# CGM Intervention in Teens and Young Adults with T1D (CITY):

## A Randomized Clinical Trial to Assess the Efficacy and Safety of Continuous Glucose Monitoring in Young Adults 14-<25 with Type 1 Diabetes

**Version Number: 3.0**

**9 APR 2018**

# KEY ROLES

*Provide a list of persons, companies, and/or groups serving in **key roles** in the conduct or oversight of the trial. This should include the medical monitor, investigator responsible for the overall conduct of the trial (Protocol Chair), JCHR Director of the Coordinating Center (JCHR PI)), and any clinical laboratory(ies), reading centers, or other key central units.*

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|---|---|
| | |
| **Protocol Chair/Director** | |
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| **Title** | Chief, Pediatric, Adolescent & Young Adult Section, Senior Investigator |
| **Institution Name** | Joslin Diabetes Center |
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| **JCHR Coordinating Center Director** | |
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| **Medical Monitor** | |
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| **Title** | Executive Director |
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| | |
| **Medical Monitor** | |
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| | |
| **Name, degree** | |
| **Title** | |
| **Institution Name** | |

# VERSION HISTORY

The following table lists versions of the protocol.

| VERSION NUMBER | AUTHOR | APPROVER | EFFECTIVE DATE | REVISION DESCRIPTION |
|---|---|---|---|---|
| 1.0 | TJ Mouse | Kellee Miller | 17AUG2017 | Original protocol version |
| 2.0 | TJ Mouse | Kellee Miller | 10NOV2017 | Changes to eligibility criteria to remove certain blinded run-in CGM requirements. Allowance of 2 Week Visit for CGM Group to be either in clinic or a remote telemedicine contact. Removed mention of cognitive testing. Updated statistical analysis chapter. Correction of typos. |
| 3.0 | Kellee Miller | | | Amendment to extension phase to include 2nd randomization |

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# LIST OF ABBREVIATIONS

*Add any abbreviations used in the protocol document. The use of abbreviations should be minimized to only those that are commonly known.*

| ABBREVIATION | DEFINITION |
|---|---|
| **A1C** | Hemoglobin A1C (also HbA1c) |
| **AE** | Adverse Event |
| **BGM** | Blood Glucose Meter |
| **BLINDED CGM** | Receiver does not display CGM values, trends, or glucose alerts/alarms in real time. Receiver provides use prompts and features such as calibration requests, device failures, troubleshooting icons, event markers, etc |
| **CGM** | Continuous Glucose Monitoring |
| **CRA** | Clinical Research Associate |
| **CRF** | Case Report Form |
| **CSII** | Continuous Subcutaneous Insulin Infusion |
| **DCCT** | Diabetes Control & Complications Trial |
| **DKA** | Diabetic Ketoacidosis (as defined by the DCCT) involves 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 |
| **DM** | Diabetes Mellitus |
| **EDC** | Electronic Data Capture |
| **eGFR** | Estimated Glomerular Filtration Rate: a renal function test determined by a blood test for creatinine |
| **EQ5D** | EuroQol 5D PRO measure |
| **HCP** | Health Care Professional |
| **IRB** | Institutional Review Board |
| **ITT** | Intent to treat (analysis) |
| **MDI** | Multiple Daily Injections |
| **mg/dL** | Milligrams per deciliter |
| **POC** | Point of Care |
| **PP** | Per Protocol (analysis) |
| **PRO** | Patient Reported Outcome |
| **QALY** | Quality-Adjusted Life-Years |
| **QoL** | Quality of Life |
| **RCT** | Randomized Controlled Trial |
| **RT-CGM** | Real-Time Continuous Glucose Monitoring System |
| **SAE** | Serious Adverse Event |

| | |
|---|---|
| **SEVERE HYPOGLYCEMIA** | Reduced cognitive function, diaphoresis, tachycardia, coma and seizure. Hypoglycemia is deemed severe if the event required assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that the subject was unable to treat his or herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. |
| **SMBG** | Self-Monitored Blood Glucose |
| **SC** | Study Coordinator |
| **T1DM** | Type 1 Diabetes Mellitus |
| **T2DM** | Type 2 Diabetes Mellitus |
| **UADE** | Unanticipated Adverse Device Effect |

# PROTOCOL SUMMARY

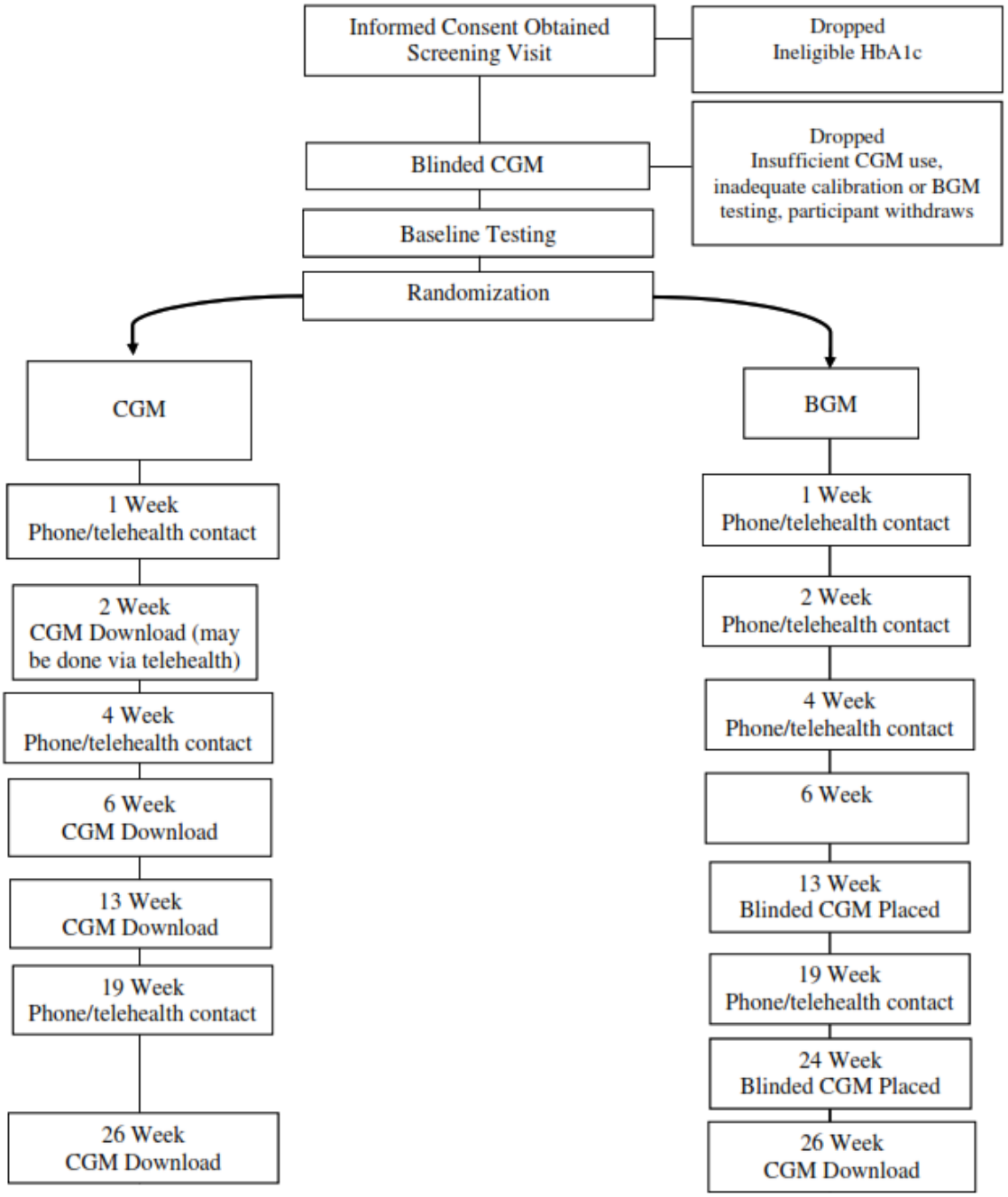
| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| **Title** | CGM Intervention in Teens and Young Adults with T1D (CITY): A Randomized Clinical Trial to Assess the Efficacy and Safety of Continuous Glucose Monitoring in Young Adults 14-<25 with Type 1 Diabetes |
| **Précis** | Adolescents and young adults with T1D and poor glycemic control (age 14-< 25 years, T1D duration >12 months, HbA1c 7.5-<11.0%, using an insulin pump or MDI)) will be randomly assigned to either CGM or BGM for a 6 month period (phase 1). Sample size will be 150. The primary outcome assessment will be HbA1c after 6 months. Secondary outcomes will include HbA1c, CGM metrics (control group will wear blinded CGM at 13 and 24 weeks), and quality of life measures. The randomized trial will be followed by a 6-month extension study (Phase 2) during which the BGM group will be randomized to receive real-time CGM with or without alarms set for high and low glucose alerts and the CGM group will be given a choice to use or not use alarms. |
| **Investigational Device** | Dexcom CGM |
| **Objectives** | Phase 1: The primary objective of phase 1 is to assess the efficacy and safety of CGM compared with BGM in adolescents and young adults age 14 to 24 years with type 1 diabetes (T1D). A secondary objective will be to assess the degree of perseverance with CGM use and identify potential factors associated with high and low CGM use to help inform future interventions to enhance CGM use. The latter findings will have relevance for the adoption of future technologies involving automated insulin delivery.<br>Phase 2: The primary objective of phase 2 is to assess durability of use and sustained glycemic benefit for the phase 1 CGM group over a 12 month period and to explore the effect of CGM without alarms on glucose control, quality of life, CGM use and satisfaction compared with CGM with alarms turned on in the phase 1 BGM group. |
| **Study Design** | Phase 1: 6-month parallel group randomized clinical trial (RCT) comparing an intervention group using CGM with a control group using BGM<br>• The RCT will be preceded by a screening period in which blinded CGM will be used to assess compliance and as data for baseline assessment.<br>Phase 2: The Phase 1 RCT will be followed by an extension study which will include a 2nd randomization for the BGM group to either:<br>• Real-time CGM with alarms for low and high glucose<br>• Real-time CGM without alarms for low and high glucose (alarm for low glucose < 55 mg/dl will remain on)<br>The phase 1 CGM group will continue to use CGM either with or without alarms. |
| **Number of Sites** | **Up to 15** |
| **Endpoints** | Primary Efficacy Outcome: HbA1c at 26 weeks adjusted for baseline HbA1c.<br>Key Secondary Efficacy Outcomes: CGM metrics (time in sensor glucose range 70-180 mg/dl, time > 180 mg/dl, , time > 300 mg/dl, time < 54 mg/dl, time < 70 mg/dl, coefficient of variation, mean glucose)<br>Key Safety Outcomes: Occurrence of DKA and SH events |

| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| | Other Key Outcomes: patient reported outcomes on quality of life, glucose monitoring satisfaction<br>Exploratory outcomes for phase 2 will include all of the above as well as CGM use |
| **Population** | **Key Inclusion Criteria**<br>• Type 1 diabetes<br>• Age 14-<25 years at time of consent<br>• Diabetes duration ≥ 1 year<br>• HbA1c 7.5% to <11.0% (Point of care device or local lab)<br>• Insulin regimen involves either use of an insulin pump or at least 3 multiple daily injections of basal and bolus (meal time) analogue insulin. Insulin pump must not have been started within 3 months of consent with no plans to change regimens in the next 6 months<br>• Perform at least 2 blood glucose meter checks per day from self-report at screening and an average of at least 2 checks per day from meter download during pre-randomization blinded CGM wear<br>• Blinded CGM must be used a minimum of 200 hours (equivalent to 8.3 days) with an average of at least 1.8 calibrations per day during the blinded CGM screening period.<br>**Key Exclusion Criteria**<br>• Use of unblinded personal RT-CGM and/or flash CGM, outside of a research study, as part of real-time diabetes management in the last 3 months<br>• More than 1 episode of DKA in the past 6 months as defined in the adverse events chapter.<br>• Need for use of acetaminophen or acetaminophen-containing products on a regular basis during the 6 months of the trial |
| **Sample Size** | 150 |
| **Treatment Groups for Phase 1 RCT** | Random assignment (1:1) to CGM or BGM |
| **Participant Duration** | 6-12 months |
| **Protocol Overview/Synopsis** | 1. Informed consent obtained.<br>2. After consent is signed and eligibility is determined, a blinded CGM sensor will be inserted. Training will be provided on insertion of the sensor, its use in blinded mode, and sensor calibration. Participants will insert a second sensor at home after approximately 7 days and continue using the blinded sensor for an additional 7 days. Participants will use their own home blood glucose meter for CGM calibrations and regular blood glucose monitoring. If the participant does not have a downloadable meter then a meter and test strips will be provided by the study<br>3. The participant will return around 14 to 21 days to assess the blinded CGM data for eligibility to continue into the RCT. For eligibility:<br>• CGM must be used for at least 200 hours and calibrated on average at least 1.8 times per day. Meter download of fingersticks must average at least 2 times per day (if insufficient CGM data, blinded CGM may be repeated at investigator discretion).<br>4. Eligible participants will be randomly assigned to the CGM or BGM control group.<br>• Participants in the CGM group will be instructed on how to utilize the CGM data for diabetes management and participants |

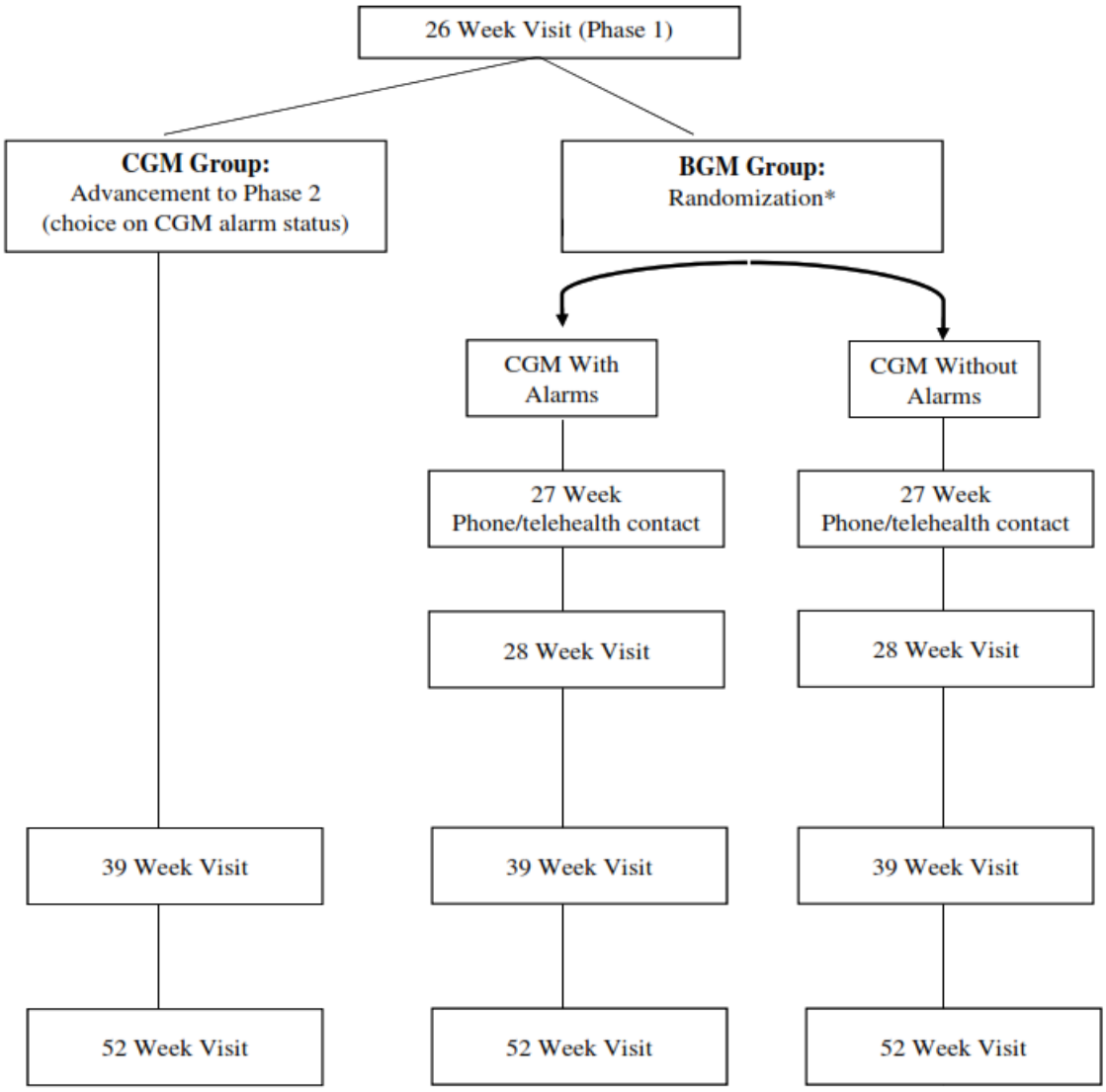
| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| | in the BGM group will receive instructions on how to optimally use SMBG in their diabetes management including checking at least 4 times daily and adjusting insulin doses as indicated. Both groups will be given the same guidelines for HbA1c and glucose targets.<br>• A participant 'social marketing' handout will be used to encourage consistent and durable CGM use in the CGM group by noting how the addition of CGM – a relatively new diabetes technology – can reduce the workload of T1D self-care while optimizing glycemic outcomes (reduced BG monitoring and therapeutic dosing with CGM use).<br>5. Visits will occur at 2 weeks (CGM group only and may be done as telehealth chat if warranted), 6 weeks, 13 weeks and 26 weeks. Contacts by phone or video telehealth chat will occur at 1 week, 2 weeks (CGM group may have in person visit if needed) 4 weeks, and 19 weeks. The BGM group will have an extra blinded sensor placement visit at 24 weeks.<br>• Blinded study sensors will be placed at 13 and 24 weeks for the control group and worn for 7 and 14 days respectively, with instructions to calibrate at least 2 times per day using BGM. Participants will return the blinded CGM by mail following the 13 week visit and in person at the 26-week visit for which they will be asked to come to clinic 2 weeks prior to the 26-week visit for sensor placement and return the CGM at the 26-week visit.<br>6. After the 26-week visit, Phase 2 will initiate<br>• Participants in the BGM group will be randomized to real-time CGM with or without alarms and followed for 6 months. The CGM group will continue using CGM and be given a choice whether or not to turn alarms off. Visits will occur at 2 weeks (for BGM group) and at 39 and 52 weeks. |

# SCHEMATIC OF STUDY DESIGN

**Phase 1:**



**Phase 2:**




*Participants in the BGM group who do not wish to be randomized to no alarms will be given the opportunity to initiate CGM with alarms and followed for 6 months following same Phase 2 visit schedule as those randomized

# SCHEDULE OF STUDY VISITS AND PROCEDURES

## Phase 1: Randomized Trial

| Visit – weeks from Rand<br>Visit or Contact | Screening<br>V | Rand<br>V | 1w<br>C | [a]2w<br>V or C | 4w<br>C | 6w<br>V | 13w<br>V | 19w<br>C | 24w<br>V BGM Only | 26w<br>V |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Window** | | | ±3 d | ±7d | | ±7d | ±7d | ±7d | ±7d | ±7d |
| **Blinded CGM Placement and training on placing sensor*** | X | | | | | | X* | | X* | |
| **Real Time CGM Initiated (CGM Group)** | | X | | | | | | | | |
| **Review diabetes management (CGM training for CGM group as needed)** | X | X | X | X | X | X | X | X | | X |
| **Pre-randomization compliance assessment** | | X | | | | | | | | |
| **HbA1c-point of care** | X[a] | | | | | X | X | | | X |
| **Blood draw or finger stick for central lab HbA1c sample and C-peptide + glucose at rand only** | | X | | | | | X | | | X |
| **Physical Exam including height, weight and blood pressure** | X | | | | | | X | | | X |
| **Skin Assessment** | | X | | X | | X | X | | | X |
| **CGM download** | | X | X[b] | X | X[b] | X | X | X[b] | | X |
| **Questionnaires[c]** | X | | | | | | X | | | X |
| **Medical history, medications and/or adverse events ascertainment** | X | X | X | X | | X | X | X | X | X |

*For control group and for participants in CGM group who have discontinued real-time CGM use (if willing)

[a]A historical HbA1c measures within 30 days of screening visit may be used instead

[b]BGM group will have a phone call or video chat. CGM group will have option for either phone call/video chat or visit.

[c]CGM group asked to download CGM at home if possible

[d] Questionnaires include Hypoglycemia Confidence, Diabetes Technology Attitudes, Pittsburg Sleep Quality, Life Events Checklist, Problem Areas in Diabetes (PAID) Survey, Glucose Monitoring Satisfaction Survey, Benefits and Barriers of CGM and Share, and CGM Self Efficacy. Participants who discontinue CGM during the study will be asked to complete an additional questionnaire at the subsequent study visit.

**Phase 2: Extension Phase 2nd Randomization**

| Visit or Phone-weeks | 26w (same visit as 26 week for Phase 1) | 27 week phone call/ video chat Phase 1 BGM Only | 28w Visit Phase 1 BGM Only | 39w Visit | 52w Visit |
|---|---|---|---|---|---|
| **Visit Window** | | **±3d** | **±7d** | **±7d** | **±14d** |
| **Randomization to CGM with or without alarms (Phase 1 BGM group)*** | **X** | | | | |
| **CGM Real-time Placement & Training (Phase 1 BGM group)** | **X** | **X** | **X** | | |
| **Skin Assessment** | **X** | | **X** | **X** | **X** |
| **Review Diabetes Management** | **X** | **X** | **X** | **X** | **X** |
| **HbA1c-point of care** | **X** | | | **X** | **X** |
| **HbA1c-central lab** | **X** | | | **X** | **X** |
| **Physical Exam including height, weight and BP** | **X** | | | **X** | **X** |
| **Skin assessment** | **X** | | **X** | **X** | **X** |
| **Data download** | **X** | | **X** | **X** | **X** |
| **Questionnaires** | **X** | | | | **X** |
| **Medical history, medications and/or adverse events ascertainment** | **X** | **X** | **X** | **X** | **X** |

*Participants in the BGM group who do not wish to be randomized to no alarms will be given the opportunity to initiate CGM with alarms and followed for 6 months following same Phase 2 visit schedule as those randomized

# Chapter 1: Background Information

## 1.1 Introduction

Glycemic control remains suboptimal in the overwhelming majority of adolescents and young adults with type 1 diabetes, with only 17% of adolescents 13-17 years old and only 14% of older teens and young adults ages 18-25 attaining HbA1c goals of <7.5% and <7%, respectively (1). Advanced diabetes technologies, in general, and continuous glucose monitors (CGM), in particular, offer opportunities to improve glycemic control without increasing the occurrence of severe hypoglycemia. However, adolescents and young adults have not embraced CGM like their adult counterparts, likely due to many factors, including poor CGM device performance in early devices, alerts and alarms considered more nuisance than benefit, and the additional efforts needed to utilize the device (insertion, calibration, etc.) with no reduction in overall diabetes self-care efforts as BG monitoring remained fundamental to BG management. In addition, the vulnerable age group of adolescents and young adults encounter many competing distractions, like academics, athletics, social activities, work, etc., that compete with attention to diabetes self-care tasks, especially if additional effort and attention is needed. Notably, a recent study in adolescents aimed at identifying motivations for BG monitoring identified that teens were 2.3 times more likely to check their BG levels when they wanted to 'fit-in' and keep up with their peers, suggesting a means to motivate these young patients to use CGM to aid in their maintaining and supporting their daily routines (2).

The JDRF CGM RCT highlighted the reality of CGM use in adolescents and young adults. CGM usage was substantially lower in 15 to 24 year olds than in younger children 8-14 or in adults aged 25+. After 6 months, only 30% of the adolescents and young adults were using CGM 6 or more days per week and 14% had discontinued CGM (including 1 drop-out). This contrasts with 83% of those 25 years old or older using CGM consistently at least 6 days per week for the 6 month trial with only 6% discontinuing CGM use (including 2 drop-outs) and 50% of those 8-14 years old using CGM at least 6 days per week for the 6 month trial with only 4% discontinuing CGM use (no drop-outs) (3). However, among those who were using CGM on a daily or near-daily basis, improvement in glycemic control was similar, independent of age group.

## 1.2 Rationale

Substantial improvements have been made in CGM technology since the conduct of the JDRF CGM RCT. Indeed, CGM performance has now approached that of BG monitoring technology with MARD of 10% or less for the Dexcom 505 algorithm in both pediatric and adult patients with diabetes (4, 5). Nevertheless, CGM use by adolescents and young adults remains low, with the most recent T1D Exchange data finding CGM used by only 17% of 14 to 24 year olds. A recently published study with a protocol approximating usual practice of poorly-controlled adults with type 1 diabetes (T1D) using multiple daily injections of insulin (mean baseline HbA1c 8.5%) found that ~ 90% of participants used CGM (Dexcom G4 with 505 software) $\geq$6 days/week over the entire 6 months with only 2 or 102 (2%) discontinuing CGM (6). A substantial and significant reduction in HbA1c, hyperglycemia, and hypoglycemia was seen compared with the usual care control group. CGM Satisfaction Scale scores were extremely

high, much higher than they were in the JDRF CGM RCT. These study results in device-naïve adults suggests that greater persistence with CGM use and improvements in glycemic control may now be possible in adolescents and young adults. In addition, the improved performance of CGM devices and the recognized improvements in glycemic control in association with CGM use have supported the recent FDA ruling in December 2016 to approve non-adjunctive use of the Dexcom CGM device. Thus, it is timely to evaluate if the vulnerable group of adolescents and young adults with suboptimal glycemic control will embrace CGM uptake as well as consistent (at least 6 days per week) and durable (for 6 months) use of CGM, especially now that CGM can used non-adjunctively, reducing some of the previous burden associated with CGM use.

In Phase 2, in addition to assessing sustained benefit of CGM in the CGM group we plan to assess whether reducing the burden of CGM caused by alerts and alarms improves glycemic control. Comparing CGM with and without alarms is of particular interest in the adolescent and young adult population who have reported alarm fatigue as reason for CGM discontinuation in previous studies (7, 8). In this phase, we also plan to explore whether removing alarms increases use of the CGM and improves satisfaction.

## 1.3 Potential Risks and Benefits of the CGM Device

### 1.3.1 Known Potential Risks

There is a small risk of using CGM for insulin dosing, without a confirmatory BGM measurement, due to the accuracy of the sensor and the possibility of an adverse event if the CGM glucose value substantially deviates from the true glucose level, particularly when CGM data are used to determine the amount of a corrective insulin bolus. This risk will be mitigated by providing guidelines for when a confirmatory BGM measurement should be performed and advising participants to check the blood glucose when symptoms or expectations do not match the CGM reading. (Of note, as outlined above, the FDA on December 20, 2016 approved this non-adjunctive use of the Dexcom G5 mobile system CGM as a replacement for BGM as used in this study.)

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

During each follow-up visit, each site where a CGM sensor has been worn will be assessed by study personnel. If a skin reaction is classified as severe (the observation is extremely noticeable and bothersome to participant and may indicate infection or risk of infection or potentially life-

threatening allergic reaction), treatment for the reaction will be administered and an Adverse Event Form will be completed.

Finger sticks may produce pain and/or ecchymosis at the site.

As part of the study, participants will complete psychosocial questionnaires which include questions about their private attitudes, feelings and behavior related to diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon. If study participants express emotional distress, study staff will assist with referrals to appropriate mental health resources as needed.
There is a possible risk of unsecured communication during the telehealth contacts.
The study may include other risks that are unknown at this time.

#### 1.3.2 Known Potential Benefits

It is expected that CGM devices will have an important role in the management of diabetes in adolescents and young 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.

#### 1.3.3 Risk Assessment

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

#### 1.3.4 General Considerations

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

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

# Chapter 2: Study Enrollment and Screening

## 2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of at least 150 participants completing the trial. A maximum of 200 individuals may be enrolled in the study in order to achieve this goal. Participants who have signed consent and started the screening process may be permitted to continue into the trial, if eligible, even if the randomization goal has been reached.

Study participants will be recruited from up to 15 clinical centers in the United States. All eligible participants will be included without regard to gender, race, or ethnicity.

The study will aim to meet the following enrollment quotas:

- At least 33% of participants using multiple daily injections for insulin delivery
- At least 33% using pump for insulin delivery.
- At least 33% of participants with an HbA1c $\geq$ 9.0%.
- At least 33% of participants between the ages of 19 and 24 years of age.

Recruitment may be restricted in order to achieve the targeted quotas.

### 2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. 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 >18 years old, the study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the informed consent form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

For potential participants under 18 years of age, a parent/legal guardian (referred to subsequently as "parent") will be provided with the informed consent form to read and will be given the opportunity to ask questions. Potential participants meeting the IRB's minimum age of assent will be given the consent form or an assent form depending on IRB requirements to read and discuss with his/her parents and study personnel. If the parent and adolescent agree to participate, the informed consent form and assent Form (if applicable) will be signed. A copy of the consent form will be provided to the participant and his/her parent and another copy will be added to the participant's study record.

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 the study-specific information that 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.

A participant is considered enrolled when the informed consent form has been signed.

If a participant turns 18 years old during the course of the study, the consenting process will be repeated and the participant must sign a new consent form.

## 2.2 Participant Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1) Clinical diagnosis of T1D
2) Age 14-<25 years
3) Diabetes duration ≥ 1 year
4) Total daily insulin requirement ≥ 0.4 units/kg/day
5) HbA1c 7.5% to <11.0% *(Point of care device or local lab measured within 30 days of consent or at the time of screening visit)*
6) Insulin regimen involves a consistent modality of insulin administration with either use of an insulin pump or at least 3 multiple daily injections of basal and bolus (meal time) analogue insulin. Insulin pump must not have been started within 3 months of consent with no plans to change regimens in the next 6 months
7) Perform at least 2 blood glucose meter checks per day from self-report at screening and an average of at least 2 checks per day from meter download during blinded CGM run in
8) Blinded CGM must be used a minimum of 200 hours (equivalent to 8.3 days) with an average of 1.8 calibrations per day during the blinded CGM screening period.
9) Participant comprehends written and spoken English
10) Participant understands the study protocol and agrees to it (if applicable)

## 2.3 Participant Exclusion Criteria

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

Individuals who meet any of the following criteria are <u>not</u> eligible for the study:

1) Use of unblinded personal CGM and/or flash CGM, , as part of real-time diabetes management in the last 3 months
2) Skin reaction from adhesive that would preclude participation in the randomized trial
3) Started on non-insulin medication for blood glucose control within the past 3 months or plans to begin within the next 6 months
4) The presence of a significant medical disorder that in the judgment of the investigator will affect the wearing of the sensors (such as a skin condition), or the completion of any aspect of the protocol.
5) More than 1 episode of DKA in the past 6 months as defined in the adverse events chapter.
6) The presence of any of the following diseases:

- Asthma or any condition present in the last 6 months where treatment is a systemic or daily inhaled corticosteroid
  - *Intermittent treatment with inhaled corticosteroids does not exclude subjects from enrollment*
- Cystic fibrosis
- Addison's disease
  - Adequately treated thyroid disease and celiac disease do not exclude subjects from enrollment

7) Inpatient psychiatric treatment in the past 6 months or daily intensive outpatient psychiatric day treatment in the past 3 months.
8) Pregnant (positive test confirmed at screening) or planning to become pregnant in the next 12 months.
9) Need for use of acetaminophen or acetaminophen-containing products on a regular basis during the 6 months of the Phase 1 trial
10) Participation in a diabetes related intervention study in the past 6 weeks.
11) Any medical, psychological or social situation where per investigator discretion it may be difficult for participant to participate fully in the intervention
12) Any condition, per investigator assessment, that could impact reliability of the A1C measurement, such as (but not limited to) hemoglobinopathy, hemolytic anemia, chronic liver disease; chronic GI blood loss, red blood cell transfusion or erythropoietin administration within 3 months prior to screening

## 2.4 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by study personnel and local laboratory testing if needed to screen for exclusionary medical conditions.

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion.

### 2.4.1 Data Collection and Testing

A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or designee (a physician, fellow, nurse practitioner or a physician assistant).

The following procedures will be performed/data collected/eligibility criteria checked and documented:

- Inclusion and exclusion criteria assessed
- Demographics (date of birth, sex, race and ethnicity)
- Socioeconomic status
- Contact information (retained at the site and not entered into study database)
- Medical history
- Concomitant medications
- Physical examination to include:
  - Weight, height

- Vital signs including measurement of blood pressure and pulse
- Fingerstick or blood draw for:
  - HbA1c level measured using a point of care device or local lab will be used to assess eligibility unless a historical value is available within 30 days of the screening visit.
- Urine or serum pregnancy test for all women who have reached menarche and are premenopausal and are not surgically sterile
- Participant questionnaires including CGM Self Efficacy, Problem Areas in Diabetes (PAID) Survey--pediatric version, Glucose Monitoring Satisfaction, Hypoglycemia Confidence, Diabetes Technology Attitudes, Sleep Quality, Life Events, and Benefits and Barriers of CGM and Share
- Questionnaires may be done at the screening visit or from home between the screening and randomization visits.

### 2.4.2 Blinded Continuous Glucose Monitoring

If eligibility is confirmed, a blinded CGM sensor will be inserted as instructed by study personnel and the participant will be instructed on its use and care. Additional sensors 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 200 hours (equivalent to 8.3 days) with an average of 1.8 calibrations per day and a minimum average of 2 BGM measurements per day from meter download during the blinded wear

### 2.4.3 Blood Glucose Meters

A downloadable blood glucose meter is required for this study. Otherwise eligible participants who do not have a downloadable meter may be provided a meter and test strips for use during the study. It is estimated that approximately 10% of enrollees will require a study meter to be provided.

Screening procedures will last approximately 2 hours.

# Chapter 3: Pre-randomization Blinded CGM Wear

## 3.1 Assessment of Blinded CGM Data and Blood Glucose Meter

The participant will return around 14-21 days after the blinded CGM sensor was placed.

The CGM data will be downloaded and reviewed to assess whether (1) the participant has used the CGM for at least 200 hours (equivalent to 8.3 days) (2) at least an average of 1.8 calibrations per day

Participants not meeting the CGM usage requirement may be given a second opportunity to wear the blinded CGM sensor at investigator discretion with protocol chair or Coordinating Center Director approval

The home blood glucose meter(s) will be downloaded to verify that an average of at least 2 SMBG measurements per day were performed.

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

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

Blinded CGM data should not be reviewed with the participants prior to randomization. After randomization the blinded data may be reviewed with participants in the CGM group for diabetes management but should NOT be reviewed with BGM group participants.

When possible the site personnel downloading and reviewing CGM data for eligibility should not be involved in the diabetes management for the participant.

# Chapter 4: Phase 1 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., unable to complete the frequent visits in the first month), initiation of the randomized trial can be deferred for up to 2 weeks.

The purpose of the visit will include the following:

- Assessment of frequency of use of the CGM and BGM
- Assessment of skin reaction in areas where a CGM sensor was worn
- Collection of blood sample to send to the central laboratory for HbA1c and C-peptide + glucose
- Randomization to the CGM 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 Randomization

Participants who have met eligibility requirements for home glucose monitoring and use of the CGM will be randomly assigned with equal probability to one of 2 groups (1:1):

1. CGM
2. BGM

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

- The Jaeb Center for Health Research (JCHR) will construct a Master Randomization List using a permuted block design.
    - Randomization will be stratified by clinical site

## 4.3 Study Supplies

The CGM group will be given sensors, receivers and transmitters.
A blood glucose meter and test strips (4 per day) will be provided to any participant who does not use a downloadable meter. It is anticipated around 10% of participants will need a study provided meter and strips.

## 4.4 Blood Samples

A blood sample will be obtained and sent to the central lab for:

- HbA1c
- Random C-peptide + glucose

## 4.5 Initial Management Instructions

In both groups, adjustments in insulin management will be made as indicated following HbA1c and glucose targets outlined in procedure manual. Each group will be provided with instruction sheets regarding diabetes management pertinent to their treatment group.

The CGM group will be instructed on use and care of the CGM including sensor insertion and calibration. Education will be provided as to how to use the CGM in real time to make management decisions. A participant 'social marketing' handout will be used to encourage consistent and durable CGM use in the CGM group by noting how the addition of CGM – a relatively new diabetes technology – can reduce the workload of T1D self-care while optimizing glycemic outcomes (reduced BG monitoring and therapeutic dosing with CGM use).

Diabetes management education will take place for both groups at all visits. Blinded CGM data should not be reviewed with BGM group for diabetes management.

# Chapter 5: Phase 1 Randomized Trial Procedures

## 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 provided guidelines for when to confirm the CGM reading with a home BGM value including when hypo/hyperglycemia symptoms are discrepant from the CGM reading or if there are other reasons to doubt the CGM reading.

CGM data will be downloaded prior to or during the study visit.

### 5.1.2 Control Group

A BGM will be used for a finger stick blood glucose check with a recommendation of at least 4 times a day. BGM data will be downloaded (if available) and reviewed with the participant at each visit.

## 5.2 Follow-up Visits and Contacts

### 5.2.1 Follow-up Visits

Follow-up visits will occur at the following:

- 1 week (± 3 days) – telephone or video telehealth contact
- 2 weeks (± 7 days) – In person visit optional for CGM group and telephone or video telehealth contact for BGM group
- 4 weeks (±7 days) – telephone or video telehealth contact
- 6 weeks (±7 days)
- 13 weeks (±7 days)
- 19 weeks (±7 days) – telephone or video telehealth contact
- 26 weeks (±7 days)*

  **BGM group will come into clinic at 24 weeks for a blinded sensor placement and bring back the CGM at the 26 week visit approximately 14 days later*

The 2 week visit may be done via video/telehealth for CGM group unless there is a concern with CGM devices or safety that require an office visit

### 5.2.2 Procedures at Follow-up Visits

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

- Assessment of adherence to BGM and CGM and use of CGM features
- Solicitation of the occurrence of adverse events, including severe hypoglycemia and diabetic ketoacidosis
- Skin assessment (CGM group only)
- Assessment of device malfunctions

- Review of glucose data and pump data (if available) and recommendations for changes in diabetes management
- HbA1c determination using a point of care device or local lab (6 weeks, 13 weeks, 26 weeks)
- Collection of a blood sample to send to the central laboratory for HbA1c determination (13 weeks, 26 weeks)
- Completion of questionnaires (13 weeks, 26 weeks)
    - PAID Survey
    - Glucose Monitoring Satisfaction
    - Hypoglycemia Confidence
    - Diabetes Technology Attitudes
    - Sleep Quality
    - Life Events
    - Benefits and barriers of CGM and Share
    - CGM Self Efficacy
    - Participants who discontinue CGM will be asked to complete an additional questionnaire asking about reasons for discontinuation at the visit following the discontinuation.

### 5.2.3 Use of Blinded CGM by Control Group

Blinded study sensors will be placed at 13 and 24 weeks for the control group and worn for 7 and 14 days respectively, with instructions to calibrate at least 2 times per day using BGM.
The blinded sensor data will not be viewed by study staff involved in the care of the participant.

At the 13 week visit, participants will either send the CGM back to the clinic using a prepaid envelope or bring the CGM to the clinic. At the 26-week visit the participant will be asked to come to clinic 2 weeks prior to the 26-week visit for sensor placement and to return the CGM at the 26-week visit.

At the 26-week visit, sensor wear may be repeated if there are fewer than 200 hours of glucose measurements.

#### 5.0.1 Unscheduled Visits

Additional visits and contacts can be made as needed.

# Chapter 6: Phase 2 Extension

## 6.1 2nd Randomization

## 6.2 CGM Group

Participants in the CGM group will be given the opportunity to continue CGM using the newest commercially available version for an additional 6 months, and choose whether to turn alarms off or continue using CGM with alarms. Participants who stop using CGM will continue to be followed during the extension phase if they choose to stay in the study.

CGM supplies will be provided for the duration of the extension phase. Site contact with the participant will be expected to approximate usual care (see schedule of events).

## 6.3 Control Group

Participants in the BGM group will be will be given the opportunity to initiate CGM after completion of the 26-week visit, provided that at least 200 hours of blinded CGM data were obtained prior to the 26-week visit. Willing participants will be randomized to the newest available version of Dexcom CGM either with or without alarms turned on. The low glucose alarm of < 55mg/dl will remain on and cannot be shut off.

Participants may repeat blinded wear prior to 26-week visit if needed at investigator discretion.

Participants not willing to be randomized to no alarms will be given the newest available version of CGM and continued to be followed for 6 months following same visit schedule as those randomized to alarms vs. no alarms.

- Participants will be instructed on use of the CGM and how to use CGM and BGM data to adjust diabetes management.

Participants will have a telephone or video telehealth contact at 1 week (27 weeks from study start) and a visit 2 weeks (28 weeks from study start) after CGM initiation for CGM training.

## 6.4 Visit Schedule and Procedures

All participants will have visits at 39 weeks (±7 days), and 52 weeks (±14 days). Additional visits and phone contacts can be made as indicated.

Visit procedures will be similar as those described in section 5.2.2 for the Phase 1 RCT.

## 6.5 Study Supplies

The newest approved version of the Dexcom CGM will be used. Dexcom receivers, transmitter and sensors will be provided for the duration of Phase 2.

# Chapter 7: Study Devices

## 7.1 Description of the Intervention Device

### 7.1.1 Continuous Glucose Monitoring

The study CGM will included an unmodified Dexcom G5 Mobile transmitter and sensors. This is an FDA-approved device system in adults and pediatrics with no changes to its hardware or firmware components. The CGM sensor will be replaced at least one every seven days. A newer CGM version may be used if one becomes commercially available during the course of the study. Participants may choose to use either the Dexcom G5 Mobile Receiver or their personal smartphone as the receiver display device using the Dexcom Mobile application.

The blinded CGM sensor used in this study is the Dexcom G4 Platinum Professional with 505 software that is identical to the G5 software, made by Dexcom, Inc. The Dexcom G4 Platinum Professional is not FDA approved for use in pediatrics and therefore its use in this study will be investigational in participants < 18 years of age. However, since the glucose values for the blinded CGM will not be used for diabetes management, the investigators have determined that use of the blinded CGM in this protocol meets the criteria for the study to be classified as a nonsignificant risk device study as it does not meet any of the criteria from section 812.3 (m) of the FDA investigational device exemption regulation 21 CFR 812. As such an IDE is not required. The Dexcom G4 Platinum Professional uses the same sensor and software algorithm as the Dexcom G5 Mobile which is approved for pediatric patients.

## 7.2 Blood Glucose Meter and Strips

Participants who do not have a downloadable meter will be provided with a study meter and strips so that the meter can be downloaded.

## 7.3 Study Device Accountability Procedures

Device accountability procedures will be detailed in the site procedures manual.

## 7.4 Safety Measures

### 7.4.1 Blood Glucose Meter Testing

- Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labelling of the study CGM device.

### 7.4.2 CGM Calibration

Throughout the study, participants will be instructed to calibrate the study CGM in accordance with manufacturer labelling.

### 7.4.3 Hypoglycemia Threshold Alarm and Safety Protocol

In Phase 1 the starting alarm threshold for real-time CGM will be standardized and outlined in the CGM training materials and manuals. During the course of the study, participants will be permitted to change this setting.

For the BGM group who initiates CGM in phase 2 the CGM with alarms group will have the same starting threshold recommended for the CGM group in phase 1. The CGM without alarms group will only have the alarm for blood glucose < 55 mg/dl set.

If a participant receives a CGM hypoglycemia threshold alarm or notes that the CGM glucose is below the hypoglycemia threshold alarm value, confirmatory fingerstick testing should be performed. Instructions for treating a hypoglycemic event and when to perform a confirmatory fingerstick test are included in the participant materials and procedure manuals. .

### 7.4.4 Hyperglycemia Threshold Alarm and Safety Protocol

In Phase 1 the starting hyperglycemia alarm thresholds for real-time CGM will be standardized across participants with details included in the CGM training procedures and manuals. During the course of the study, participants will be permitted to change this setting.

For the BGM group who initiates CGM in phase 2 the CGM with alarms group will have the same starting threshold recommended for phase 1 CGM group. The CGM without alarms group will have hyperglycemia alarms and alerts turned off.

If a participant receives a CGM hyperglycemia threshold alarm or notes that the CGM glucose is above the hyperglycemia threshold alarm value, confirmatory fingerstick testing may performed as warranted.

# Chapter 8: Testing Procedures and Questionnaires

Human Factors (HF) assessments are made up of tests and procedures that tap in to the "human side" of having type 1 diabetes and using a diabetes device like CGM. HF assessments cut across the acceptability, usability, and efficacy of CGM from the perspective of the user. Further, HF assessments help to understand expectations, attitudes, and behaviors that influence the use and response to using (or not using) CGM. Objective and subjective measures will be used and are listed in table **1**. In total, each session of assessments should take 30 minutes to complete surveys. Surveys will be completed at baseline, 13, 26, and 52 (extension) weeks. In addition participants who discontinue real-time CGM will be asked to complete an additional survey at the next study visit subsequent to CGM discontinuation.

**Table 1. Human Factors Assessment Battery**

| ***Measure*** | ***Construct Measured / Relevant Points*** |
|---|---|
| ***Surveys*** | |
| CGM Self Efficacy (Laffel)(9) | All participants complete this 15 item measure that evaluates the extent to which CGM users have confidence in their ability to optimally use CGM. |
| PAID Survey (Laffel)(10) | This survey measures youth-reported burden related to type 1 diabetes management. The survey includes 20 items and takes 5 minutes to complete. |
| Glucose Monitoring Satisfaction (Polonsky)(11) | This recently validated survey is an outgrowth of DirecNet and JDRF CGM surveys. It has been reduced to 15 items and evaluates treatment satisfaction/burden. |
| Hypoglycemia Confidence (Polonsky)(12) | Includes 8 different common situations where hypoglycemia occurs (e.g., physical activity, driving) and evaluates level of confidence it can be managed in those situations. (8 items) |
| Diabetes Technology Attitudes (Hood)(13) | Survey developed to measures perceptions about the benefits of diabetes technology and devices. (5 items) |
| Sleep Quality(14) | Pittsburgh Sleep Quality Index evaluates sleep patterns and disruptions, and reasons for disruptions. (9 items) |
| Life Events(15) | List of life events commonly occurring in this age range (e.g., moving out of home, change in relationships, work) and degree perceived as stressful. (10 items) |
| Benefits and barriers of CGM and Share | List of situations (e.g., able to share data, glycemic events, physical activity) and designation of whether they are barriers or benefits. (16 items per section with 2 sections) |
| ***CGM Discontinuation*** | |
| Human Factors Survey (Hood) (13) | Participants who discontinue CGM will be asked to complete this survey. (3 items) |

# Chapter 9: Adverse Events, Device Issues, and Stopping Rules

## 9.1 Adverse Events

### 9.1.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation.

Serious Adverse Event (SAE): Any untoward medical occurrence that:

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

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form).

Device Complaints: A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint.

Device Malfunction: Any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3)

### 9.1.2 Reportable Adverse Events

For this protocol, a reportable adverse event includes any untoward medical occurrence that meets one of the following criteria:

1) A serious adverse event
2) An Adverse Device Effect as defined in section 9.1.1, unless excluded from reporting in section 9.2
3) An Adverse Event occurring in association with a study procedure
4) Hypoglycemia meeting the definition of severe hypoglycemia as defined below
5) Diabetic ketoacidosis (DKA) as defined below

Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events unless associated with an Adverse Device Effect. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

Pregnancy occurring during the study will be recorded.

#### 9.1.2.1 Hypoglycemic Events

Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when the following definition for severe hypoglycemia is met: 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.

#### 9.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following criteria is met: (1) the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below, or (2) in the absence of DKA if evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis.

Hyperglycemic events are classified as DKA if the following are present:

- 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

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 to verify the coding and the reporting that is required.

### 9.1.3 Relationship of Adverse Event to Study Device

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 device.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Yes

There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

No

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

### 9.1.4 Intensity of Adverse Event

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

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

### 9.1.5 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality.

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

### 9.1.6 Outcome of Adverse Event

The outcome of each reportable adverse event will be classified by the investigator as follows:

- RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).
- ONGOING – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
    - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.

All clinically significant abnormalities of clinical laboratory measurements or adverse events occurring during the study and continuing at study termination should be followed by the participant's physician and evaluated with additional tests (if necessary) until diagnosis of the underlying cause, or resolution. Follow-up information should be recorded on source documents.

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

## 9.2 Reportable Device Issues

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

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

- Component disconnections
- CGM sensors lasting fewer than 7 days or longer per the approved duration of sensor use per the manufacturer
- CGM tape adherence issues

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

## 9.3 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The occurrence of pregnancy will be reported on an AE Form.

## 9.4 Timing of Event Reporting

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

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

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

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

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

Upon receipt of a UADE report, the Jaeb Center will investigate the UADE and if indicated, report the results of the investigation to the sites and central IRB (2).

In the case of a CGM transmitter, receiver or sensor device malfunction, information will be forwarded to Dexcom by the site personnel and/or the Jaeb Center, to be handled by their complaint management system.

## 9.5 Stopping Criteria

### 9.5.1 Participant Discontinuation of Study Device

Rules for discontinuing study device use are described below.

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped

- Participant pregnancy

Even if the study device is discontinued, the participant will be encouraged to remain in the study through the final study visit.

#### 9.5.2 Criteria for Suspending or Stopping Overall Study

Study activities could be suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

The DSMB will be informed of all related, serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. The DSMB will request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

The study medical monitor will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. The medical monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

## 9.6 Independent Safety Oversight

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

## 9.7 Risks

The potential risks associated with use of the study device are described in section 1.3. Additional risks are minor and/or infrequent and include:

- Pain, bruising, redness, or infection from blood draws
- Loss of confidentiality
- Stress from completing quality of life questionnaires

# Chapter 10: Miscellaneous Considerations

## 10.1 Participant Compensation

Participant compensation will be specified in the informed consent form.

## 10.2 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal. Participants who cross over into the other treatment arm (i.e. start CGM in BGM group or stop CGM in CGM group) should continue to be followed in the study

## 10.3 Confidentiality

For security and confidentiality 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. De-identified participant information may also be provided to research sites involved in the study.

## 10.4 Participant Access to Device at Study Closure

Participants who complete the study will be able to keep the study BGM and CGM devices, assuming that commercially-availabledevices were used and the devices are functioning at the end of the study.

# Chapter 11: Statistical Considerations

## 11.0 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.

## 11.1 Statistical Hypotheses

- Null hypothesis: There is no difference in the HbA1c at 26 weeks adjusted for baseline between those using CGM and those using BGM.
- Alternative hypothesis: There is a nonzero difference in HbA1c at 26 weeks adjusted for baseline between those using CGM and those using BGM.

## 11.2 Sample Size

Data from two studies was used to estimate standard deviation of HbA1c at 6 months adjusted for baseline, the JDRF CGM RCT and the Metformin RCT (3,6). In the JDRF CGM RCT there were N=39 usual care subjects and N=48 CGM subjects who met the criteria: 14-<25 years of age and baseline HbA1c 7.5% - <11.0%. After adjusting for the correlation between baseline and 6-month HbA1c, the effective SD was 0.58% (95% CI: 0.47% to 0.74%) for the usual care group and 0.55% (95% CI: 0.46% to 0.69%) for the CGM group. In the Metformin RCT there were N=46 control group subjects who met the criteria age ≥14 and baseline HbA1c 7.5% - <11.0%. After adjusting for the correlation between baseline and 6-month HbA1c, the effective SD was 0.73% (95% CI: 0.61% to 0.92%).

Sample size calculations assume a two-tailed test, a type I error of 5%, a power of 90%, and a 1:1 randomization. The following table shows total sample size for various standard deviations and treatment effects (not adjusted for dropouts). Half would be assigned to each group.

| Treatment Group Difference in Mean HbA1c | Effective Standard Deviation | | | |
|---|---|---|---|---|
| | 0.6% | 0.7% | 0.8% | 0.9% |
| 0.6% | 46 | 60 | 78 | 98 |
| 0.5% | 64 | 86 | 110 | 140 |
| 0.4% | 98 | 132 | 172 | 216 |

Assuming a treatment group difference of 0.5% and a conservative estimate of standard deviation of 0.9% the total sample size would be 140. Increasing by approximately 10% to account for dropouts would mean a total sample size of 150, which is 75 in each group.

## 11.3 Outcome Measures

*Primary Efficacy Endpoint:*

- HbA1c at 26 weeks adjusted for baseline

*Secondary Efficacy Endpoints:*

*HbA1c*

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

*Glucose Control*

- CGM % time in range 70-180 mg/dl
- CGM mean glucose
- CGM glucose variability measured by coefficient of variation

*Hyperglycemia*

- CGM % time > 180 mg/dl
- CGM % time > 300 mg/dl

*Hypoglycemia*

- CGM % time < 54 mg/dl
- CGM % time < 70 mg/dl
- Rate of CGM measured hypoglycemic episodes (using <54 mg/dL)

*Quality of Life and Other Questionnaires*

- CGM Self Efficacy
- PAID Survey
- Glucose Monitoring Satisfaction
- Hypoglycemia Confidence
- Diabetes Technology Attitudes
- Sleep Quality

Each of the CGM metrics will be calculated over 24 hours. In addition, time in range (70-180 mg/dl) and % time <54 mg/dl will be calculated separately for daytime (6am-<10pm) and nighttime (10pm-<6am).

Indices will be calculated at baseline and during follow-up as follows:

- Baseline: CGM variables will be calculated based on data obtained in the 2 weeks prior to randomization. Note that only subjects who used the CGM for a minimum of 200 hours and had an average of 1.8 calibrations per day during the blinded CGM screening period are eligible to be randomized.

- Follow-up: For approximately 1 week after the 13 week visit and 2 weeks after the 24 week visit, 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.

### 11.4 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 subjects who meet the following requirements:
    - Both treatment groups:
        - ≥ 216 hours of follow-up data (equivalent to 72 hours per week)
        - 26 week visit within ± 28 days of the target 26 week visit date
    - BGM group:
        - Average ≥ 4 BGM measurements per day
        - Did not start using a non-study CGM device
    - CGM group:
        - Average ≥ 5 days per week of CGM use

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

### 11.5 Analysis of the Primary Efficacy Endpoint

The primary endpoint is the change in HbA1c from baseline to 26 weeks adjusted for baseline. Mean ± SD for the 26-week HbA1c values or summary statistics appropriate to the distribution will be given for each treatment group.

Primary analysis will be done using direct likelihood. A longitudinal linear regression model will be fit with the central laboratory HbA1c value at baseline, 13 weeks and 26 weeks as the dependent variable. The local HbA1c measurement will be included as an auxiliary variable in the model when available. This model will adjust for site as a random effect. Separate treatment arm effects will be modelled at 13 and 26 weeks by including a treatment by time interaction. Primary analysis will report the point estimate, 95% confidence interval and p-value for the treatment group difference at 26 weeks. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or non-parametric

methods will be used instead. However, previous experience suggests that HbA1c values will follow an approximate normal distribution.

*Missing Data*

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

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

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

### 11.6 Analysis of the Secondary Endpoints

*CGM Metrics*

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

*Binary HbA1c Outcomes*

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

*Quality of Life*

For all questionnaires, responses to individual questions and the overall scores will be summarized by treatment group. For those questionnaires listed above as an outcome measure, the overall score at 26 weeks will be compared between treatment groups using a linear model adjusting for the baseline value and site as a random effect. Regression diagnostics will be performed similarly as described above for the primary outcome.

*Missing Data*

There will be no imputation of any missing data for secondary outcomes. Analyses will be available cases only.

### 11.7 Safety Analyses

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

- Number of adverse events
- Number of subjects with at least one event

- Number of serious adverse events
- Number of subjects with at least one serious adverse event
- Number of adverse events thought by investigator to be related to study intervention
- Number of subjects who stopped the intervention in response to an adverse event
- Number of severe hypoglycemic events as defined in the Adverse Events Chapter
- Number of subjects experiencing at least one severe hypoglycemic event
- SH incidence rates (Kaplan-Meier and per 100 person-years)
- Number of diabetic ketoacidosis events, as defined in the Adverse Events Chapter
- Number of subjects experiencing at least one diabetic ketoacidosis event
- DKA incidence rates (Kaplan-Meier and per 100 person-years)

If there are enough events for statistical analysis, the SH and DKA incidence rates will be compared between treatment groups using Poisson regression with the number events as the outcome, the number of follow-up years as an offset, and the baseline value as a covariate.

### 11.8 Protocol Adherence and Retention

The following tabulations and analyses will be performed according to treatment group:

- A flow chart accounting for all subjects according to treatment group for all visits
- Visit completion rates for each follow-up visit
- Phone contact completion rates
- Protocol deviations
- Number of and reasons for unscheduled visits and phone calls

### 11.9 Baseline Descriptive Statistics

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

### 11.10 Device Issues

For each reportable device issue as defined in section 9.2, the following will be tabulated:

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

### 11.11 Planned Interim Analyses

Not applicable.

### 11.12 Sub-Group Analyses

Subgroup analyses/assessments of effect modification (interaction) will be conducted for the primary outcome. These analyses will be considered exploratory. Additionally, interpretation of the analyses will depend on whether the overall analysis demonstrates a significant treatment

group difference; in the absence of such an overall difference, subgroup analyses will be interpreted with caution. The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the models used for the primary analyses.

The baseline factors listed below will be assessed. Categories for continuous variables will be utilized to display the data only. :

- Age <18 and ≥18
- HbA1c <9% and ≥9%
- Insulin method: pump versus injection
- Detectable C-peptide
- Gender
- Race-ethnicity

### 11.13 Multiple Comparison/Multiplicity

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

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

### 11.14 Exploratory Analyses

No exploratory analyses are planned.

### 11.15 Additional Tabulations and Analyses

The following tabulations will be performed by treatment group:

- Total daily insulin dose per kg
- Basal insulin dose per kg
- Bolus insulin dose per kg
- Number of injections per day for injection users
- Number of subjects who changed insulin method
- BGM checks/day

Insulin dose, number of injections, and BGM checks/day will be compared between treatment groups using a linear model adjusted for baseline value and site as a random effect. Regression diagnostics will be performed as described above for the primary outcome.

*13 Week Analysis*

Analysis at 13 weeks will be performed for time in range 70-180 mg/dL, mean glucose, % time < 70 mg/dL, % time <54 mg/dL, % time >180 mg/dL, % time >250 mg/dL, coefficient of variation and HbA1c. Analysis will parallel the 26-week analysis described above.

*CGM Group*

For the CGM group, mean ± SD or summary statistics appropriate to the distribution will be reported for days of CGM use per week by visit. A linear model will be used to identify possible factors associated with CGM use.

In addition, we will tabulate the use of the Dexcom Share feature by visit.

### 11.16 Phase 2

All analyses for phase 2 will be considered exploratory.

#### 11.16.1 Within Group Comparisons

For both phase 1 treatment groups, summary statistics will be given for all outcomes listed above at phase 1 baseline (pre-randomization), 26 weeks, and 52 weeks. In addition, boxplots will be used to display the outcomes by phase 1 treatment group and visit over the whole 12 month period.

One objective of phase 2 is to assess durability of use and sustained glycemic benefit for the phase 1 CGM group over a 12 month period. A paired t-test will be used to evaluate the change in HbA1c and CGM metrics from baseline to 52 weeks and the change in CGM use from phase 1 to phase 2. If an outcome is skewed, a Wilcoxon rank sum test will be used instead.

For the phase 1 BGM group, a paired t-test will be used to evaluate the change in HbA1c and CGM metrics from phase 2 baseline (26 weeks) to 52 weeks.

#### 11.16.2 Treatment Group Comparisons

A second objective of phase 2 is to explore the effect of CGM with and without alarms on glucose control, quality of life, and CGM use. Participants in the BGM group from phase 1 will be re-randomized at the 26 week visit, if they are willing, to their phase 2 treatment group. Only those who are randomized in phase 2 will be included in the analysis of alarms.

Summary statistics appropriate to the distribution will be given by phase 2 treatment group for all of the outcomes listed above in phase 1 (HbA1c, CGM metrics, and quality of life), as well as days per week of CGM use. CGM metrics will be calculated using all available data between 26 weeks and 52 weeks. HbA1c and quality of life metrics will be assessed as the change from 26 to 52 weeks.

Each outcome will be compared between phase 2 treatment groups analogous to what was described for phase 1. Missing data and dropouts will also be handled in the same way as phase 1.

Although all outcomes in phase 2 are exploratory, days of CGM use per week and % time in range 70-180 mg/dL are considered the co-primary outcomes for phase 2.

It is possible that subjects may decide to turn their alarms on or off despite their phase 2 treatment group assignment. Therefore, we will perform the analysis as intent-to-treat and also as-treated.

### 11.16.3 Multiple Comparisons

For the treatment group comparison of the co-primary outcomes, CGM use and % time in range 70-180 mg/dL, we will use Hochberg's step-up procedure to control the family wise error rate at 0.05. For all other comparisons, we will use the adaptive Benjamini-Hochberg procedure to control the false discovery rate, similar to phase 1.

### 11.16.4 Additional Tabulations

- Actual use of alarms and alarm settings by phase 2 treatment group and visit
- Number of participants in the phase 1 CGM group who restarted CGM after discontinuing during phase 1
- Adverse events will be summarized as described above
- Comparison of CGM use between device types if a different device is used for phase 2 than phase 1

# Chapter 12: Data Collection and Monitoring

## 12.1 Case Report Forms and Device Data

The main study data are collected through a combination of electronic case report forms (CRFs) and electronic device data files obtained from the study software and individual hardware components. These electronic device files and electronic CRFs from the study website are considered the primary source documentation.

When data are directly collected in electronic case report forms, this will be considered the source data. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

## 12.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## 12.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report

- Agent/Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

### 12.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements that is deemed to have a reasonable possibility of impacting participant safety, participant rights or study integrity. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly when appropriate.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

# Chapter 13: Ethics/Protection of Human Participants

## 13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

## 13.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

## 13.3 Informed Consent Process

### 13.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### 13.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The study monitor, other authorized representatives, representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited

to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at JCHR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by JCHR research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at JCHR.

# Chapter 14: References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