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# T1D Exchange

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**Wireless Innovation for Seniors with Diabetes Mellitus (WISDM)**

Version 3.2  
04-16-18

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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).

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

## 172 173 **1.2 Continuous Glucose Monitoring**

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

179  
180 Several randomized trials have demonstrated the efficacy of CGM when it is used on a regular basis by  
181 individuals with T1D, particularly adults (20-23). Among individuals with HbA1c levels above target,  
182 improvement has been demonstrated in HbA1c levels and in a reduction in biochemical hypoglycemia.  
183 Among individuals with HbA1c levels at or below target, CGM has been demonstrated to reduce  
184 biochemical hypoglycemia while at the same time maintaining excellent HbA1c levels better than a  
185 control group (24). While these trials have found consistent glycemic benefit with CGM use, it is clear  
186 that the amount of benefit is related to the amount of CGM use (22, 23).

187  
188 In addition, regular CGM users have reported substantial satisfaction with use of the device and improved  
189 QOL (25). The JDRF funded RCT of CGM in children and adults showed a modest improvement in  
190 hypoglycemia fear associated with CGM use in the adult cohort, but no changes in other more general  
191 measures of QOL (23). Langendam et al. found no benefit of continuous glucose monitoring on QOL in  
192 their Cochrane Review, although only 5 of 22 studies included QOL outcomes (26). However, all of these  
193 studies used earlier generation CGM devices. Based on the extremely high compliance with daily CGM  
194 use in recently completed trials coordinated by the Jaeb Center for Health Research using the Dexcom G4  
195 or G5 sensor, substantially higher patient satisfaction and improvement in QOL is likely with the current  
196 generation Dexcom device.

197  
198 CGM can alert when blood glucose is low or trending downward and this information can be  
199 automatically shared with others; features that may be particularly helpful for those at risk for SH.  
200 Polonsky and Hessler surveyed existing CGM users and found that older age was associated with a  
201 greater perceived benefit in hypoglycemia safety and interpersonal support, although the mean age of this  
202 sample was 41 years (25). Despite its potential benefits to reduce hypoglycemia and hypoglycemia fear,  
203 CGM is used by only a small proportion of older adults with T1D. In the T1D Exchange registry, only  
204 19% of adults over the age of 60 are using CGM, a percentage that likely over-represents CGM use in this  
205 age group since all of the registry participants, by selection, are seen by an endocrinologist who has a  
206 practice focused on T1D.

207  
208 None of the CGM randomized trials have included a substantial number of participants 60 years or older  
209 (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  $\geq 60$  years old with T1D for  $\geq 20$  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  $\geq 60$  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.

260 **1.5 Protocol Synopsis**

261 **1.5.1 Study Objective**

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

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

266

267 **1.5.2 Study Design**

268 6-month parallel group randomized clinical trial (RCT) comparing an intervention group using CGM with  
269 a control group following usual care (without CGM).

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

272

273 The RCT will be followed by an extension study

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

276

277 **1.5.3 Major Eligibility Criteria**

- 278 • Clinical diagnosis of T1D
- 279 • Age  $\geq 60.0$  years
- 280 • Insulin regimen involves either use of an insulin pump or multiple daily injections of insulin.
- 281 • No use of real-time CGM for diabetes management in past 3 months
- 282 • HbA1c  $\leq 10.0\%$
- 283 • Individual does not have a diagnosis of dementia

284

285 **1.5.4 Sample Size and Treatment Groups**

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

288

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

- 291 • CGM
- 292 • BGM

293

294 **1.5.5 Visit and Phone Contact Schedule During RCT**

295 Following randomization, the CGM Group will have a study visit at 10 days, while the BGM group will  
296 have a phone call for the 10 day contact. In-clinic study visits for both groups will occur at 4, 8, 16 and  
297 26 weeks. In addition to the in-clinic study visits, the BGM group will have blinded sensor placement  
298 visits one week prior to each of the 8, 16, and 26 week visits.

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300 **1.5.6 Main RCT Outcome Measures**

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

302 Secondary outcomes:

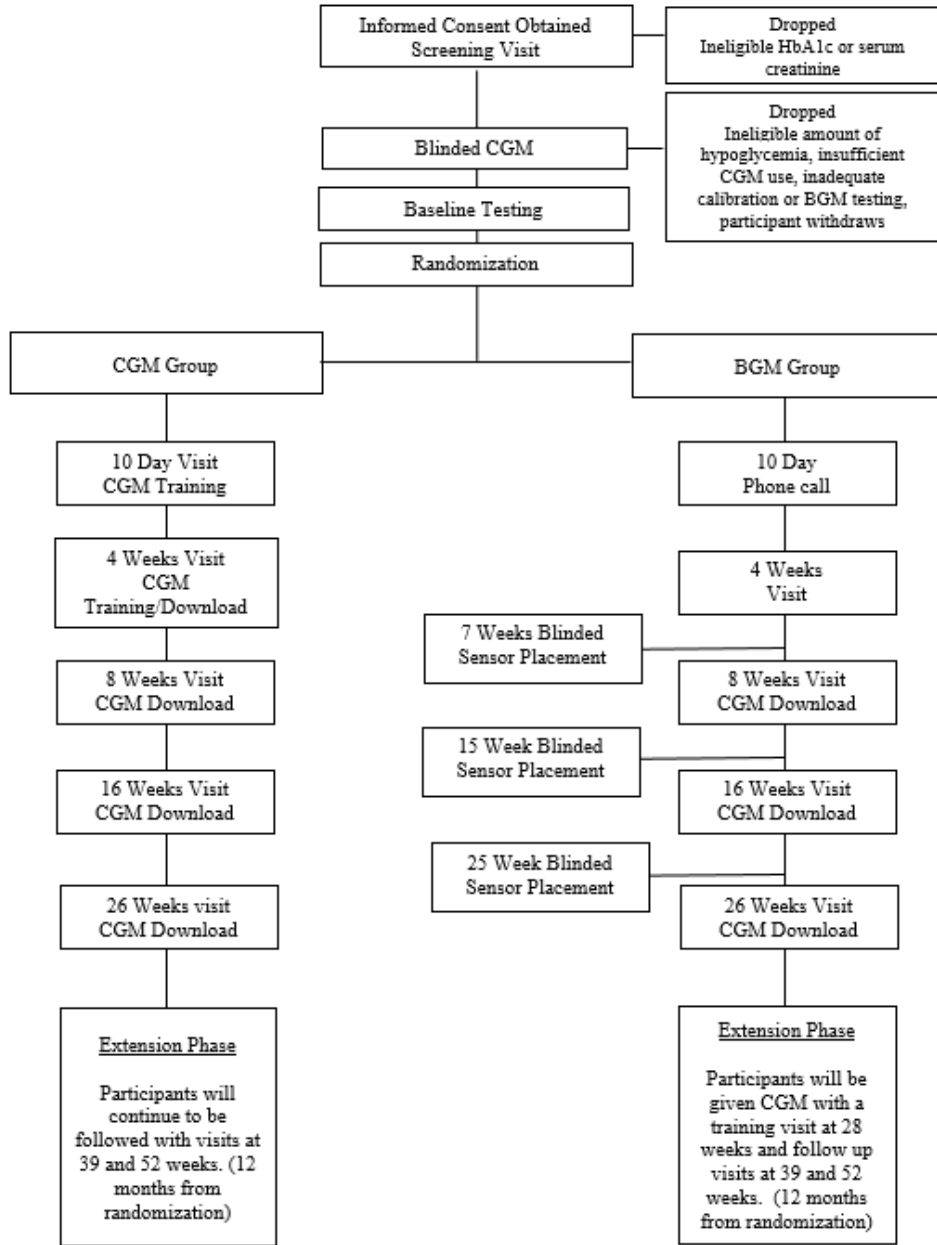
- 303 • Patient Reported Outcome measures: fear of hypoglycemia, attitudes towards hypoglycemia and  
304 hyperglycemia, diabetes distress, glucose monitoring satisfaction, general quality of life,  
305 emotional well-being
- 306 • HbA1c
- 307 • Episodes of severe hypoglycemia and diabetic ketoacidosis
- 308 • 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

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

<sup>a</sup>If not collected as usual care in the prior 30 days from the screening visit.

<sup>b</sup>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.

<sup>c</sup> Completed in Redcap or on paper if Redcap not possible.

<sup>d</sup>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

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**Main Randomized Trial**

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

330

<sup>a</sup>Study visit for CGM group. Phone call for BGM group

331

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

332

333

<sup>c</sup>Blinded CGM placement will occur in clinic one week prior to each of the 8, 16 and 26 week study visits.

334

335

<sup>d</sup>For CGM group only

336

337

<sup>e</sup>Completed at randomization visit if not already completed at screening visit or from home prior to randomization visit.

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339

<sup>f</sup>Completed in Redcap or on paper if Redcap not possible. Includes hypoglycemic fear survey, PROMIS QOL, Diabetes Distress,

340

Hypoglycemic Unawareness, Glucose Monitoring Satisfaction Survey,

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

**Extension Phase**

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

<sup>a</sup>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

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## 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.

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

400

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

404

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

407

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

410

411

## CHAPTER 2: ELIGIBILITY AND SCREENING VISIT

### 2.1 Study Population

Approximately 250-300 individuals  $\geq 60$  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 ( $< 95^{\text{th}}$  percentile pediatric and  $< 30$  kg/m<sup>2</sup> 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  $\geq 60$  years
- 3) HbA1c  $\leq 10.0\%$  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*

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

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

### 470 **2.3.2 Exclusion**

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

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

### 497 **2.4 Screening and Baseline Data Collection**

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

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

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

624

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

626

#### 627 **4.6 Initial Management Instructions**

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

632

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

635

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

638

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

640

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

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## 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)

- 693 ○ Hypoglycemia Fear Survey
- 694 ○ Diabetes Distress Scale (DDS)
- 695 ○ Glucose Monitoring System Satisfaction Survey (GMSS)
- 696 ○ Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health
- 697 Short Form
- 698 ○ Hypoglycemia Unawareness Assessment –Clarke survey
- 699 ○ Preferring Hypoglycemia Scale
- 700 ○ Cost utility questionnaires including EQ-5D-5L and SF-12V2
- 701 ○ NIH Cognitive Toolbox
- 702 ○ NIH Emotions Toolbox
- 703

### 704 **5.2.2 Phone Contacts**

705 A phone contact will be scheduled at the following times:

- 706 • 10 days ( $\pm 3$  days) – BGM group only
- 707

708 The purpose of the phone contact will be:

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

712 Additional phone contacts may be performed as needed.

713

### 714 **5.3 Use of Blinded CGM by BGM Group**

715 A blinded CGM sensor will be placed for the BGM group and worn for 7 days, with instructions to

716 calibrate using the study provided BGM as indicated by the current sensor labeling.

717

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

719 study visits.

720

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

722

723 The blinded sensor data will not be viewed by study staff involved in the care of the participant at the 8

724 and 16 week visits.

725

726 At the 26-week visit, sensor wear may be repeated for up to 7 additional days if there are fewer than 96

727 hours of glucose measurements for the blinded sensor wear between the 25 and 26 week visits. The 26-

728 week visit will be deferred if blinded sensor wear is repeated.

## CHAPTER 6: EXTENSION STUDY

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### 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](http://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.nihttoolbox.org](http://www.nihttoolbox.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.nihttoolbox.org](http://www.nihttoolbox.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,



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

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

857

858 **No**

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

862

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

867

868 Adverse events will be coded using the MedDRA dictionary.

869

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

873

874 **8.3 Reporting Serious Adverse Events and Unexpected Adverse Device Events**

875 A serious adverse event is any untoward occurrence that:

876

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

886

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

889

890 Serious or unexpected device-related adverse events must be reported to the Coordinating Center within  
891 24 hours via completion of the online serious adverse event form.

892

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

896

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

899

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

903

904 Each principal investigator is responsible for reporting serious study-related adverse events and abiding  
905 by any other reporting requirements specific to their institution.  
906

#### 907 **8.4 Reportable Device Issues**

908 All adverse device effects, device complaints, and device malfunctions will be reported irrespective of  
909 whether an adverse event occurred, except in the following circumstances.  
910

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

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

922

#### 923 **8.5 Data and Safety Monitoring Board**

924 A Data and Safety Monitoring Board (DSMB) will provide independent monitoring of the study protocol  
925 including adverse events and device issues with potential impact on participant safety. Cumulative  
926 adverse event data will be semi-annually tabulated for review by the DSMB. Following each DSMB data  
927 review, a summary will be made available for submission to Institutional Review Boards. A list of  
928 specific adverse events to be reported to the DSMB expeditiously will be compiled and included as part of  
929 the DSMB Standard Operating Procedures.  
930

#### 931 **8.6 Risks and Discomforts**

##### 932 **8.6.1 CGM Sensor Inaccuracy**

933 There is a small risk of using CGM for insulin dosing, without a confirmatory BGM measurement, due to  
934 the accuracy of the sensor and the possibility of an adverse event if the CGM glucose value substantially  
935 deviates from the true glucose level, particularly when an insulin bolus is given. This risk has been  
936 mitigated by advising participants to check the blood glucose when symptoms or expectations do not  
937 match the CGM reading.  
938

##### 939 **8.6.2 Skin Reactions**

940 There is a low risk for developing a local skin infection at the site of the sensor needle placement.  
941 Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies.  
942 Sensors may fracture in situ on rare occasions. In the rare instances when this has occurred in the past,  
943 consulting physicians and surgeons have recommended not to remove the wire fragment from beneath the  
944 skin as long as there are no symptoms of infection or inflammation. In the event that signs and/or  
945 symptoms of infection or inflammation arise such as redness, swelling, and pain subjects should consult  
946 with the investigator or prescribing physician for the best course of action. If there is no portion of the  
947 broken sensor wire fragment visible above the skin, attempts to remove it without medical guidance are  
948 not advised.  
949

950  
951 During each follow-up visit, each site where a CGM sensor has been worn will be assessed by study  
952 personnel. Both acute and non-acute changes will be assessed (as described on the case report form and  
953 in the Procedures Manual). If a skin reaction is classified as severe (the observation is extremely  
954 noticeable and bothersome to participant and may indicate infection or risk of infection or potentially life-  
955 threatening allergic reaction) an Adverse Event Form will be completed.

956  
957 **8.6.3 Fingerstick Blood Glucose Measurements**

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

959  
960 **8.6.4 Psychosocial Questionnaires**

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

965  
966 The study may include other risks that are unknown at this time.

967  
968

## 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.

1019  
1020 The study may be discontinued if recommended by the DSMB for safety or other reasons or if funding for  
1021 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.



1060 **10.4 Efficacy Endpoints**

1061  
1062 Primary Efficacy Endpoint

- 1063 - % time <70 mg/dL

1064 Secondary Efficacy Endpoint

1065 - *Hypoglycemia*

- 1066 • % time <54 mg/dL  
1067 • % time <60 mg/dL  
1068 • Rate of CGM measured hypoglycemic events (using <54 mg/dL)

1069 - *HbA1c*

- 1070 • change in HbA1c from baseline to 26 weeks  
1071 • % with HbA1c < 7.0%  
1072 • % with HbA1c < 7.5%  
1073 • % with relative reduction ≥ 10%  
1074 • % with absolute reduction ≥ 0.5%  
1075 • % with absolute reduction ≥ 1%  
1076 • % with absolute reduction ≥ 1% or HbA1c < 7.0%

1077 - *Glucose Control*

- 1078 • % time in range 70-180 mg/dL  
1079 • mean glucose  
1080 • glycemic variability measured by coefficient of variation

1081 - *Hyperglycemia*

- 1082 • % time >180 mg/dL  
1083 • % time >250 mg/dL  
1084 • % time >300 mg/dL

1085 - *Quality of Life/Patient Reported Outcome Questionnaires*

- 1086 • Hypoglycemia Fear Survey  
1087 • Diabetes Distress Scale (DDS)  
1088 • Glucose Monitoring System Satisfaction Survey (GMSS)  
1089 • Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Short  
1090 Form  
1091 • Hypoglycemia Unawareness Assessment –Clarke survey  
1092 • Preferring Hypoglycemia Scale  
1093 • NIH toolbox emotions battery

1094 - *Cognition*

- 1095 • Change in cognitive tests measured with NIH toolbox

1096 - *Cost utility assessments*

- 1097 • EQ-5D-5L  
1098 • SF-12V2  
1099

1100 Each of the CGM metrics will be calculated over 24 hours, at nighttime (10pm-<6am), and daytime  
1101 (6am-<10pm). Separate indices will be calculated at baseline and during follow-up as follows:

- 1102 • Baseline: CGM metrics will be calculated based on data obtained in the run-in period prior to  
1103 randomization. Note that only subjects who used the CGM for a minimum of 240 hours over at least  
1104 10 out of 14 days with an average of at least 1.8 calibrations per day, and had a minimum average  
1105 of 2 BGM measurements per day during the blinded CGM screening period are eligible to be  
1106 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  $\pm$  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  $\pm$  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.

1155 Separate treatment arm effects will be modelled at 16 and 26 weeks by including a treatment by time  
1156 interaction. The point estimate, 95% confidence interval and p-value at 26 weeks will be reported.  
1157

1158 For binary HbA1c outcomes, the number and percent of subjects will be calculated by randomization group.  
1159 Randomization groups will be compared using a logistic regression model adjusting for baseline HbA1c  
1160 and site as a random effect. A risk adjusted difference and a 95% confidence interval will be calculated  
1161 from the model.  
1162

#### 1163 CGM Metrics

1164 Mean  $\pm$  SD or summary statistics appropriate to the distribution will be given by treatment group. Each  
1165 glycemic index will be compared between treatment groups by using a linear model adjusting for the  
1166 baseline value and site as a random effect. A 95% confidence interval will be reported for the difference  
1167 between the treatment groups based on the linear model. Residual values will be examined for an  
1168 approximate normal distribution. If values are highly skewed then a transformation or a non-parametric  
1169 method based on ranks will be used instead.  
1170

#### 1171 Quality of Life/Patient Reported Outcome Questionnaires

1172 Mean  $\pm$  SD or summary statistics appropriate to the distribution will be given by treatment group. Each  
1173 outcome will be compared between randomization groups by using a linear model adjusting for the  
1174 baseline value and site as a random effect. Regression diagnostics will be performed similarly as  
1175 described above for the primary outcome. For each component of the Emotions Battery we will compare  
1176 the derived T-score.  
1177

#### 1178 NIH Toolbox Cognition Assessment

1179 For the cognition assessment we will use the uncorrected Cognition Fluid Composite score. Mean  $\pm$  SD or  
1180 summary statistics appropriate to the distribution will be given by treatment group. The score will be  
1181 compared between treatment groups by using a linear model adjusting for the baseline value and site as a  
1182 random effect. Regression diagnostics will be performed similarly as described above for the primary  
1183 outcome.  
1184

#### 1185 Cost Utility Assessments

1186 Incremental cost-effectiveness ratios (ICERs) will be calculated, expressed as the average difference in  
1187 net total costs between the intervention and BGM group, divided by the average difference in quality-  
1188 adjusted life years. If the preliminary analyses demonstrate that the intervention is both cost-saving and  
1189 beneficial (rendering the ICERs moot), we will instead calculate projected total net health benefits for the  
1190 intervention, compared to usual care. Quality-adjusted life years (QALYs) will be constructed by  
1191 combining information on morbidity and mortality events with utility scores (preference-weighted health-  
1192 related quality of life) derived from the SF-12V2 and EQ-5D-5L-5L health utility instrument. The ICERs  
1193 will be calculated according to generally recognized best practices, using two different timeframes and  
1194 scopes: (1) using cost and QALY inputs derived directly from observed data and (2) employ spreadsheet  
1195 modeling to project lifetime costs and health benefits, using parameter estimates derived from a literature  
1196 review conducted specifically for this task.  
1197

1198 The specific methods to be performed will be described in a separate document.  
1199

#### 1200 Missing Data

1201 There will be no imputation of any missing data for secondary outcomes. Analyses will be available  
1202 cases only. The analysis of HbA1c uses direct likelihood to handle the missing data.  
1203

1204 **10.8 Safety Analysis**

1205 All reportable adverse events will be tabulated by treatment group in a listing of each reported Medical  
1206 Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ  
1207 Class. Details will be provided in a listing of each event.

1208  
1209 In addition, the following will be tabulated by treatment group:

- 1210 • Number of adverse events
- 1211 • Number of participants with at least one event
- 1212 • Number of serious adverse events
- 1213 • Number of participants with at least one serious adverse event
- 1214 • Number of unexpected device events
- 1215 • Number of unexpected serious device events
- 1216 • Number of hospitalizations and reasons for and length of the hospitalization
- 1217 • Number of ER visits and reasons for the visit
- 1218 • Number of falls and injuries
- 1219 • Number of adverse events thought by investigator to be related to study device
- 1220 • Number of participants who stopped the intervention in response to an adverse event
- 1221 • Hypoglycemic Events
  - 1222 ○ Number of severe hypoglycemic events as defined in the Adverse Events Chapter
  - 1223 ○ Number of severe hypoglycemic events associated with seizure or loss of consciousness
  - 1224 ○ Number of participants experiencing at least one severe hypoglycemic event
  - 1225 ○ Number of participants experiencing at least one severe hypoglycemic event associated with
  - 1226 seizure or loss of consciousness
- 1227 • DKA Events
  - 1228 ○ Number of diabetic ketoacidosis events, as defined in the Adverse Events Chapter
  - 1229 ○ Number of participants experiencing at least one diabetic ketoacidosis event

1230  
1231 If there are enough events for analysis, the number of device-related events, falls, ER visits,  
1232 hospitalizations, SH adverse events, and DKA events will be compared between treatment groups using  
1233 Poisson regression with the number events as the outcome, the number of follow-up years as an offset,  
1234 and whether the subject had an event in the previous 12 months (SH and DKA models) as a covariate. The  
1235 analysis of rate of CGM defined hypoglycemic events (described above in the analysis of secondary  
1236 endpoints) can also be interpreted as a safety analysis.

1237  
1238 **10.10 Protocol Adherence and Retention**

1239 The following will be performed according to treatment group:

- 1240 • A flow chart accounting for all participants for all visits
- 1241 • Tabulation of visit and phone contact completion rates for each follow-up visit
- 1242 • Tabulation of protocol deviations
- 1243 • Tabulation of modifications in diabetes management during the study
- 1244 • Tabulation of number and reasons for unscheduled visits and phone calls
- 1245 • Tabulation of device issues

1246  
1247 **10.11 Baseline Descriptive Statistics**

1248 Appropriate summary statistics will be tabulated by treatment group for baseline demographic and clinical  
1249 characteristics.

1250

1251 **10.12 Device Issues**

1252 For each reportable device issue as defined in section 8.4, the following will be tabulated:

- 1253 • Onset date of the event
- 1254 • Description of the event
- 1255 • Intensity of the event
- 1256 • Seriousness of the event
- 1257 • Whether the event required treatment
- 1258 • Outcome of the event

1259

1260 **10.13 Planned Interim Analyses**

1261 Formal interim efficacy analyses are not planned as it is anticipated that recruitment will be completed  
1262 prior to having sufficient outcome data for a meaningful analysis. Safety analyses will be performed at  
1263 least every 6 months for review by the DSMB.

1264

1265 **10.14 Pre-planned Sub-Group Analyses**

1266 Subgroup analyses/assessments of effect modification (interaction) will be conducted for the primary  
1267 outcome. These analyses will be considered exploratory. Additionally, interpretation of the analyses will  
1268 depend on whether the overall analysis demonstrates a significant treatment group difference; in the  
1269 absence of such an overall difference, subgroup analyses will be interpreted with additional caution. The  
1270 general approach for these exploratory analyses will be to add an interaction term for the subgroup factor  
1271 by treatment into the models used for the primary analyses. The baseline factors listed below will be  
1272 assessed.

- 1273 • Age
- 1274 • Age at T1D diagnosis
- 1275 • Baseline time spent < 70 mg/dL
- 1276 • Baseline glycemic variability (coefficient of variation)
- 1277 • Baseline HbA1c
- 1278 • T1D duration
- 1279 • Gender
- 1280 • Race-ethnicity
- 1281 • Baseline scores on cognitive measures
- 1282 • Baseline assessment of hypoglycemic unawareness
- 1283 • Preserved C-peptide at baseline

1284

1285 **10.15 Multiple Comparison/Multiplicity**

1286 The primary analysis involves a single treatment arm comparison for just one primary efficacy endpoint,  
1287 so no correction for multiple comparisons will be performed.

1288

1289 For the secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-  
1290 Hochberg procedure.

1291

1292 **10.16 Exploratory Analyses**

1293 An outcome combining hypoglycemia and hyperglycemia measures will be assessed and defined further in  
1294 the SAP.

1295 **10.17 Additional Tabulations and Analyses**

1296 Analysis on 16-week data will parallel the 26-week analyses with regard to CGM metrics and HbA1c.

1297

1298 Analysis of all primary and secondary outcomes and the number of severe hypoglycemic adverse events  
1299 will be replicated separately for pump users and MDI users. The interpretation of the analyses will depend  
1300 on whether the overall analysis demonstrates a significant treatment group difference; in the absence of  
1301 such an overall difference, this analyses will be interpreted with caution.

1302

1303 The median and IQR of average number of BGM checks/day will be tabulated by treatment group.

1304

1305 For the CGM group, days/week of CGM use will be tabulated by and visit and overall. The association  
1306 between frequency of CGM use and use of the SHARE or follow feature and outcomes will be evaluated,  
1307 as well as factors associated with increased use of CGM.

1308

1309 **10.18 Extension Study**

1310 Analyses will be conducted within each treatment group comparing the 26-week RCT visit data (which  
1311 serves as the baseline for this phase) with the data from the 13-week and 26-week visit data of this phase  
1312 (study weeks 39 and 52). The variables assessed in these analyses will be similar to those described for the  
1313 RCT. Pre-post comparisons will be made using parametric or nonparametric methods as indicated. Safety  
1314 analyses will be similar to those described for the RCT.

1315

1316 Analyses include but are not limited to the following:

1317

- Boxplots with data from both phases displaying outcomes from baseline to the end of the extension phase by randomization group at each visit

1318

- Paired t-test to compare the control group at extension phase baseline vs. 26 weeks of extension phase for the primary outcome

1319

- Similar analysis for CGM outcomes and questionnaires

1320

- 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

1321

- Any adverse events will be summarized as described above

1322

1323

1324

1325

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1

## VERSION HISTORY

2 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

3

# WIRELESS INNOVATION FOR SENIORS WITH DIABETES MELLITUS (WISDM)

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STATISTICAL ANALYSIS PLAN V2.0



### 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	<div style="display: flex; align-items: center;"> <div style="margin-right: 20px;"> <p style="font-size: 24px; margin: 0;">Kellee Miller</p>  </div> <div style="font-size: 10px; line-height: 1.2;">             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           </div> </div>
Protocol Chair: Richard Pratley	 <div style="margin-left: 20px; font-family: cursive;"> <p>20 MAR 2019</p> </div>

1 **1. Study Overview**

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

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

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

13 **2. Changes from the Protocol Statistical Analysis Chapter**

14 The following table summarizes the changes in the planned analysis that will be described in this  
15 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.

16 **3. Statistical Hypothesis**

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

21 **4. Sample Size and Statistical Power**

22 Data from the JDRF CGM RCT was used to estimate standard deviation of the % of time spent  
23 <70 mg/dL at 26 weeks adjusted for baseline (3). Among 138 BGM group participants who  
24 spent at least 2% of time <70 mg/dL during the baseline run-in, the estimated % of time < 70  
25 mg/dL at baseline was 8% (115 minutes per day) and at 26 weeks was 7% (95% CI 6%, 8%)  
26 (100 minutes per day). The standard deviation of the 26-week time < 70 mg/dL adjusted for  
27 correlation with baseline was 4.5% (95% CI 4.0%, 5.0%) (65 minutes per day). For a  
28 conservative estimate the lower end of the BGM group estimate at 26-weeks (6%) and the upper  
29 end of the confidence interval for the standard deviation (5%) was used for sample size selection.

30  
31

**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

32 From Table 1 above, it can be seen that a sample size of 120 for a 1:1 randomization would have  
33 90% power with a type 1 error rate of 5% (2-tailed) to detect a difference in time <70 mg/dL,  
34 assuming the true treatment effect is a 50% reduction in the time spent <70 mg/dL and the  
35 effective standard deviation is 5%.

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

## 42 **5. Efficacy Endpoints**

### 43 Primary Efficacy Endpoint

- 44 • CGM % time <70 mg/dL

### 45 Secondary Efficacy Endpoint

#### 46 *Hypoglycemia*

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

#### 51 *HbA1c*

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

- 54 • % with HbA1c < 7.5%
- 55 • % with relative reduction  $\geq$  10%
- 56 • % with absolute reduction  $\geq$  0.5%
- 57 • % with absolute reduction  $\geq$  1%
- 58 • % with absolute reduction  $\geq$  1% or HbA1c < 7.0%

59 *Glucose Control*

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

64 *Hyperglycemia*

- 65 • CGM % time >180 mg/dL
- 66 • CGM % time >250 mg/dL
- 67 • CGM % time >300 mg/dL

68 *Quality of Life/Patient Reported Outcome Questionnaires*

- 69 • Hypoglycemia Fear Survey (HFS) Worry Subscale
- 70 • Diabetes Distress Scale (DDS)
- 71 • Glucose Monitoring System Satisfaction Survey (GMSS)
- 72 • Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health
- 73 Short Form
  - 74 ○ Physical
  - 75 ○ Mental
- 76 • Hypoglycemia Unawareness Assessment –Clarke survey
- 77 • Preferring Hypoglycemia Scale
- 78 • NIH Toolbox Emotions Battery
  - 79 ○ Fear
  - 80 ○ Sadness
  - 81 ○ Positive Affect
  - 82 ○ Perceived Stress
  - 83 ○ Self-Efficacy
  - 84 ○ Emotional Support
  - 85 ○ Instrumental Support

86 *Cognition*

- 87 • NIH Toolbox Cognition Battery

88 *Cost utility assessments*



- 89 • EQ-5D
- 90 • SF-12

## 91 **5.1. CGM Outcomes**

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

### 93 Baseline

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

### 101 26 week follow-up

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

106 To get a comparable sample of data from the CGM group (who are being asked to wear CGM  
107 continually during the study), sensor data will be used from day -7 to day -1 prior to each of the  
108 8, 16, and 26 week visit. If this results in <72 hours of data for a visit, then we will go backwards  
109 another day until we obtain at least 72 hours of data or reach day -14, whichever occurs first. If  
110 the visit was missed, we will use the target visit date instead. The data will be pooled to calculate  
111 the glyceic metrics.

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

### 117 Hypoglycemic Events

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

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

### 126 Daytime vs. Nighttime

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

## 132 **5.2. HbA1c and Questionnaire Outcomes**

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

## 137 **6. Analysis Datasets and Sensitivity Analyses**

### 138 **6.1. Analysis Datasets**

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

### 144 **6.2. Sensitivity Analysis**

#### 145 Per-protocol Analysis

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

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

- 153 • Both groups:
  - 154 ○ Eligible for the study
  - 155 ○  $\geq$  168 hours of follow-up data
  - 156 ○ 26 week visit within  $\pm$  28 days of the target 26 week visit date (Day 182 post-  
157 randomization)

- 158 • CGM group:
  - 159 ○ Average  $\geq 5$  days per week of CGM use (see section 0 for details of how this is
  - 160 calculated), which equates to  $>70\%$  compliance with the CGM intervention
- 161 • BGM group:
  - 162 ○ Average  $\geq 3$  BGM measurements per day (see section 17.3 for details of how this
  - 163 is calculated)
  - 164 ○ Did not initiate non-study CGM before reaching 168 hours of follow-up blinded
  - 165 CGM data

### 166 Confounding

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

### 173 Missing Data

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

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

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

## 182 **7. Analysis of the Primary Efficacy Endpoint**

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

### 185 **7.1. Included Subjects**

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

### 188 **7.2. Statistical Methods**

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

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

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

## 199 **8. Analysis of the Secondary Efficacy Endpoints**

### 200 **8.1. HbA1c**

201 Mean  $\pm$  SD values for the change in central lab HbA1c from baseline to 26-weeks or summary  
202 statistics appropriate to the distribution will be given for each treatment group. A longitudinal  
203 linear regression model will be fit with the central laboratory HbA1c value at baseline, 16 weeks  
204 and 26 weeks as the dependent variable. The local HbA1c measurement will be included as an  
205 auxiliary variable in the model when available. This model will adjust for site as a random effect.  
206 Separate treatment arm effects will be modelled at 16 and 26 weeks by including a treatment by  
207 time interaction. We will report the point estimate, 95% confidence interval and p-value for the  
208 treatment group difference in the central lab HbA1c at 26 weeks. This model adjusts for baseline  
209 HbA1c by forcing the treatment groups to have the same mean value at baseline. Inclusion of the  
210 16 week data in the same model allows it to predict any missing values at 26 weeks analogous to  
211 imputation. Residual values will be examined for an approximate normal distribution. If values  
212 are highly skewed then a transformation or a non-parametric method based on ranks will be used  
213 instead. However, previous experience suggests that HbA1c values will follow an approximate  
214 normal distribution.

215 The analysis windows for the lab and local HbA1c are:

- 216 • Baseline: Randomization -56 days to + 14 days
- 217 • 16 weeks: Day 112 from randomization  $\pm$  56 days
- 218 • 26 weeks: Day 182 from randomization  $\pm$  56 days

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

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

227 **8.2. CGM Metrics**

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

236 **8.3. Quality of Life/Patient Reported Outcome Questionnaires**

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

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

252 **8.4. NIH Toolbox Cognition Assessment**

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

260 **8.5. Cost Utility Assessments**

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

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

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

## 276 **8.6. Missing Data**

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

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

## 280 **9. Safety Analysis**

### 281 **9.1. Definitions**

#### 282 Adverse Events Related to Device Issues

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

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

#### 295 Severe Hypoglycemia

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

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

### 305 Diabetic Ketoacidosis

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

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

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

## 317 **9.2. Adverse Events Summary**

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

325 For each event the following information will be reported:

- 326 • Onset date of the event
- 327 • Description of the event
- 328 • Intensity of the event
- 329 • Seriousness of the event
- 330 • Whether the event was related to the study procedure or device
- 331 • Outcome of the event

### 332 9.3. Comparison of Safety Outcomes between Treatment Groups

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

- 336 • Number of adverse events
- 337 • Number of participants with at least one event
- 338 • Number of serious adverse events
- 339 • Number of participants with at least one serious adverse event
- 340 • Number of unexpected device events
- 341 • Number of unexpected serious device events
- 342 • Number of hospitalizations and reasons for and length of the hospitalization
- 343 • Number of ER visits and reasons for the visit
- 344 • Number of falls and injuries
- 345 • Number of adverse events thought by investigator to be related to study device
- 346 • Number of participants who stopped the intervention in response to an adverse event
- 347 • Hypoglycemic Events
  - 348 ○ Number of severe hypoglycemic events as defined in the Adverse Events Chapter
  - 349 ○ Number of severe hypoglycemic events associated with seizure or loss of
  - 350 consciousness
  - 351 ○ Number of participants experiencing at least one severe hypoglycemic event
  - 352 ○ Number of participants experiencing at least one severe hypoglycemic event
  - 353 associated with seizure or loss of consciousness
- 354 • DKA Events
  - 355 ○ Number of diabetic ketoacidosis events, as defined in the Adverse Events Chapter
  - 356 ○ Number of participants experiencing at least one diabetic ketoacidosis event

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

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

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

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



368 **10. Protocol Adherence and Retention**

369 The following will be performed according to treatment group:

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

377 **11. Baseline Descriptive Statistics**

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

- 380 • Age
- 381 • Baseline time spent < 70 mg/dL
- 382 • Baseline glycemic variability
- 383 • Baseline HbA1c
- 384 • T1D duration
- 385 • Age at diagnosis
- 386 • Gender
- 387 • Race-ethnicity
- 388 • Highest level of education
- 389 • Annual household income
- 390 • Insurance status
- 391 • Insulin delivery method
- 392 • Total daily dose of insulin/kg
- 393 • Previous CGM use
- 394 • History of severe hypoglycemic event in past 12 months
- 395 • Preserved C-peptide at baseline

396 **12. Device Issues**

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

- 398 • Type of device
- 399 • Type of device issue
- 400 • Onset date of the event
- 401 • If the issue was related to an AE
- 402 • If it was not related, the likelihood an AE could have occurred

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

### 405 **13. Planned Interim Analyses**

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

### 409 **14. Pre-planned Sub-Group Analyses**

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

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

- 419       • Age
- 420       • Baseline time spent < 70 mg/dL
- 421       • Baseline glycemic variability (coefficient of variation)
- 422       • Baseline HbA1c
- 423       • T1D duration
- 424       • Age of Diagnosis
- 425       • Gender
- 426       • Race-ethnicity (White non-Hispanic vs. non-White)
- 427       • Education (Some college or less vs, college graduate or more)
- 428       • Baseline scores on cognitive measures
- 429       • Baseline assessment of hypoglycemic unawareness (Aware/Uncertain vs. Reduced  
430        Awareness)
- 431       • Detectable C-peptide at baseline
- 432       • Number of SH events in the previous 12 months (0 vs.  $\geq 1$ )

### 433 **15. Multiple Comparison/Multiplicity**

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

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

- 439 • HbA1c Outcomes
- 440 • Overall CGM Metrics
- 441 • Daytime CGM Metrics
- 442 • Nighttime CGM Metrics
- 443 • Questionnaires
- 444 • Subgroup Analysis
- 445 • HbA1c Outcomes (Pump Only)
- 446 • HbA1c Outcomes (MDI Only)
- 447 • CGM Metrics (Pump Only)
- 448 • CGM Metrics (MDI Only)
- 449 • Questionnaires (Pump Only)
- 450 • Questionnaires (MDI Only)

## 451 **16. Exploratory Analyses**

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

- 455 1. Rank all subjects from smallest to largest CGM % time <70 mg/dL and CGM % time  
 456 >180 mg/dL.
- 457 2. For each subject sum the rank of CGM % time <70 mg/dL and CGM % time >180  
 458 mg/dL.

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

## 461 **17. Additional Tabulations and Analyses**

### 462 **17.1. 16 Week Analysis**

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

### 467 **17.2. Pump and MDI Analysis**

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

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

### 476 **17.3. BGM Checks**

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

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

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

### 491 **17.4. CGM Group**

#### 492 Frequency of CGM Use

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

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

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

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

### 512 CGM Features

513 We will tabulate use of the following features by visit:

- 514 • Dexcom mobile application
- 515 • Dexcom SHARE feature
- 516 • Use of CGM to dose insulin and how often

## 517 **18. Extension Study**

518 Participants in the CGM group will be given the opportunity to continue CGM and followed for  
519 6 months. Participants in the BGM Group will be provided with a real-time CGM and sensors,  
520 unless the participant declines in which case the participant will be discontinued from the study.  
521 CGM supplies will be provided for the duration of the extension phase, but BGM test strips will  
522 need to be supplied by the participant. Site contact with the participant will be expected to  
523 approximate usual care. BGM group participants participating in the extension phase will receive  
524 CGM training during the 26 week visit of the RCT and will have an additional CGM training  
525 visit at approximately 28 weeks. Additional study visits will occur at 39 and 52 weeks for both  
526 groups. Procedures during these visits will reflect those completed at the 16 and 26 week RCT  
527 visits, respectively.

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

534 Analyses include but are not limited to the following:

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

543 **19. Post Hoc Analysis Added after Version 1.0**

544 The following tabulations will be performed by treatment group:

- 545 • Total daily insulin dose per kg
- 546 • Basal insulin dose per kg
- 547 • Bolus insulin dose per kg
- 548 • Number of short-acting injections per day for injection users
- 549 • Number of bolus doses per day for pump users

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

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

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

561 **20. References**

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