size Estimates for Primary Hypoglycemia Outcome (% of time < 70 mg/dL)

SD	Power	Treatment Relative Reduction		
		33%	**50%**	**66%**
4%	**80%**	132	58	36
	85%	150	66	40
	90%	174	78	48
4.5%	**80%**	166	74	44
	85%	188	84	50
	90%	220	98	58
5%	**80%**	204	**90**	54
	85%	232	102	62
	90%	270	**120**	72

From Table 1 above, it can be seen that a sample size of 120 for a 1:1 randomization would have 90% power with a type 1 error rate of 5% (2-tailed) to detect a difference in time <70 mg/dL, assuming the true treatment effect is a 50% reduction in the time spent <70 mg/dL and the effective standard deviation is 5%.

Using the same assumptions, a sample size of 90 would have 80% power for secondary analyses conducted separately for pump and injection users (without adjusting for multiple comparisons). In order to accommodate these important secondary analyses and to account for participants with incomplete follow up, the sample size was selected to be 200 with the goal of having 180 participants complete the trial. With this sample size the power will be 98% for the primary analysis under the assumptions described above.

10.4 Efficacy Endpoints

Primary Efficacy Endpoint

- % time <70 mg/dL

Secondary Efficacy Endpoint

- *Hypoglycemia*
  - % time <54 mg/dL
  - % time <60 mg/dL
  - Rate of CGM measured hypoglycemic events (using <54 mg/dL)
- *HbA1c*
  - change in HbA1c from baseline to 26 weeks
  - % with HbA1c < 7.0%
  - % with HbA1c < 7.5%
  - % with relative reduction ≥ 10%
  - % with absolute reduction ≥ 0.5%
  - % with absolute reduction ≥ 1%
  - % with absolute reduction ≥ 1% or HbA1c < 7.0%
- *Glucose Control*
  - % time in range 70-180 mg/dL
  - mean glucose
  - glycemic variability measured by coefficient of variation
- *Hyperglycemia*
  - % time >180 mg/dL
  - % time >250 mg/dL
  - % time >300 mg/dL
- *Quality of Life/Patient Reported Outcome Questionnaires*
  - Hypoglycemia Fear Survey
  - Diabetes Distress Scale (DDS)
  - Glucose Monitoring System Satisfaction Survey (GMSS)
  - Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Short Form
  - Hypoglycemia Unawareness Assessment –Clarke survey
  - Preferring Hypoglycemia Scale
  - NIH toolbox emotions battery
- *Cognition*
  - Change in cognitive tests measured with NIH toolbox
- *Cost utility assessments*
  - EQ-5D-5L
  - SF-12V2

Each of the CGM metrics will be calculated over 24 hours, at nighttime (10pm-<6am), and daytime (6am-<10pm). Separate indices will be calculated at baseline and during follow-up as follows:

- Baseline: CGM metrics will be calculated based on data obtained in the run-in period prior to randomization. Note that only subjects who used the CGM for a minimum of 240 hours over at least 10 out of 14 days with an average of at least 1.8 calibrations per day, and had a minimum average of 2 BGM measurements per day during the blinded CGM screening period are eligible to be randomized.

- Follow-up: For approximately 1 week prior to the 8, 16, and 26 week visits, each subject in the BGM group will wear a blinded CGM to obtain data to calculate glycemic variables. All blinded data for the BGM group will be used in the analysis. To get a comparable sample of data from the CGM group (who are being asked to wear CGM continually during the study), data from similar time points will be used. The data will be pooled to calculate the glycemic metrics.

All other endpoints will be assessed at 26 weeks.

10.5 Analysis Datasets and Sensitivity Analyses

- Intention-to-Treat (ITT) Analysis Dataset will include all randomized participants.
- Safety Analysis Dataset will include all enrolled participants irrespective of whether the study was completed.
- Per-Protocol Analysis Dataset will include only compliant participants. It will be limited to participants who have at least 168 hours of CGM data and will exclude participants in BGM Group who started CGM prior to having 168 hours of blinded CGM data or who averaged fewer than 3 BGM measurements per day, and exclude those in the CGM group who were using CGM less than 5 days we week on average.

The primary analysis will follow the intention-to-treat principle. It will include all randomized participants, the data from whom will be analyzed in the group to which the participants were assigned through randomization. Available sensor data will be pooled; no minimum amount of CGM data will be required for inclusion in the analysis.

A per-protocol analysis will be performed to provide additional information regarding the magnitude of treatment effect. The per-protocol analysis will only be performed if at least 10% of randomized participants would be excluded by these criteria.

The intent-to-treat analysis is considered primary and if the results of the per-protocol analysis and intent-to-treat analysis differ, the per-protocol analysis will be interpreted with caution.

10.6 Analysis of the Primary Efficacy Endpoint

Mean ± SD or summary statistics appropriate to the distribution will be given by treatment group for percent of time spent <70 mg/dL. Percent of time <70 mg/dL will be compared between treatment groups by using a linear model adjusting for the baseline value and site as a random effect. A 95% confidence interval will be reported for the difference between the treatment groups based on the linear model. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or a non-parametric method based on ranks will be used instead.

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated in a sensitivity analysis by including factors potentially associated with the outcome for which there is an imbalance between groups.

10.7 Analysis of the Secondary Efficacy Endpoints

HbA1c

Mean ± SD values for the change in HbA1c from baseline to 26-weeks or summary statistics appropriate to the distribution will be given for each treatment group. The analysis of HbA1c will be done using direct likelihood. A longitudinal linear regression model will be fit with the central laboratory HbA1c value at baseline, 16 weeks and 26 weeks as the dependent variable. The local HbA1c measurement will be included as an auxiliary variable in the model when available. This model will adjust for site as a random effect.

Separate treatment arm effects will be modelled at 16 and 26 weeks by including a treatment by time interaction. The point estimate, 95% confidence interval and p-value at 26 weeks will be reported.

For binary HbA1c outcomes, the number and percent of subjects will be calculated by randomization group. Randomization groups will be compared using a logistic regression model adjusting for baseline HbA1c and site as a random effect. A risk adjusted difference and a 95% confidence interval will be calculated from the model.

CGM Metrics

Mean ± SD or summary statistics appropriate to the distribution will be given by treatment group. Each glycemic index will be compared between treatment groups by using a linear model adjusting for the baseline value and site as a random effect. A 95% confidence interval will be reported for the difference between the treatment groups based on the linear model. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or a non-parametric method based on ranks will be used instead.

Quality of Life/Patient Reported Outcome Questionnaires

Mean ± SD or summary statistics appropriate to the distribution will be given by treatment group. Each outcome will be compared between randomization groups by using a linear model adjusting for the baseline value and site as a random effect. Regression diagnostics will be performed similarly as described above for the primary outcome. For each component of the Emotions Battery we will compare the derived T-score.

NIH Toolbox Cognition Assessment

For the cognition assessment we will use the uncorrected Cognition Fluid Composite score. Mean ± SD or summary statistics appropriate to the distribution will be given by treatment group. The score will be compared between treatment groups by using a linear model adjusting for the baseline value and site as a random effect. Regression diagnostics will be performed similarly as described above for the primary outcome.

Cost Utility Assessments

Incremental cost-effectiveness ratios (ICERs) will be calculated, expressed as the average difference in net total costs between the intervention and BGM group, divided by the average difference in quality-adjusted life years. If the preliminary analyses demonstrate that the intervention is both cost-saving and beneficial (rendering the ICERs moot), we will instead calculate projected total net health benefits for the intervention, compared to usual care. Quality-adjusted life years (QALYs) will be constructed by combining information on morbidity and mortality events with utility scores (preference-weighted health-related quality of life) derived from the SF-12V2 and EQ-5D-5L-5L health utility instrument. The ICERs will be calculated according to generally recognized best practices, using two different timeframes and scopes: (1) using cost and QALY inputs derived directly from observed data and (2) employ spreadsheet modeling to project lifetime costs and health benefits, using parameter estimates derived from a literature review conducted specifically for this task.

The specific methods to be performed will be described in a separate document.

Missing Data

There will be no imputation of any missing data for secondary outcomes. Analyses will be available cases only. The analysis of HbA1c uses direct likelihood to handle the missing data.

10.8 Safety Analysis

All reportable adverse events will be tabulated by treatment group in a listing of each reported Medical Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ Class. Details will be provided in a listing of each event.

In addition, the following will be tabulated by treatment group:

- Number of adverse events
- Number of participants with at least one event
- Number of serious adverse events
- Number of participants with at least one serious adverse event
- Number of unexpected device events
- Number of unexpected serious device events
- Number of hospitalizations and reasons for and length of the hospitalization
- Number of ER visits and reasons for the visit
- Number of falls and injuries
- Number of adverse events thought by investigator to be related to study device
- Number of participants who stopped the intervention in response to an adverse event
- Hypoglycemic Events
    - Number of severe hypoglycemic events as defined in the Adverse Events Chapter
    - Number of severe hypoglycemic events associated with seizure or loss of consciousness
    - Number of participants experiencing at least one severe hypoglycemic event
    - Number of participants experiencing at least one severe hypoglycemic event associated with seizure or loss of consciousness
- DKA Events
    - Number of diabetic ketoacidosis events, as defined in the Adverse Events Chapter
    - Number of participants experiencing at least one diabetic ketoacidosis event

If there are enough events for analysis, the number of device-related events, falls, ER visits, hospitalizations, SH adverse events, and DKA events will be compared between treatment groups using Poisson regression with the number events as the outcome, the number of follow-up years as an offset, and whether the subject had an event in the previous 12 months (SH and DKA models) as a covariate. The analysis of rate of CGM defined hypoglycemic events (described above in the analysis of secondary endpoints) can also be interpreted as a safety analysis.

10.10 Protocol Adherence and Retention

The following will be performed according to treatment group:

- A flow chart accounting for all participants for all visits
- Tabulation of visit and phone contact completion rates for each follow-up visit
- Tabulation of protocol deviations
- Tabulation of modifications in diabetes management during the study
- Tabulation of number and reasons for unscheduled visits and phone calls
- Tabulation of device issues

10.11 Baseline Descriptive Statistics

Appropriate summary statistics will be tabulated by treatment group for baseline demographic and clinical characteristics.

10.12 Device Issues

For each reportable device issue as defined in section 8.4, the following will be tabulated:

- Onset date of the event
- Description of the event
- Intensity of the event
- Seriousness of the event
- Whether the event required treatment
- Outcome of the event

10.13 Planned Interim Analyses

Formal interim efficacy analyses are not planned as it is anticipated that recruitment will be completed prior to having sufficient outcome data for a meaningful analysis. Safety analyses will be performed at least every 6 months for review by the DSMB.

10.14 Pre-planned Sub-Group Analyses

Subgroup analyses/assessments of effect modification (interaction) will be conducted for the primary outcome. These analyses will be considered exploratory. Additionally, interpretation of the analyses will depend on whether the overall analysis demonstrates a significant treatment group difference; in the absence of such an overall difference, subgroup analyses will be interpreted with additional caution. The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the models used for the primary analyses. The baseline factors listed below will be assessed.

- Age
- Age at T1D diagnosis
- Baseline time spent < 70 mg/dL
- Baseline glycemic variability (coefficient of variation)
- Baseline HbA1c
- T1D duration
- Gender
- Race-ethnicity
- Baseline scores on cognitive measures
- Baseline assessment of hypoglycemic unawareness
- Preserved C-peptide at baseline

10.15 Multiple Comparison/Multiplicity

The primary analysis involves a single treatment arm comparison for just one primary efficacy endpoint, so no correction for multiple comparisons will be performed.

For the secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure.

10.16 Exploratory Analyses

An outcome combining hypoglycemia and hyperglycemia measures will be assessed and defined further in the SAP.

10.17 Additional Tabulations and Analyses

Analysis on 16-week data will parallel the 26-week analyses with regard to CGM metrics and HbA1c.

Analysis of all primary and secondary outcomes and the number of severe hypoglycemic adverse events will be replicated separately for pump users and MDI users. The interpretation of the analyses will depend on whether the overall analysis demonstrates a significant treatment group difference; in the absence of such an overall difference, this analyses will be interpreted with caution.

The median and IQR of average number of BGM checks/day will be tabulated by treatment group.

For the CGM group, days/week of CGM use will be tabulated by and visit and overall. The association between frequency of CGM use and use of the SHARE or follow feature and outcomes will be evaluated, as well as factors associated with increased use of CGM.

10.18 Extension Study

Analyses will be conducted within each treatment group comparing the 26-week RCT visit data (which serves as the baseline for this phase) with the data from the 13-week and 26-week visit data of this phase (study weeks 39 and 52). The variables assessed in these analyses will be similar to those described for the RCT. Pre-post comparisons will be made using parametric or nonparametric methods as indicated. Safety analyses will be similar to those described for the RCT.

Analyses include but are not limited to the following:

- Boxplots with data from both phases displaying outcomes from baseline to the end of the extension phase by randomization group at each visit
- Paired t-test to compare the control group at extension phase baseline vs. 26 weeks of extension phase for the primary outcome
- Similar analysis for CGM outcomes and questionnaires
- The number of hours of sensor data obtained in the week prior to the 13 and 26 week visits of the extension phase will be tabulated
- Any adverse events will be summarized as described above

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VERSION HISTORY

The following table outlines changes for the WISDM protocol:

VERSION NUMBER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	N/A	Original protocol version. Never actively used for enrollment of patients.
2.0	4/10/2017	Corrected Schedule of Visits and Procedures table and other minor modifications. Never actively used for enrollment of patients.
3.0	8/30/2017	Updated text for consistency and further clarification and added items inadvertently omitted throughout the protocol. Added Cost Utility Questionnaires to specific timepoints. Removed Functional Activities Questionnaire from the Extension Phase. Added the study is being conducted using the most currently approved version of the Dexcom CGM system available at the time of study initiation. The average number of calibrations per day was updated from 2 to 1.8. Corrected assessment order for questionnaires at the 26-week visit. Added there will be no participant compensation for unscheduled visits. Updated statistics chapter to match currently approved protocol template at JCHR. Added more detail and clarification to statistics chapter. Only version used for enrollment of patients

WIRELESS INNOVATION FOR SENIORS WITH DIABETES MELLITUS (WISDM)

STATISTICAL ANALYSIS PLAN V2.0

JAEB CENTER FOR HEALTH RESEARCH
15310 Amberly Drive | Suite 350 | Tampa, FL 33647 | 813.975.8690

Version History

The following table outlines changes made to the Statistical Analysis Plan.

Version Number	Protocol Version	Author	Approver	Effective Date	Study Stage
1.0	3.2	Lauren Kanapka	Craig Kollman	10/30/18	No analyses done
2.0	3.2	Lauren Kanapka	Craig Kollman	3/19/19	RCT phase has been completed by all participants. Analysis from version 1.1 completed and presented to study group and T1DX network at March 2019 T1DX annual meeting.

Version Number	Revision Description
1.0	Original Version
2.0	1) Edited the safety analysis for the case where a treatment group has zero events 2) Added insulin analysis

Approvals

Role	Digital Signature or Handwritten Signature/Date
Author: Lauren Kanapka	Lauren Kanapka I am the author of this document 2019-03-20 15:07-04:00
Senior Statistician: Craig Kollman	Craig Kollman I am approving this document 2019-03-20 15:14-04:00
JCHR Coordinating Center Director: Kellee Miller	Kellee Miller Digitally signed by Kellee Miller DN: cn=Kellee Miller ou=T1Dx Reason: I am approving this document Location: Date: 2019-03-25 09:25-04:00
Protocol Chair: Richard Pratley	20 MAR 2019

1. Study Overview

This document outlines the statistical analysis to be performed for the WISDM study. The approach to sample size and statistical analyses for this study are summarized below.

This is a multi-center, randomized, parallel study to assess the efficacy and safety of CGM compared with BGM in adults aged 60 or older with type 1 diabetes (T1D). Eligible subjects will be randomized to a treatment arm based on a 1:1 ratio, stratified by clinical site. The study includes a 2-3 week run-in phase where subjects will wear a blinded CGM to collect baseline data and assess competency and compliance in using the CGM device. Subjects who satisfy the minimum use requirements will be eligible to be randomized. The primary RCT involves 4 follow-up visits and 1 phone contact with 2 additional visits for blinded sensor placement in the BGM group

All analysis will compare the BGM to the CGM treatment arm. All p-values will be two-sided.

2. Changes from the Protocol Statistical Analysis Chapter

The following table summarizes the changes in the planned analysis that will be described in this document from what was originally detailed in the protocol.

Description of Change	Reason	Study Stage
Definition of nighttime for the purpose of analyzing CGM metrics was changed from 10pm-<6am to 12am-<6am	New recommendations on the definition of nighttime (1;2)	Follow-up safety data has been presented to the DSMB but no separate day and night analysis has been performed.

3. Statistical Hypothesis

- Null hypothesis: There is no difference in hypoglycemia (time spent <70 mg/dL) between those using CGM and those using BGM.
- Alternative hypothesis: There is a nonzero difference in hypoglycemia (time spent <70 mg/dL) between those using CGM and those using BGM.

4. Sample Size and Statistical Power

Data from the JDRF CGM RCT was used to estimate standard deviation of the % of time spent <70 mg/dL at 26 weeks adjusted for baseline (3). Among 138 BGM group participants who spent at least 2% of time <70 mg/dL during the baseline run-in, the estimated % of time < 70 mg/dL at baseline was 8% (115 minutes per day) and at 26 weeks was 7% (95% CI 6%, 8%) (100 minutes per day). The standard deviation of the 26-week time < 70 mg/dL adjusted for correlation with baseline was 4.5% (95% CI 4.0%, 5.0%) (65 minutes per day). For a conservative estimate the lower end of the BGM group estimate at 26-weeks (6%) and the upper end of the confidence interval for the standard deviation (5%) was used for sample size selection.

Table 1. Sample Size Estimates for Primary Hypoglycemia Outcome (% of time < 70 mg/dL)

SD	Power	Treatment Relative Reduction		
		33%	50%	66%
4%	80%	132	58	36
	85%	150	66	40
	90%	174	78	48
4.5%	80%	166	74	44
	85%	188	84	50
	90%	220	98	58
5%	80%	204	**90**	54
	85%	232	102	62
	90%	270	**120**	72

From Table 1 above, it can be seen that a sample size of 120 for a 1:1 randomization would have 90% power with a type 1 error rate of 5% (2-tailed) to detect a difference in time <70 mg/dL, assuming the true treatment effect is a 50% reduction in the time spent <70 mg/dL and the effective standard deviation is 5%.

Using the same assumptions, a sample size of 90 would have 80% power for secondary analyses conducted separately for pump and injection users (without adjusting for multiple comparisons). In order to accommodate these important secondary analyses and to account for participants with incomplete follow up, the sample size was selected to be 200 with the goal of having 180 participants complete the trial. With this sample size the power will be 98% for the primary analysis under the assumptions described above.

5. Efficacy Endpoints

Primary Efficacy Endpoint

- CGM % time <70 mg/dL

Secondary Efficacy Endpoint

Hypoglycemia

- CGM % time <54 mg/dL
- CGM % time <60 mg/dL
- Rate of CGM measured hypoglycemic events (using <54 mg/dL, see the definition in section 5.1)

HbA1c

- Change in HbA1c from baseline to 26 weeks
- % with HbA1c < 7.0%

- % with HbA1c < 7.5%
- % with relative reduction ≥ 10%
- % with absolute reduction ≥ 0.5%
- % with absolute reduction ≥ 1%
- % with absolute reduction ≥ 1% or HbA1c < 7.0%

Glucose Control

- CGM % time in range 70-180 mg/dL
- CGM mean glucose
- CGM glycemic variability measured by coefficient of variation (expressed as a percentage)

Hyperglycemia

- CGM % time >180 mg/dL
- CGM % time >250 mg/dL
- CGM % time >300 mg/dL

Quality of Life/Patient Reported Outcome Questionnaires

- Hypoglycemia Fear Survey (HFS) Worry Subscale
- Diabetes Distress Scale (DDS)
- Glucose Monitoring System Satisfaction Survey (GMSS)
- Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Short Form
    - Physical
    - Mental
- Hypoglycemia Unawareness Assessment –Clarke survey
- Preferring Hypoglycemia Scale
- NIH Toolbox Emotions Battery
    - Fear
    - Sadness
    - Positive Affect
    - Perceived Stress
    - Self-Efficacy
    - Emotional Support
    - Instrumental Support

Cognition

- NIH Toolbox Cognition Battery

Cost utility assessments

- EQ-5D
- SF-12

5.1. CGM Outcomes

Indices will be calculated at baseline and during follow-up as described below.

Baseline

CGM metrics will be calculated based on data obtained in the run-in period prior to randomization. Note that only subjects who used the CGM for a minimum of 240 hours over at least 10 out of 14 days with an average of at least 1.8 calibrations per day, and had a minimum average of 2 BGM measurements per day during the blinded CGM screening period are eligible to be randomized. There may be cases in which subjects start the run-in period but then get delayed before resuming again. To avoid large gaps in the data we will go back from randomization 30 days and then if necessary, 1 day at a time further until 240 hours of data are available.

26 week follow-up

For approximately 1 week prior to each of the 8, 16, and 26 week visits, each subject in the BGM group will wear a blinded CGM to obtain data to calculate glycemic variables. For this group, all post-randomization blinded data before the 26 week visit, if completed, or day 182 from randomization for subjects who dropped out will be used in the analysis.

To get a comparable sample of data from the CGM group (who are being asked to wear CGM continually during the study), sensor data will be used from day -7 to day -1 prior to each of the 8, 16, and 26 week visit. If this results in <72 hours of data for a visit, then we will go backwards another day until we obtain at least 72 hours of data or reach day -14, whichever occurs first. If the visit was missed, we will use the target visit date instead. The data will be pooled to calculate the glycemic metrics.

If a participant in the BGM group initiates real-time CGM with a non-study device and does not agree to also wear a blinded sensor at an 8, 16, or 26 week visit, but we are able to obtain their real time data, we will select a sample of data for that visit as described above for the CGM group. If a participant in the CGM group discontinues real-time CGM but agrees to wear a blinded sensor for a visit, we will include this data.

Hypoglycemic Events

Hypoglycemic events will be calculated as the number of hypoglycemic events per week of CGM data at baseline and follow-up. A hypoglycemic event is defined as 15 consecutive minutes with a sensor glucose value <54 mg/dL. At least 2 sensor values <54 mg/dL that are 15 or more minutes apart plus no intervening values ≥54 mg/dL are required to define an event. The end of the hypoglycemic event is defined as a minimum of 15 consecutive minutes with a sensor glucose concentration ≥70 mg/dL. At least 2 sensor values ≥70 mg/dL that are 15 or more

minutes apart with no intervening values <70 mg/dL, are required to define the end of an event. When a hypoglycemic event ends, the study participant becomes eligible for a new event.

Daytime vs. Nighttime

All CGM metrics will be calculated over 24 hours. In addition, all metrics will be calculated separately for daytime (6am-<12am) and nighttime (12am-<6am). Nighttime is defined differently than was stated in the protocol, but is pre-specified here. The daytime and nighttime versions of % time <70 mg/dL will be considered secondary endpoints, whereas the 24 hour version is the primary outcome.

5.2. HbA1c and Questionnaire Outcomes

All other non-CGM endpoints will be assessed at 26 weeks adjusted for baseline. The analysis window for these endpoints at the 26 week visit will be Day 182 from randomization ± 56 days. The analysis window for baseline will be randomization -56 days to +14 days. If no value is available within the analysis window, the endpoint will be treated as missing.

6. Analysis Datasets and Sensitivity Analyses

6.1. Analysis Datasets

- Intention-to-Treat (ITT) Analysis Dataset will include all randomized participants.
- Safety Analysis Dataset will include all enrolled participants irrespective of whether the study was completed.
- Per-Protocol Analysis Dataset will include only compliant participants. Compliance for each randomization group is defined below.

6.2. Sensitivity Analysis

Per-protocol Analysis

Per-protocol analysis will be limited to the primary outcome and will only be conducted if this dataset results in at least 10% of the subjects being excluded. The intent-to-treat analysis is considered primary and the per-protocol analysis is a sensitivity analysis. If the results of the per-protocol analysis and intent-to-treat give inconsistent results, exploratory analyses will be performed to evaluate possible factors contributing to the differences.

Subjects are considered compliant and will be included in the per protocol analysis if they meet the following criteria:

- Both groups:
  - Eligible for the study
  - ≥ 168 hours of follow-up data
  - 26 week visit within ± 28 days of the target 26 week visit date (Day 182 post-randomization)

- CGM group:
  - Average ≥ 5 days per week of CGM use (see section 0 for details of how this is calculated), which equates to >70% compliance with the CGM intervention
- BGM group:
  - Average ≥ 3 BGM measurements per day (see section 17.3 for details of how this is calculated)
  - Did not initiate non-study CGM before reaching 168 hours of follow-up blinded CGM data

Confounding

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. The primary analysis described below will include a pre-specified list of covariates. As an additional sensitivity analysis, any baseline demographic or clinical characteristics observed to be imbalanced between treatment groups will be added as covariates to the analyses of the primary outcome. The determination of a meaningful baseline imbalance will be based on clinical judgement and not a p-value.

Missing Data

It is worth emphasizing that any statistical method for handling missing data makes a number of untestable assumptions. The goal will be to minimize the amount of missing data in this study so that results and conclusions will not be sensitive to which method is used.

To that end, sensitivity analyses will be performed to explore whether results are similar when using different methods. The following methods will be applied:

- Direct likelihood (primary analysis described above)
- Rubin's multiple imputation (sensitivity analysis)
- Available cases only (sensitivity analysis)

7. Analysis of the Primary Efficacy Endpoint

The primary outcome will be a treatment group comparison of the percentage of sensor values in the hypoglycemic range (<70 mg/dL) adjusted for baseline.

7.1. Included Subjects

The primary analysis for this study will follow intention-to-treat as mentioned above and so will include all randomized subjects, regardless of how much CGM data is available.

7.2. Statistical Methods

Mean ± SD or summary statistics appropriate to the distribution will be given by treatment group for percent of time spent <70 mg/dL.

Primary analysis will be done using direct likelihood. A longitudinal linear regression model will be fit with the percent of time spent <70 mg/dL at baseline and follow-up (defined above) as

the dependent variable. This model will adjust site as a random effect. Primary analysis will report the point estimate, 95% confidence interval and p-value for the treatment group difference at follow-up. This model adjusts for baseline percent of time spent <70 mg/dL by forcing the treatment groups to have the same mean value at baseline. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or a non-parametric method based on ranks will be used instead.

8. Analysis of the Secondary Efficacy Endpoints

8.1. HbA1c

Mean ± SD values for the change in central lab HbA1c from baseline to 26-weeks or summary statistics appropriate to the distribution will be given for each treatment group. A longitudinal linear regression model will be fit with the central laboratory HbA1c value at baseline, 16 weeks and 26 weeks as the dependent variable. The local HbA1c measurement will be included as an auxiliary variable in the model when available. This model will adjust for site as a random effect. Separate treatment arm effects will be modelled at 16 and 26 weeks by including a treatment by time interaction. We will report the point estimate, 95% confidence interval and p-value for the treatment group difference in the central lab HbA1c at 26 weeks. This model adjusts for baseline HbA1c by forcing the treatment groups to have the same mean value at baseline. Inclusion of the 16 week data in the same model allows it to predict any missing values at 26 weeks analogous to imputation. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or a non-parametric method based on ranks will be used instead. However, previous experience suggests that HbA1c values will follow an approximate normal distribution.

The analysis windows for the lab and local HbA1c are:

- Baseline: Randomization -56 days to + 14 days
- 16 weeks: Day 112 from randomization ± 56 days
- 26 weeks: Day 182 from randomization ± 56 days

Where the windows overlap, priority will be given to the randomization and 26 week visits. If no result is available in the window, it will be considered missing.

The binary outcomes will be calculated using the central laboratory HbA1c values and analysis will be available cases only. Comparisons of the binary outcomes will be done using a logistic regression model adjusted for baseline HbA1c with site as a random effect. For the baseline adjustment, the central lab value will be used where available, otherwise the local value will be used instead. A risk adjusted difference and a 95% confidence interval will be calculated from the model.

8.2. CGM Metrics

Mean ± SD or summary statistics appropriate to the distribution will be given by treatment group. Each CGM metric will be compared between treatment groups by using a longitudinal linear regression model with the baseline and follow-up value as the dependent variable. The model will adjust for site as a random effect. A 95% confidence interval will be reported for the difference between the treatment groups at follow-up. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or a non-parametric method based on ranks will be used instead. Overall, daytime, and nighttime versions of each CGM metric will be analyzed separately.

8.3. Quality of Life/Patient Reported Outcome Questionnaires

For all questionnaires, results will be tabulated for each individual item on each questionnaire by treatment group. For each questionnaire, a summary score will be calculated as defined in the scoring guide, if available, otherwise the score will be based on the average response and then scaled accordingly. For the PROMIS short form, hypoglycemia unawareness assessment, and the functional activities questionnaire, all questions included in the score must be answered in order to calculate the score. For all other questionnaires, at least 75% of the questions must be completed to be scored. This 75% rule will be applied separately for the total score and each subscale so it is possible the sample size will be different for some subscales. The derived T-score will be used for the components of the Emotions Battery.

Mean ± SD or summary statistics appropriate to the distribution will be given by treatment group. For the questionnaires listed as an outcome measure above, the summary score will be compared between treatment groups by using a longitudinal linear regression model with the baseline and 26 week score as the dependent variable. The model will adjust for site as a random effect. Regression diagnostics will be performed similarly as described above for the primary outcome.

8.4. NIH Toolbox Cognition Assessment

For the cognition assessment we will use the uncorrected Cognition Fluid Composite score. Mean ± SD values (or summary statistics appropriate to the distribution) for the score at baseline and 26 weeks will be given by treatment group. The score will be compared between treatment groups by using a longitudinal linear regression model with the baseline and 26 week score as the dependent variable. The model will adjust for baseline picture vocabulary score and site as a random effect. Regression diagnostics will be performed similarly as described above for the primary outcome.

8.5. Cost Utility Assessments

Incremental cost-effectiveness ratios (ICERs) will be calculated, expressed as the average difference in net total costs between the intervention and BGM group, divided by the average difference in quality-adjusted life years. If the preliminary analyses demonstrate that the

intervention is both cost-saving and beneficial (rendering the ICERs moot), we will instead calculate projected total net health benefits for the intervention, compared to usual care. Quality-adjusted life years (QALYs) will be constructed by combining information on morbidity and mortality events with utility scores (preference-weighted health-related quality of life) derived from the SF-12 and EQ-5D-5L health utility instrument. The ICERs will be calculated according to generally recognized best practices, using two different timeframes and scopes: (1) using cost and QALY inputs derived directly from observed data and (2) employ spreadsheet modeling to project lifetime costs and health benefits, using parameter estimates derived from a literature review conducted specifically for this task.

The cost utility assessment will not be performed by JCHR; it will be performed by the University of Southern California (USC). The specific methods to be performed will be described in a separate document.

8.6. Missing Data

Missing data for the primary and secondary outcomes will be handled using direct likelihood.

Where baseline HbA1c is used as a covariate, the baseline central lab value will be used when available, otherwise the local screening value will be used instead.

9. Safety Analysis

9.1. Definitions

Adverse Events Related to Device Issues

The following device issues are anticipated and will not be reported on a Device Issue Form but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than 7 days
- CGM tape adherence issues
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement that don't meet criteria for AE reporting

Severe Hypoglycemia

A severe hypoglycemic event is defined as an event requiring assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively

to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Diabetic Ketoacidosis

Hyperglycemic events are recorded as Adverse Events if evaluation or treatment was obtained from a health care provider or if the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT), and had all of the following:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

In addition, hyperglycemia not meeting the definition of DKA will be reported as an adverse event if emergency evaluation or treatment was obtained at a health care facility; these events are considered Adverse Events and not Serious Adverse Events (SAE) unless one of the criteria for SAE is met.

9.2. Adverse Events Summary

All reportable adverse events will be tabulated by treatment group in a listing of each reported Medical Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ Class. All events that occurred after the day of randomization and on or before the day of the 26-week visit will be included. If the subject did not complete their 26-week visit then all events that occurred on or before day 182 from randomization will be included. Pre-randomization adverse events will be listed separately. Any events that occur after the 26 week visit (or day 182) will be included in the analysis of the extension phase.

For each event the following information will be reported:

- Onset date of the event
- Description of the event
- Intensity of the event
- Seriousness of the event
- Whether the event was related to the study procedure or device
- Outcome of the event

9.3. Comparison of Safety Outcomes between Treatment Groups

Treatment group comparisons will exclude events that occurred pre-randomization. For the following outcomes, mean ± SD or summary statistics appropriate to the distribution will be tabulated by treatment group.

- Number of adverse events
- Number of participants with at least one event
- Number of serious adverse events
- Number of participants with at least one serious adverse event
- Number of unexpected device events
- Number of unexpected serious device events
- Number of hospitalizations and reasons for and length of the hospitalization
- Number of ER visits and reasons for the visit
- Number of falls and injuries
- Number of adverse events thought by investigator to be related to study device
- Number of participants who stopped the intervention in response to an adverse event
- Hypoglycemic Events
    - Number of severe hypoglycemic events as defined in the Adverse Events Chapter
    - Number of severe hypoglycemic events associated with seizure or loss of consciousness
    - Number of participants experiencing at least one severe hypoglycemic event
    - Number of participants experiencing at least one severe hypoglycemic event associated with seizure or loss of consciousness
- DKA Events
    - Number of diabetic ketoacidosis events, as defined in the Adverse Events Chapter
    - Number of participants experiencing at least one diabetic ketoacidosis event

If there are enough events for analysis, the number of device-related events, falls, ER visits, hospitalizations, SH adverse events, and DKA events will be compared between treatment groups using Poisson regression with the number events as the outcome, the number of follow-up years as an offset, and whether the subject had an event in the previous 12 months (SH and DKA models) as a covariate. If there are outliers, then robust Poisson regression will be used.

In the case where one treatment group has zero events during the RCT phase, Poisson regression will not work. In this case we will instead use Fisher's exact test to compare the number of events between treatment groups.

There will be no adjustment for multiple comparisons for safety outcomes.

The analysis of rate of CGM defined hypoglycemic events (described above in the analysis of secondary endpoints) can also be interpreted as a safety analysis.

10. Protocol Adherence and Retention

The following will be performed according to treatment group:

- A flow chart accounting for all participants for all visits
- Tabulation of visit and phone contact completion rates for each follow-up visit
- Tabulation of protocol deviations
- Tabulation of modifications in diabetes management during the study – insulin regimen change or change in use of non-insulin medications for blood glucose control
- Tabulation of number and reasons for unscheduled visits and phone calls
- Tabulation of device issues

11. Baseline Descriptive Statistics

Appropriate summary statistics will be tabulated by treatment group for the following baseline demographic and clinical characteristics.

- Age
- Baseline time spent < 70 mg/dL
- Baseline glycemic variability
- Baseline HbA1c
- T1D duration
- Age at diagnosis
- Gender
- Race-ethnicity
- Highest level of education
- Annual household income
- Insurance status
- Insulin delivery method
- Total daily dose of insulin/kg
- Previous CGM use
- History of severe hypoglycemic event in past 12 months
- Preserved C-peptide at baseline

12. Device Issues

For each reportable device issue, the following will be tabulated:

- Type of device
- Type of device issue
- Onset date of the event
- If the issue was related to an AE
- If it was not related, the likelihood an AE could have occurred

- Whether the event met the definition for an Unanticipated Adverse Device Effect (UADE)

13. Planned Interim Analyses

Formal interim efficacy analyses are not planned as it is anticipated that recruitment will be completed prior to having sufficient outcome data for a meaningful analysis. Safety analyses will be performed at least every 6 months for review by the DSMB.

14. Pre-planned Sub-Group Analyses

Subgroup analyses/assessments of effect modification (interaction) will be conducted for the primary outcome. These analyses will be considered exploratory. Additionally, interpretation of the analyses will depend on whether the overall analysis demonstrates a significant treatment group difference; in the absence of such an overall difference, subgroup analyses will be interpreted with additional caution. The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the models used for the primary analyses.

The baseline factors listed below will be assessed. The p-value for any categorical variable will only be calculated if there are a minimum of 10 subjects per treatment.

- Age
- Baseline time spent < 70 mg/dL
- Baseline glycemic variability (coefficient of variation)
- Baseline HbA1c
- T1D duration
- Age of Diagnosis
- Gender
- Race-ethnicity (White non-Hispanic vs. non-White)
- Education (Some college or less vs, college graduate or more)
- Baseline scores on cognitive measures
- Baseline assessment of hypoglycemic unawareness (Aware/Uncertain vs. Reduced Awareness)
- Detectable C-peptide at baseline
- Number of SH events in the previous 12 months (0 vs. ≥1)

15. Multiple Comparison/Multiplicity

The primary analysis involves a single treatment arm comparison for just one primary outcome measure, so no correction for multiple comparisons will be performed.

For the secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure. For these analyses, the adjusted p-value and 95% confidence interval will be reported. The categories for FDR correction will be:

- HbA1c Outcomes
- Overall CGM Metrics
- Daytime CGM Metrics
- Nighttime CGM Metrics
- Questionnaires
- Subgroup Analysis
- HbA1c Outcomes (Pump Only)
- HbA1c Outcomes (MDI Only)
- CGM Metrics (Pump Only)
- CGM Metrics (MDI Only)
- Questionnaires (Pump Only)
- Questionnaires (MDI Only)

16. Exploratory Analyses

The metrics typically used to assess overall glycemic control such as time in range or HbA1c tend to be dominated by changes in hyperglycemia. A metric that equally weights hypoglycemia and hyperglycemia will be calculated as follows:

1. Rank all subjects from smallest to largest CGM % time <70 mg/dL and CGM % time >180 mg/dL.
2. For each subject sum the rank of CGM % time <70 mg/dL and CGM % time >180 mg/dL.

This outcome will be summarized and compared between treatment groups using the same approach as the analysis of the secondary CGM metrics detailed above.

17. Additional Tabulations and Analyses

17.1. 16 Week Analysis

Analysis at 16 weeks will be performed for all CGM metrics and HbA1c. Analysis will parallel the 26-week analysis described above. The 16 week CGM metrics will be calculated using follow-up data from the 8 and 16 week visits only. The analysis window for the 16 week HbA1c will be Day 112 from randomization ± 28 days.

17.2. Pump and MDI Analysis

Analysis of all primary and secondary outcomes and the number of severe hypoglycemic adverse events will be replicated separately for pump users and MDI users. Only overall CGM metrics (not separated for day and night) and total scores for questionnaires (not subscales) will be included. The interpretation of the analyses will depend on whether the overall analysis demonstrates a significant treatment group difference; in the absence of such an overall difference, this analyses will be interpreted with caution. Only those who did not switch insulin

delivery method during the RCT phase will be included and where a participant is using both pump and injections, they will be considered a pump user.

17.3. BGM Checks

At each visit the average number of BGM measurements over the previous 7 days is recorded in the case report form. The average number of BGM checks per day will be calculated as follows for baseline and follow-up:

- Baseline: We will prioritize the download value at the randomization visit, but if that is not available we will use the download at screening visit, and then if that is not available, the self-report at the screening visit.
- Follow-up: The data from each visit will be averaged to give an overall average number of BGM measurements per day. Priority will be given to downloaded data but self-reported data will be used if downloaded data are missing.

The median and IQR of average number of BGM checks/day will be tabulated by treatment group at baseline and follow-up. Treatment group comparison will be done using a longitudinal linear regression model with the BGM checks at baseline and follow-up as the dependent variable. This model will adjust for site as a random effect. If values are highly skewed then a transformation or a non-parametric method based on ranks will be used instead.

17.4. CGM Group

Frequency of CGM Use

The frequency of CGM use will be calculated for the CGM group only. Frequency will be calculated as a number of days per week

Since the CGM memory is limited to 28 days, average CGM use per week will only be assessed for the 4 weeks prior to each of the 4, 8, 16, and 26 week visits. Only unblinded data (data from the G5) will count towards CGM use. If a visit is missed or if a subject drops out before a visit and there is no available data, it will be counted as zero use. In the case where visit(s) occurred out of window and so the time between two visits was less than 4 weeks, compliance for the latter visit will only be assessed using the data that has been collected since the previous visit. Only one reading is required to count a day as positive CGM use. Days per week will be calculated by totaling the days with a CGM reading, dividing by the total assessed days, then multiplying by 7. If a visit was missed or the subject dropped out before the visit, the number of days assessed is assumed to be 28.

The median and IQR for days/week of CGM use will be tabulated by visit and overall. Overall CGM use will be tabulated by the following baseline characteristics: age, T1D duration, education, cognition status, gender, insulin method, HbA1c, history of SH event, hypoglycemic unawareness, hypoglycemia fear, and diabetes distress. In addition, overall CGM use will be

tabulated by the following characteristics at follow-up: SHARE use and glucose monitoring satisfaction. SHARE use is defined as the subject indicating they used the SHARE feature at both the 16 week and 26 week visit.

CGM Features

We will tabulate use of the following features by visit:

- Dexcom mobile application
- Dexcom SHARE feature
- Use of CGM to dose insulin and how often

18. Extension Study

Participants in the CGM group will be given the opportunity to continue CGM and followed for 6 months. Participants in the BGM Group will be provided with a real-time CGM and sensors, unless the participant declines in which case the participant will be discontinued from the study. CGM supplies will be provided for the duration of the extension phase, but BGM test strips will need to be supplied by the participant. Site contact with the participant will be expected to approximate usual care. BGM group participants participating in the extension phase will receive CGM training during the 26 week visit of the RCT and will have an additional CGM training visit at approximately 28 weeks. Additional study visits will occur at 39 and 52 weeks for both groups. Procedures during these visits will reflect those completed at the 16 and 26 week RCT visits, respectively.

Analyses will be conducted within each treatment group comparing the 26-week RCT visit data (which serves as the baseline for this phase) with the data from the 13-week and 26-week visit data of this phase (study weeks 39 and 52). The variables assessed in these analyses will be similar to those described for the RCT. Pre-post comparisons will be made using parametric or nonparametric methods as indicated. Safety analyses will be similar to those described for the RCT.

Analyses include but are not limited to the following:

- Boxplots with data from both phases displaying outcomes from baseline to the end of the extension phase by randomization group at each visit
- Paired t-test to compare the control group at extension phase baseline vs. 26 weeks of extension phase for the primary outcome
- Similar analysis for CGM outcomes and questionnaires
- The number of hours of sensor data obtained in the week prior to the 13 and 26 week visits of the extension phase will be tabulated
- Any adverse events will be summarized as described above

19. Post Hoc Analysis Added after Version 1.0

The following tabulations will be performed by treatment group:

- Total daily insulin dose per kg
- Basal insulin dose per kg
- Bolus insulin dose per kg
- Number of short-acting injections per day for injection users
- Number of bolus doses per day for pump users

Insulin dose, number of short-acting injections for injection users, and number of bolus doses for pump users will be compared between treatment groups using a direct likelihood model similar to the primary outcome. A longitudinal linear regression model will be fit with the summary score at baseline and 26 weeks as the dependent variable. All models will adjust for site as a random effect and the insulin dose model will also adjust for insulin delivery method. Only subjects who do not switch insulin method during phase the RCT phase will be included. The analysis will report the p-value for the pairwise treatment group differences at 26 weeks.

Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or a non-parametric method based on ranks will be used instead.

The false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure. A correction category will be added for these insulin comparisons.

20. References

1. Beyond A1C Writing Group. Need for regulatory change to incorporate beyond A1C glycemic metrics. Diabetes Care. 2018;41:e92-e94.
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3. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008;359(14):1464-76.