T1D Exchange

A Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Adults with Type 1 Diabetes

Version 2.0
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CHAPTER 1: INTRODUCTION

1.1 Introduction and Rationale

Continuous glucose monitoring (CGM) offers the opportunity to improve glycemic control, including a reduction in hypoglycemia. Several randomized trials have demonstrated the efficacy of CGM when it is used on a regular basis by individuals with type 1 diabetes (T1D), particularly in adults. In the Juvenile Diabetes Research Foundation (JDRF) CGM multicenter clinical trial, among adults with HbA1c ≥7.0% randomly assigned to either continuous glucose monitoring or to a control group, there was a significant improvement in HbA1c from baseline to 26 weeks among those in the CGM group, without an increase in hypoglycemia (1-5). The frequency of a combined outcome of a 26-week HbA1c level less than 7.0% and no severe hypoglycemic events was 30% in the CGM group and 7% in the control group (P=0.006) . In a companion trial of individuals with well controlled T1D (HbA1c <7.0%), a reduction in biochemical hypoglycemia and better HbA1c levels occurred in the CGM group compared with the control group. In children, the benefit of CGM was dampened by a lower frequency of CGM use, but among those who used CGM regularly, the benefit was of similar magnitude to what was seen in adults. The Eurythmics trial of intensively treated adults with type 1 diabetes and an HbA1c at entry ≥8.2% found a 1.2% HbA1c reduction (p<0.001) in the CGM-augmented Continuous Subcutaneous Insulin Infusion (CSII) group when compared with the group which continued their self-monitoring blood glucose regimen, with no increase in number or severity of hypoglycemic episodes (6). In the STAR 3 trial, among adults, the absolute reduction in the mean HbA1c level was 1.0% in the sensor-augmented pump-therapy group compared with 0.4% in the injection-therapy group (P<0.001), with no increase in hypoglycemia.(7)

Current Food and Drug Administration (FDA) labeling for the commercially-available CGM devices requires a blood glucose measurement before a change in management is made based on the CGM glucose result. As an example, the FDA labeling for the Dexcom G4 Platinum Continuous Glucose Monitoring System states: *The [System] is a glucose monitoring device indicated for detecting trends and tracking patterns in persons age 18 and older with diabetes. The [System] is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home glucose monitoring devices* (8). FDA labeling for the MiniMed 530G System is similar. Thus, CGM is labeled as an adjunct to self-monitoring of blood glucose rather than a replacement.

The Centers for Medicare and Medicaid Services (CMS) does not provide coverage for CGM. As stated in a recent letter from CMS regarding this issue, CGM devices do not meet the Medicare definition of durable medical equipment and do not fall under any other Medicare benefit category (9). CMS made a determination that, unlike home blood glucose monitors, CGM is not intended to be used directly for making therapy adjustments and is an adjunctive device to supplement information obtained from a standard blood glucose monitor. Certain private insurers also have been reluctant to cover CGM due to its use as an adjunct to blood glucose monitoring (BGM) rather than at least partial replacement of BGM.

Although the labeling for CGM requires a BGM measurement before making a therapy adjustment, many CGM users often decide on a meal bolus based on CGM alone. On a questionnaire completed in the T1D Exchange clinic registry, only 26% of adult CGM users indicated that they always verify the CGM glucose value with BGM value before giving a meal bolus and 41% indicated that at least half of the time they don't verify the CGM glucose value before giving a meal bolus. There was no indication of a difference in severe hypoglycemia (SH) frequency between the 595 who performed a confirmatory meal BGM measurement most or all of the time and the 404 who reported BGM measurements only half of the time or less; 11.6% versus 10.6%, respectively, reported a severe hypoglycemia event in the prior 3 months.

A study comparing CGM used solely as an adjunctive device, as per the FDA labeling, versus CGM used largely in lieu of BGM measurements would provide valuable data. Since many individuals with T1D are often

using CGM alone when bolusing insulin, obtaining data on the safety and efficacy of this approach will be important. If indeed insulin dosing decisions are proven to be safe and effective using CGM alone (without BGM confirmation) compared to CGM with BGM confirmations, this study would also pave the way for a new standard diabetes management protocol and therapy that would not require eight BGM measurements (i.e. finger sticks) a day and ease the burden of managing type 1 diabetes.

1.2 Study CGM

The CGM device to be used in the study by both groups is the Dexcom G4 Platinum Continuous Glucose Monitoring System with modified algorithm designed to improve accuracy, day-to-day reliability, and consistency from sensor to sensor. This FDA-approved System includes a sensor, transmitter and receiver. It measures interstitial fluid glucose levels in the range of 40 mg/dl to 400 mg/dl every 5 minutes for up to 7 days.

Participants in both groups will use an FDA-approved BGM for blood glucose measurements. The participants randomized to use CGM without BGM confirmation will utilize a blinded version of an FDA-approved BGM at times that the protocol does not require a standard BGM measurement. The blinded device will be modified so that the glucose result is not visible to the participant, but the result will be stored in the BGM's memory for downloading.

1.3 Protocol Synopsis

A high level overview of the protocol is provided below. Details follow in subsequent sections.

Study Objective

The primary objective of the study is to determine whether the routine use of CGM without BGM confirmation is as safe and effective as CGM used as an adjunct to BGM.

Study Design

6-month parallel group multi-center randomized noninferiority clinical trial

- Preceded by a run-in period of up to 10 weeks to collect blinded baseline CGM data, to train the participants on CGM use, and to assess compliance with CGM use prior to randomization.

Patient Population

- Adults $\geq$18 years old with T1D for at least 1 year who (1) are using an insulin pump, (2) have HbA1c level $\leq$9.0%, (3) have had no severe hypoglycemia in the last 12 months requiring assistance of another individual for treatment and no events resulting in seizure or loss of consciousness in the past 3 years, and (4) have no significant hypoglycemia unawareness.

See section 2.3 for a full list of eligibility and exclusion criteria.

Sample Size

- 225 who successfully complete the run-in phase and enter the randomized trial

Treatment Groups

Participants will be randomly assigned with 2:1 probability to the CGM Only and CGM+BGM groups, respectively.

See section 4.5.2 for the definition of CGM Only group's use of CGM and a listing of circumstances when BGM will be done.

Visit and Phone Contact Schedule

Run-in Phase

- Screening visit followed by blinded CGM use for 14-21 days, then a visit to assess compliance and initiate standard CGM use.
- During standard CGM use, visit after 2, 4 and 8 weeks, with phone calls at 1, 3, and 6 weeks.

Note: Current CGM users may be eligible to skip part of the run-in phase (see section 3.1)

Randomized Trial

Following randomization, a phone contact in the first week and visits at 3, 6, 13, 19 and 26 weeks.

Outcomes

Primary Outcome

- Time in range of 70 to 180 mg/dl, measured with CGM over the full 6 months of the study

Secondary Outcomes

- Episodes of severe hypoglycemia (SH)
- Combined HbA1c and severe hypoglycemia outcome—no worsening of HbA1c by greater than 0.3% AND no severe hypoglycemia event between baseline (randomization) and 6 months
- Change in HbA1c from baseline to 6 months
- Episodes of diabetic ketoacidosis (DKA)
- Other serious adverse events
- Biochemical hypoglycemia (percentage of sensor values <70 mg/dl, <60 mg/dl, and <50 mg/dl)
- Hyperglycemic events without DKA with blood or sensor glucose value >300 mg/dl
- Ketotic events not meeting criteria for DKA with blood ketone level >0.6 mmol/L and $\geq$1.0 mmol/L
- Measures of glycemic variability: coefficient of variation
- BGM frequency
- CGM use frequency
- Quality of life
- Bolus calculator use frequency

Data Exploration

The use by the CGM Only group of a blinded BGM at times that a standard BGM measurement is not made will provide the opportunity to assess the frequency of discordance between CGM and BGM glucose measurements and the clinical outcome of each of these events, particularly with respect to clinical hypoglycemic or hyperglycemic events in the ensuing several hours. In addition, for each SH and DKA event, available CGM and BGM data will be assessed to determine if reliance on the CGM glucose profile may have contributed to the occurrence of the event. This information will be very important for developing a better understanding of the potential risks of making diabetes management decisions based on CGM alone and could help refine the principles for mitigating this risk.

1.4 Summary of Protocol

Run-in Phase

Current CGM users may skip part of the run-in phase (see section 3.1).

For non-CGM users, a blinded CGM will be used for approximately 14-21 days. The participant will return for a visit and, if the CGM use criteria have been met (at least 11 of 14 days of use and three blood glucose tests per day), a standard CGM will be provided and the participant will be instructed on how to use real-time CGM as an adjunct to BGM (as per labeling).

Following initiation of standard CGM use, visits will occur after 2, 4, and 8 weeks, with phone contacts at 1, 3, and 6 weeks.

After using standard CGM for up to 8 weeks, compliance with use of CGM and BGM over the prior 4 weeks will be assessed. To enter the randomized trial, at least 21 of 28 days of CGM use and an average of at least 4 BGM measurements on at least 90% of the days will be required.

Randomized Trial

Participants successfully completing the run-in phase will be randomly assigned to either the CGM+BGM group or the CGM Only group. Both groups will be provided with CGM devices/sensors and blood glucose meters/test strips. Both groups will use BGM for calibration of the CGM device. The CGM+BGM group will be instructed to measure the blood glucose whenever a diabetes management decision is made. The CGM Only group will be instructed to only measure the blood glucose (other than for calibration) with a standard BGM meter in certain circumstances (see section 4.5.2) and will use a blinded BGM meter at times when a standard BGM measurement is not done.

A phone contact will occur during the first week and study visits will occur after 3, 6, 13, 19 and 26 weeks. The CGM and BGM (blinded and standard) will be downloaded at each visit. HbA1c will be measured at 13 and 26 weeks. Occurrences of SH, DKA, and other reportable adverse events will be recorded.

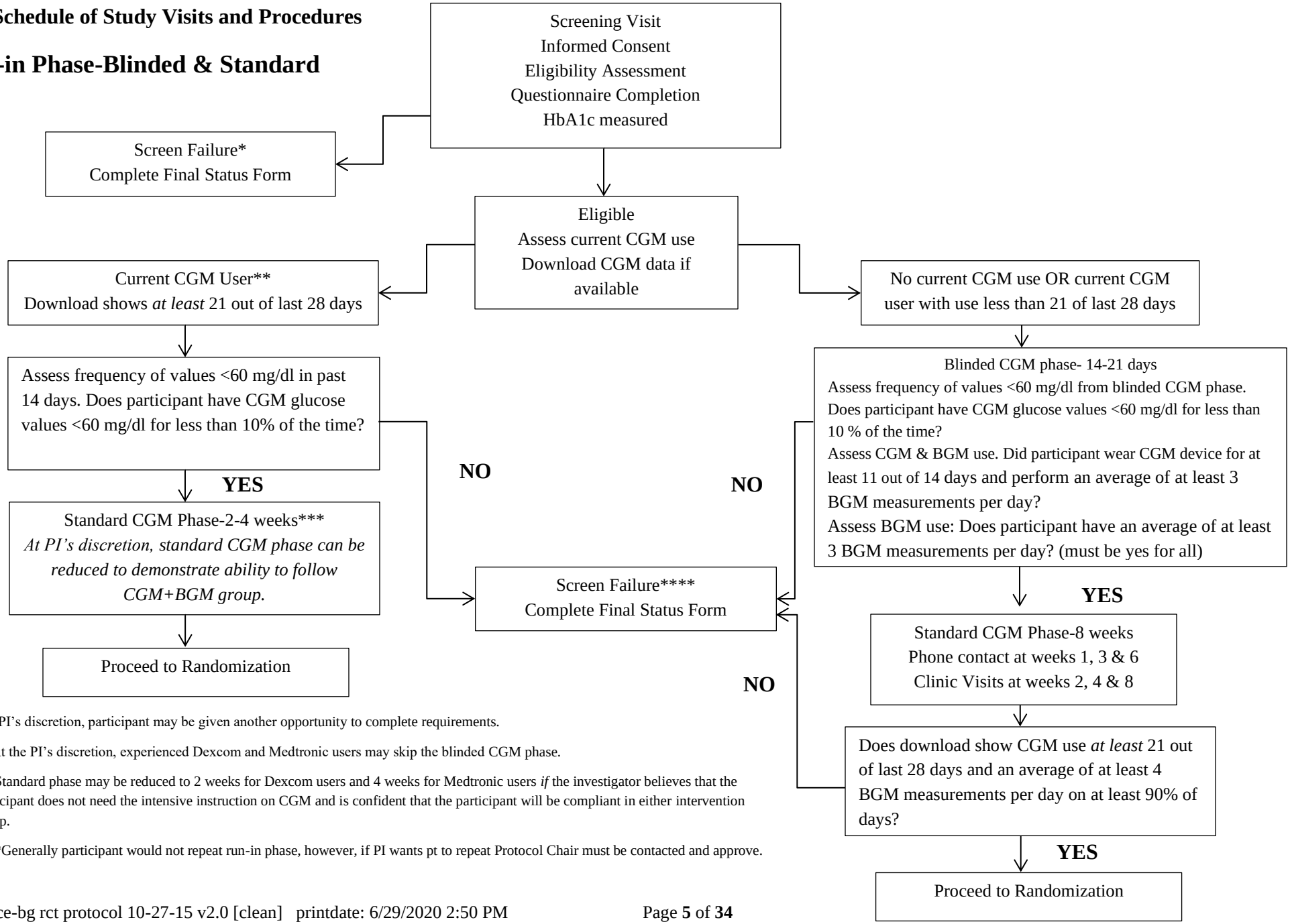
1.5 Aspects of Protocol for Risk Mitigation

The risk of using CGM alone for insulin dosing relates 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 when an insulin bolus is given. The circumstance of most concern would be an erroneous high CGM glucose value such that an overbolus of insulin would be given. Although this is expected to be a very uncommon occurrence, the protocol is taking a conservative approach by defining a patient population for the study that has demonstrated diabetes management competency, is at low risk for severe hypoglycemia and its consequences, and develops symptoms of hypoglycemia as the glucose level drops. Risk is further mitigated by defining circumstances when the participant should not rely solely on the CGM glucose value and a BGM measurement should be made.

The Appendix provides a detailed risk assessment and a listing of the participant eligibility/exclusion criteria and the aspects of the protocol that have been defined to mitigate risk.

1.6 Schedule of Study Visits and Procedures

Run-in Phase-Blinded & Standard



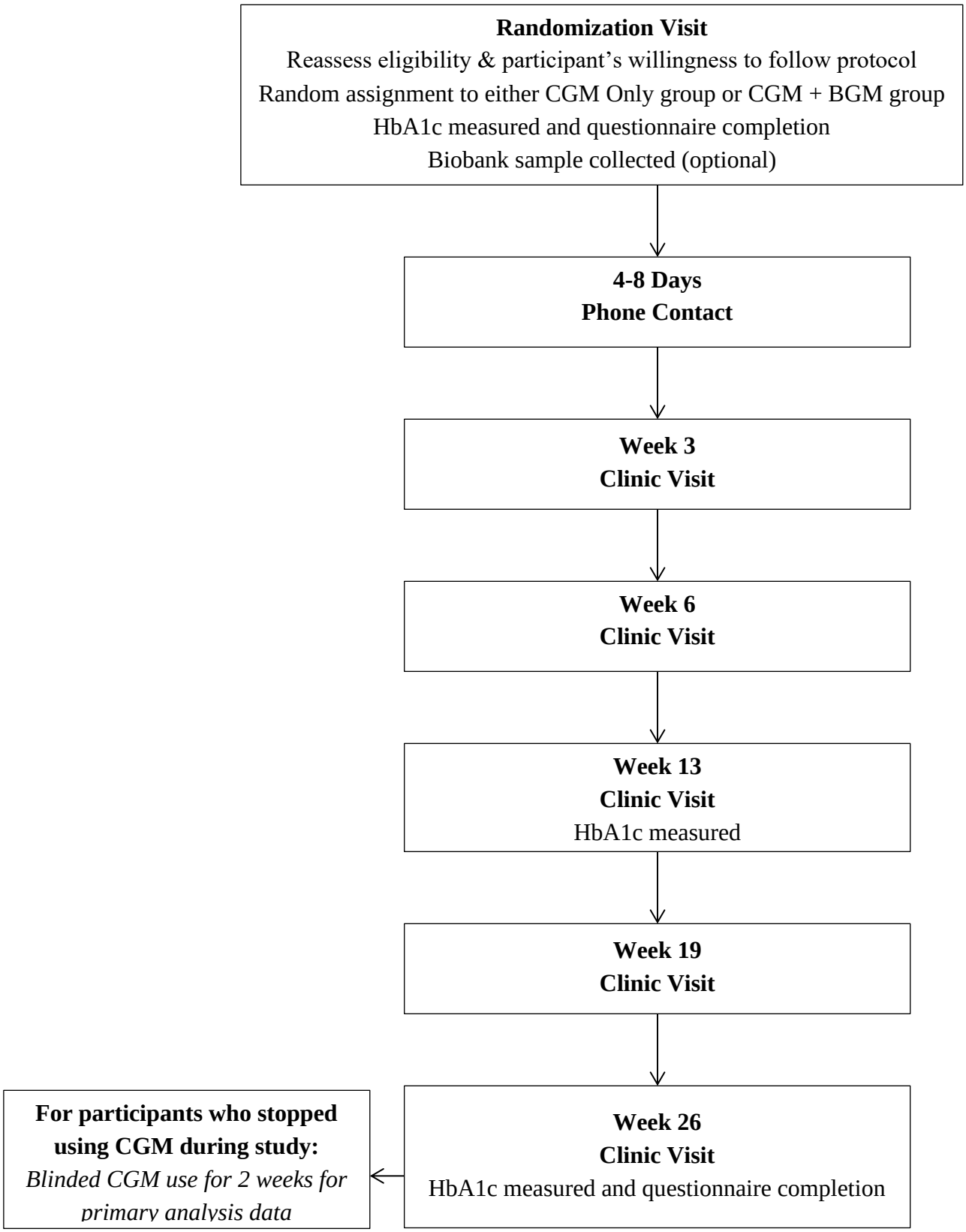
*At PI's discretion, participant may be given another opportunity to complete requirements.

** At the PI's discretion, experienced Dexcom and Medtronic users may skip the blinded CGM phase.

***Standard phase may be reduced to 2 weeks for Dexcom users and 4 weeks for Medtronic users *if* the investigator believes that the participant does not need the intensive instruction on CGM and is confident that the participant will be compliant in either intervention group.

****Generally participant would not repeat run-in phase, however, if PI wants pt to repeat Protocol Chair must be contacted and approve.

Main Study Randomization Flow Chart



Run-in Phase*

	Blinded Run-in Phase		Standard Run-in Phase					
	Screening	**14-21 d**	**1w**	**2w**	**3w**	**4w**	**6w**	**8w**
Visit or Phone	**V**	V	P	V	P	V	P	V
Informed Consent	**X**							
HbA1c-point of care or local lab	**X**							
Hypoglycemia unawareness: Clarke Survey	**X**							
Blinded CGM initiated	**X**							
Standard CGM initiated		**X**						
CGM training		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Diabetes Technology Questionnaire	**X**							
Hypoglycemia Fear Survey	**X**							
AE Assessment		**X**	**X**	**X**	**X**	**X**	**X**	**X**

* Note: Current CGM users may be eligible to skip part of the run-in phase (see section 3.1)

Randomized Trial

	Rand	4-8d	3w	6w	13w	19w	26w
Visit or Phone	**V**	**P**	**V**	**V**	**V**	**V**	**V**
HbA1c-point of care or local lab	**X**				**X**		**X**
Central lab HbA1c	**X**				**X**		**X**
Diabetes Technology Questionnaire							**X**
Hypoglycemia Fear Survey							**X**
AE Assessment		**X**	**X**	**X**	**X**	**X**	**X**
Biobank Sample Collection (optional)	**X**						

1.7 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.

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

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

The protocol is considered a significant risk device study, due to the fact that CGM is being used by one group to make treatment decisions. Therefore, an IDE from the FDA is required.

CHAPTER 2: ELIGIBILITY AND SCREENING VISIT

2.1 Study Population

Up to 350 individuals with type 1 diabetes are expected to be screened for the study so that a minimum of 225 will enter the randomized trial. Screening will continue until the recruitment target for the randomized trial is reached; so it is possible that the number screened will exceed this total depending on the proportion of participants who successfully complete the run-in phase. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Study participants who have commenced the run-in phase prior to this notification can be randomized up until the end date, which means that the recruitment goal for the randomized trial might be exceeded. The maximum number of participants in the randomized trial will be 250.

2.2 Informed Consent

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

As part of the informed consent process, each participant will be asked to sign an authorization for release of protected health information (PHI).

2.3 Eligibility and Exclusion Criteria

2.3.1 Eligibility

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

1) Clinical diagnosis of type 1 diabetes
   The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not needed.
2) Age $\geq$18 years
3) T1D duration $\geq$1 year
4) HbA1c $\leq$9.0%
   - *A local laboratory or DCA2000 or comparable point of care device will be used to assess eligibility.*
5) Use of an insulin pump for insulin delivery for at least 3 months, with no plans to discontinue pump use during the next 8 months
6) Participant is able to manage his/her diabetes with respect to insulin administration and glucose monitoring, as assessed by the investigator during the screening visit.
7) Participant understands the study protocol and agrees to comply with it, including willingness to use the study CGM and BGM.
8) No expectation that participant will be moving out of the area of the clinical center during the time period of the study, unless the move will be to an area served by another study center.

2.3.2 Exclusion

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

1) Severe hypoglycemia in the last 12 months in which the assistance of another individual was needed or seizure/loss of consciousness in the past 3 years (see section 5.1 for more detailed definition)
2) Significant hypoglycemia unawareness based on the Clarke Hypoglycemia Unawareness Survey defined as at least one of the following being present:
    - Survey score >2
    - Survey Q1 is answered as 'I no longer have symptoms when my blood sugar is low'
    - Survey Q7 response indicates that symptoms of hypoglycemia are not felt until glucose level is <50 mg/dl
    - Survey Q8 response is never or rarely to the question 'to what extent can you tell by your symptoms that your blood sugar is low'
3) More than one DKA event in the past year
4) History of seizures other than due to hypoglycemia
5) Current use of a threshold suspend pump feature (note: participant is eligible if a pump with this feature was being used but the threshold suspend was not active)
6) Myocardial infarction or stroke in past 6 months
7) Estimated Glomerular Filtration Rate (GFR) <30 obtained within the prior 12 months as part of usual care or kidney transplant
8) Most recent thyroid function test results abnormal, obtained as part of usual care within the prior 2 years
9) The presence of a significant medical or psychiatric disorder or use of a medication that in the judgment of the investigator will affect the wearing of the sensors, the completion of any aspect of the protocol, or increase risk
10) Cognitive difficulties that, in the judgment of the investigator, could impair the individual's ability to follow the protocol or increase risk
11) Initiation of a non-insulin drug for glucose control during the past 3 months, planned initiation during the next 8 months, or discontinuation of a non-insulin drug for glucose control during the past 3 months (note: individuals using a non-insulin medication for glucose control for 3 or more months are eligible provided there is no expectation that the medication will be discontinued during the time period of study participation)
12) Use of a systemic beta blocker drug
13) Regular use of oral corticosteroids
14) Anticipated need to use acetaminophen during the time course of the study
15) Inpatient psychiatric treatment in the past 6 months
16) Currently pregnant or lactating or plan to attempt getting pregnant during the time period of the study
    - Females with child-bearing potential will be queried about the possibility of pregnancy and a urine pregnancy test will be performed if there is uncertainty as to the possibility of pregnancy. They must agree to use appropriate birth control during the time period of the study. Participants will receive education regarding birth control methods which may be considered as highly effective, which are methods that can achieve a failure rate less than 1% per year when used consistently and correctly and include:
        - Combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)

- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

17) Participation in an intervention study (including psychological studies) in past 6 weeks

18) Known adhesive allergy

19) From the blinded run-in phase (or from pre-study CGM use if criteria met to skip the blinded run-in phase- see section 3.3.1), CGM values <60 mg/dl for more than 10.0% of the time

20) Unsuccessful completion of the run-in phases with respect to CGM or BGM use (see sections 3.3.1 and 3.5)

2.4 Screening and Baseline Data Collection

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

Information collected from the chart and solicited from the participant will include: medications, medical conditions, physical exam, management, demographics, socio-economic characteristics, exercise, alcohol consumption, nutrition, insulin use, other diabetes management factors, living situation, family history, social history, hospitalizations, and utilization of health care services.

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

2.4.1 Testing and Assessments

Testing and Assessments will include the following:

1) HbA1c measured using a point-of-care device or at a local lab (*a HbA1c measurement obtained as part of usual care can be used if no more than 4 weeks prior to obtaining consent)*
2) Hypoglycemic Unawareness Assessment – Clarke survey
3) Diabetes Technology Questionnaire (DTQ)
    - The DTQ consists of 30 questions regarding diabetes treatment practices and the impact on the individual of living with diabetes
4) Hypoglycemia Fear Survey
    - The survey consists of 23 questions regarding the effect of hypoglycemia or worry about hypoglycemia on the individual with diabetes

Instructions for testing administration will be detailed in a procedures manual.

2.4.2 Blinded Continuous Glucose Monitoring

A blinded CGM sensor will be inserted as described in the next chapter; unless the participant meets criteria to skip this part of the run-in phase (see section 3.1).

2.5 T1D Exchange Clinic Registry

If a participant is not already enrolled in the T1D Exchange clinic registry, he/she will become part of the registry when joining this study. As a registry participant, information from his/her medical record may be entered into the registry database at least once a year and he/she will have an opportunity to provide an email address to be contacted in the future about other studies for which he/ she may be eligible.

2.6 T1D Exchange Biobank

The T1D Exchange Biobank is designed to support ongoing and future research by qualified investigators through collection of information and biosamples from people with T1D. Samples will be used only for the study of T1D and its complications. Within this overarching purpose, multiple T1D Exchange studies will collect blood samples specifically for the T1D Exchange Biobank, whose policies and procedures will govern the release of data and samples to investigators. The T1D Exchange Biobank is directed by the Biobank Operations Center at Benaroya Research Institute, Seattle, WA and the Jaeb Center for Health Research (JCHR), Tampa, FL, who are responsible of the operations of this database and biosample repository. Specifically, the JCHR IRB reviews and approves specific protocols under which data and samples may be obtained and shared, and ensures that adequate provisions protect the privacy and confidentiality of participants and data.

In addition to samples collected as part of this randomized trial, enrolled participants may have samples collected for storage in the T1D Exchange Sample Repository. Blood drawn may include DNA, RNA, peripheral blood mononuclear cells (PBMC), serum and plasma. Participants will have the option of declining to have samples collected and stored for future use.

CHAPTER 3: RUN-IN PHASE

3.1 Introduction

There are two parts of the run-in phase:

1) Blinded CGM for 14 days to collect baseline data and assess participant's ability to wear a CGM sensor
2) Standard CGM for up to 8 weeks for CGM training and to assess participant's ability to use CGM.

Current CGM users may be able to skip part of the run-in phase. Each participant will be categorized into one of three groups based on prior CGM use:

1) Current Dexcom use, with download showing use at least 21 of last 28 days
    - Skip the blinded CGM phase and at investigator discretion can reduce the standard CGM phase to 2 weeks for the participant to demonstrate ability to follow the CGM+BGM group protocol for BGM testing.
    - Use participant's CGM data to assess amount of hypoglycemia as described in section 3.3.1.
2) Current Medtronic use, with download showing use at least 21 of 28 days
    - Skip the 14-day blinded CGM phase and at investigator discretion, can reduce the standard CGM phase to 4 weeks if the investigator believes that the participant does not need the additional instruction on CGM use planned for the rest of the standard CGM run-in phase. Training on using CGM data will still be given.
3) No current CGM use or current Dexcom or Medtronic user with use < 21 of last 28 days.
    - Complete the full blinded and standard CGM run-in phases (same as non CGM users): 14-day blinded and 8-week standard CGM run-in phases.

All participants will receive training on incorporating CGM into their diabetes management.

3.2 Blinded CGM Use

At the screening visit, a CGM sensor will be placed for participants who will complete the blinded CGM phase. The CGM receiver will be blinded so that the participant is not able to see the CGM glucose values. The participant will be instructed on sensor use including insertion of a new sensor after 7 days (or sooner if the sensor comes out). Additional sensors, a BGM, aketone meter and test strips will be provided.

Participants will be required to use the study BGM and may need to manually enter glucose values into the pump if a bolus calculator is used.

Participants will be informed that in order to be eligible for the randomized trial, the blinded CGM must be used on a minimum of 11 out of 14 days and an average of 3 blood glucose measurements must be made each day using the study BGM.

3.3 Blinded CGM Assessment/Standard CGM Initiation Visit

Enrolled participants will return 14 to 21 days after screening to assess the blinded CGM wear. The purpose of the visit will include the following:

- Assessment of compliance with the use of the CGM and BGM
- Assessment of skin reaction in areas where a CGM sensor was worn
- Assessment of frequency of CGM glucose values <60 mg/dl (for eligibility assessment)
- Initiation of standard CGM use and instructions on its use

3.3.1 Assessment of Blinded CGM and Blood Glucose Meter Data

The CGM data will be downloaded and reviewed to assess whether the participant has used the CGM on at least 11 of 14 days.

The study BGM will be downloaded to verify that at least 3 measurements were made each day on at least 13 of 14 days.

The frequency of CGM glucose values <60 mg/dl will be determined.

- Participants with values <60 mg/dl for more than 10.0% of the time will not be eligible for the randomized trial and will be discontinued from the study.
- For participants currently using a Dexcom or Medtronic CGM with a download showing use at least 21 out of the past 28 days, the last 14 days of CGM data will be used to determine the percentage of values <60 mg/dl.

Participants who are unable to meet the CGM and BGM compliance requirements will be withdrawn from the study, unless the investigator believes that there were extenuating circumstances that prevented successful completion. In such cases, the investigator will contact the protocol chair to request approval to repeat this part of the run-in phase.

3.3.2 Initiation of Standard CGM

The participant will be provided with sensors and instructed to use the CGM on a daily basis. Training will be provided as to how to use the CGM in real-time to make management decisions and how to review the data after an upload for retrospective review. If the participant did not already receive a study BGM and test strips, these will be provided. The participant will be instructed to verify the CGM glucose readings with a study BGM measurement prior to making any management decisions. Participants will be asked to perform at least 4 BGM measurements per day on the study BGM. In essence, the protocol to be followed will be the same protocol to be followed by the CGM+BGM group in the RCT.

The participant will be observed placing the sensor. The Dexcom G4 Platinum User's Guide will be provided for the participant to take home.

Participants with a home computer will be provided with the software to download the CGM. Participants without a computer (or without a compatible computer, depending on the software requirements) may be given a loaner laptop to use for the duration of their participation in the study.

3.4 Standard CGM Run-in Phase Visits and Phone Contacts

Following initiation of standard CGM use, visits will occur after 2 weeks $\pm$3 days, 4 weeks $\pm$3 days, and 8 weeks $\pm$1 week, with phone contacts at 1 week $\pm$3 days, 3 weeks $\pm$3 days, and 6 weeks $\pm$6 days.

At each visit, frequency of use of CGM will be assessed and the CGM glucose data, standard BGM data, and pump data if available will be used to advise the participant on alterations in diabetes management. Adverse events also will be assessed. The purpose of the phone call will be to address any questions the participant has regarding use of the study devices and assess any potential adverse events.

3.5 Assessment of Successful Completion of the Standard CGM Run-in Phase

After using standard CGM for up to 8 weeks, compliance with use of CGM over the prior 4 weeks will be assessed. To enter the randomized trial, $\geq$21 days of CGM use during the prior 28 days will be required. In addition, an average of $\geq$4 BGM measurements must have been made on the study BGM on at least

90% of days. For participants whose run-in phase is shortened, the number of days of CGM use and BGM testing will be accordingly reduced.

The exclusion criteria from screening will be reviewed again and if the participant is no longer eligible based on these criteria, he or she will be dropped from the study.

An assessment of CGM knowledge will be made and the participant must demonstrate sufficient competency to proceed to the RCT.

Participants who are unable to meet the CGM and BGM compliance requirements will be withdrawn from the study, unless the investigator believes that there were extenuating circumstances that prevented successful completion. In such cases, the investigator will contact the protocol chair to request approval to repeat this part of the run-in phase.

CHAPTER 4: RANDOMIZED TRIAL

4.1 Timing of Randomization Visit

The randomization visit will coincide with the completion of the standard CGM run-in phase (after 2-8 weeks of standard CGM use, depending on the participant's CGM use prior to the study).

4.2 Blood Samples

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

- HbA1c (a point-of-care or local laboratory measurement also will be made in case there is a problem with the central laboratory sample)
- Samples for Biobank storage *(optional)*: may include DNA, RNA, peripheral blood mononuclear cells (PBMC), serum and plasma. The maximum blood volume collected will not exceed 250 ml.

4.3 Randomization

Participants who have met the use criteria for CGM and BGM will be randomly assigned to one of two treatment groups in a 2:1 ratio:

1. CGM Only group
2. CGM+BGM group

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

- The Jaeb Center will construct a Master Randomization List using a permuted block design, with stratification by clinical site.

4.4 Supplies

Participants will be provided with sufficient CGM and BGM supplies to last until the next visit.

Participants randomized to the CGM Only group will be provided a separate BGM which has been configured such that the glucose values are not visible (blinded BGM).

4.5 Home Procedures and Diabetes Management

Each participant will be asked to use a CGM sensor on a daily basis, inserting a new sensor as needed.

Participant instructions will provide guidelines for using CGM as part of diabetes management.

Both groups will perform BGM measurements for sensor calibration according to Dexcom specifications.

Both groups will be instructed to perform a standard BGM measurement when the fasting CGM glucose level is >300 mg/dl. Both groups will also be instructed to perform a standard BGM measurement when the CGM glucose level during the day is >300 mg/dl for one hour. In both instances, if the BGM measurement confirms that the glucose level is >300 mg/dl, then the participant will be instructed to perform a blood ketone measurement.

Participants who discontinue use of CGM prior to 6 months will be encouraged to use CGM in blinded mode for 2 weeks at 6 months. This may necessitate an additional visit.

4.5.1 Instructions for the CGM+BGM Group

The CGM+BGM group will be instructed to continue using CGM as it was used in the standard CGM run-in phase. A BGM measurement is to be made on the study BGM before going to bed, whenever an

insulin bolus is given and when treating or attempting to prevent hypoglycemia. Additional BGM measurements can be made on the study BGM at any time that the participant desires.

4.5.2 Instructions for the CGM Only Group

The CGM Only group will be instructed to check the blood glucose with the standard study BGM for calibration of the CGM as described in the user manual and for the circumstances that are specified below. This group will make management decisions based on the CGM glucose value without a BGM confirmation measurement as long as the participant is confident that the CGM glucose value is not erroneous.

1) After insertion of a new sensor, CGM will be used as adjunctive to BGM for the first 12 hours.
2) On a sick day (Nausea, vomiting)
3) CGM will be used as adjunctive to BGM if the participant takes acetaminophen for any reason. The participant will be required to wait 4 hours after taking acetaminophen before using the CGM again for diabetes management decisions.
4) A standard BGM measurement will be made if any symptoms suggestive of hypoglycemia are present but the CGM glucose level is not hypoglycemic or dropping rapidly.
5) A standard BGM measurement will be made if 20 minutes after treating a low CGM glucose level, the CGM glucose level has not begun to rise according to participant's expectation based on past experience.
6) A standard BGM measurement will be made prior to giving an insulin bolus if the CGM glucose level is >250 mg/dl.
7) A standard BGM measurement will be made when the fasting CGM glucose is >300 mg/dl. A ketone measurement will be made if the BGM measurement confirms that the glucose is >300 mg/dl.
8) A standard BGM measurement will be made when the CGM glucose level during the day is >300 mg/dl for one hour. A ketone measurement will be made if the BGM measurement confirms that the glucose is >300 mg/dl.

Participants will be instructed to make a BGM measurement on the blinded study BGM before going to bed, whenever an insulin bolus is given and when treating or attempting to prevent hypoglycemia and a standard BGM measurement has not been made as described above. In addition, the participant may be asked to make post-prandial blinded BGM measurements at selected times.

4.5.3 Discrepancies between CGM and BGM Readings

The following instructions will be provided to participants in both groups:

1) If it has been at least 12 hours since the initial calibration and the difference between the CGM reading and a BGM value is greater than 20% of the BGM value for CGM readings >80mg/dL, or greater than 20 points for CGM readings <80mg/dL, the participant will wash his or her hands and perform another BGM measurement.

   If the difference between this second BGM measurement and the CGM is still greater than 20% of the BGM value for CGM readings >80mg/dL, or greater than 20 points for CGM readings <80mg/dL, the second BGM result will be entered into the CGM to recalibrate the sensor.

2) If a recalibration was done to correct a discrepancy between the CGM and BGM readings, the participant will wash his or her hands and perform a BGM measurement prior to the next meal. If

the two measurements still differ by greater than 20% of the BGM value for CGM readings >80mg/dL or greater than 20 points for CGM readings <80mg/dL, the sensor will be replaced.

4.6 Follow-up Visits and Phone Contacts

Following randomization, there will be a phone contact during the first week (4 to 8 days following randomization) to address any questions the participant has about the protocol (e.g., in the CGM Only group, when to do blinded and when to do standard BGM tests).

Follow up visits will occur at 3, 6, 13, 19, and 26 weeks, with a $\pm$1 week window around each target time.

Additional visits and contacts (phone, email, texts) will occur as needed.

4.6.1 Procedures at Follow-up Visits

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

- Assessment of compliance with CGM and BGM use
- Solicitation of the occurrence of reportable adverse events
- Review of glucose data and pump data and recommendations for changes in diabetes management
- Evaluation and optimization of alarm settings
- HbA1c determination using a point of care device or local lab (13 weeks, 26 weeks)
- Collection of a blood sample to send to the central laboratory for HbA1c determination (13 weeks, 26 weeks)
- Completion of the Diabetes Technology Questionnaire and Hypoglycemia Fear Survey (26 weeks)

CHAPTER 5: ADVERSE EVENTS

5.1 Definition

Reportable adverse events for this protocol include the following: severe hypoglycemia as defined below, diabetic ketoacidosis as defined below, all device-related events, and all events meeting criteria for a serious adverse event. In addition, hyperglycemia not meeting the definition of DKA will be reported as an adverse event if emergency evaluation or treatment was obtained from a health care provider; these events are considered Adverse Events and not Serious Adverse Events unless one of the criteria for SAE is met. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

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

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

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

5.2 Recording of Adverse Events

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

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

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study intervention.

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

Yes

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

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

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

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

Adverse events will be coded using the MedDRA dictionary.

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

5.3 Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward occurrence that:

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

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

Serious or unexpected related adverse events must be reported to the Coordinating Center immediately via completion of the online serious adverse event form.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 3 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 their Institutional Review Board.

5.4 Data and Safety Monitoring Board Review of Adverse Events

A Data and Safety Monitoring Board (DSMB) will provide independent monitoring of the study protocol including adverse events.

As indicated in section 5.6.2, certain events will be reported to the DSMB within 3 business days after the Coordinating Center is informed of the event.

In addition, cumulative adverse event data will be tabulated semi-annually for review by the DSMB. Following each DSMB data review, a summary will be made available for submission to Institutional Review Boards.

5.5 Risks And Discomforts

5.5.1 Hypoglycemia

Some degree of hypoglycemia can occur as part of daily living for an individual with type 1 diabetes. CGM has the potential to reduce the frequency of hypoglycemia as has been shown in several studies. However, CGM inaccuracy could increase the risk for hypoglycemia if insulin is delivered based on an erroneous sensor glucose level. Thus, theoretically the 'CGM Only' group could have this risk when the CGM value is not verified with a BGM measurement before delivering insulin.

5.5.2 Hyperglycemia

Hyperglycemia can occur for a substantial portion of the day in many individuals with type 1 diabetes. The expectation in the study is that by using CGM, the frequency and severity of hyperglycemia will be reduced. The frequency of DKA should be no greater with study participation than without study participation.

5.5.3 Skin Reactions

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

5.5.4 Fingerstick Blood Glucose Measurements

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

5.5.5 Psychosocial Questionnaires

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.

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

5.6 Study Stopping Rules

5.6.1 Criteria for Individual Participants

The conduct of the study intervention protocol will be discontinued for a participant if any of the following occur:

1) A single severe hypoglycemic event resulting in seizure or loss of consciousness or more than one event meeting the definition of severe hypoglycemic event in section 5.1 but without seizure or loss of consciousness
2) A single DKA event as defined in section 5.1, unrelated to illness
3) Participant pregnancy
4) Deterioration of diabetes control or development/deterioration of a medical condition that in the judgment of the site principal investigator carries an unacceptable level of risk for the participant to continue in the study
5) Poor compliance with the protocol that in the judgment of the site principal investigator carries an unacceptable level of risk for the participant to continue in the study
6) Participant requests withdrawal from the study

Site staff will inform the site principal investigator on the same day that the staff becomes aware that any of the above criteria have been met. The participant will be immediately discontinued from following the intervention protocol (for both groups) and will revert to usual care for diabetes management. Unless the participant withdraws from the study, the participant will be asked to return for the final study visit at 6 months.

The Coordinating Center will track #1 and #2 above to assure that the intervention protocol has been discontinued for participants meeting one of these criteria.

5.6.2 Criteria for Stopping the Overall Study

The DSMB will have the responsibility of determining if the overall study should be stopped.

Each participant withdrawal as described in section 5.6.1, except for reason #6, will be reported to the DSMB within 3 business days of the Coordinating Center being notified. In addition, all serious, related, unexpected events will be reported to the DSMB within 3 days of the Coordinating Center being notified.

The overall study will be stopped if the number of participants discontinued due to reasons #1 and #2 above in the CGM Only Group exceeds the number in the CGM+BGM Group by 3 or more at any time. However, the DSMB will have the authority to stop the study at any time because of safety concerns even if this criterion is not met.

The Coordinating Center will track all participant withdrawals. If the above rule is met (CGM Only Group exceeding CGM+BGM Group by 3 or more), an emergency meeting of the DSMB will be convened within 7 days to review the data. In addition, the DSMB Chair may request a meeting at any time.

CHAPTER 6: MISCELLANEOUS CONSIDERATIONS

6.1 Benefits

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 CGM itself will be useful for participants' diabetes self-management.

The results of the study are likely to be beneficial for patients with diabetes irrespective of the study findings.

6.2 Participant Reimbursement

The study will provide all devices and supplies needed for the study including a CGM system and sensors, BGM and test strips, a ketone meter and test strips, and other related supplies. Participants will need to return all study devices (CGM system, BGM and ketone meters) at the end of their participation in the study. The study will be paying for the costs of the research procedures that are part of the study. Costs of standard medical care for diabetes, including insulin that would occur even if the participant were not in this study, will be the participant's responsibility.

The study will be providing a $25 gift or money card per completed protocol-required visit to cover travel and other visit-related expenses. Participants who have at least one protocol-specified phone contact during the run-in phase will receive a $25 gift or money card. Additional travel expenses may be paid in select cases for participants with higher expenses.

Participants in the randomized trial who use the CGM on at least 70% of days and complete the required BGM measurements appropriately (blinded/standard depending on treatment group) will receive $200 in gift or money cards. This amount has been figured as approximately $1 per study day.

6.3 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. The investigator may withdraw a participant who is not complying with the protocol.

6.4 Confidentiality

For security purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. Information given to the coordinating center will include: diagnosis, general physical exam information (height/weight/blood pressure/etc.), insulin, questionnaire results, hemoglobin A1c results, continuous glucose monitor results, blood work results, BGM blood glucose measurements, insulin pump data, ketone measurements, information pertaining to hypoglycemic excursions and the treatment given, as well as all other study related data gathered during study visits. During each visit, the study devices will be downloaded to a computer that is secured and password protected and the files will be uploaded to the Coordinating Center via the secure website for the study. All files will include only the participant's identifier; no names or personal information will be included.

Laboratory specimens will be sent to the study central laboratory.

Data from the study may be provided to Dexcom, Inc., the company that makes the CGM and to Abbott Diabetes Care, Inc., the company that makes the BGM devices being used for the study.

CHAPTER 7: STATISTICAL CONSIDERATIONS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan (SAP) will be written and finalized prior to the completion of the study.

7.1 Sample Size Estimation

The JDRF CGM RCT data were used to estimate the mean and variance of time in range (70 to 180 mg/dL) and the correlation of the baseline and 6 month assessments for 57 participants in the CGM group who met the current protocol's eligibility criteria for age ≥25 years, HbA1c ≤8.5%, no severe hypoglycemic events in the prior 6 months, and CGM values <60 mg/dl for ≤5% of the time during the run in phase. The standard deviation for time in range at 6 months was 13% with a correlation between baseline and 6 months of 0.48 (standard deviation adjusted for correlation =11%). The 95% confidence interval for the standard deviation adjusted for the correlation is 10% to 14%. These were used to compute sample sizes in the table below

Total Sample Size Estimates

Based on 80% Power / 90% Power*

Standard Deviation	Noninferiority Limits			
	5%	**7.5%**	**10%**	**15%**
10%	$^{102}/_{140}$	$^{46}/_{64}$	$^{28}/_{36}$	$^{14}/_{18}$
11%	$^{122}/_{168}$	$^{56}/_{76}$	$^{32}/_{44}$	$^{16}/_{20}$
12%	$^{144}/_{200}$	$^{66}/_{90}$	$^{38}/_{52}$	$^{18}/_{24}$
14%	$^{196}/_{270}$	$^{88}/_{122}$	$^{50}/_{70}$	$^{24}/_{32}$

*One-sided alpha=0.05, with 1:1 allocation between treatment groups and no adjustment for dropouts.

**SD adjusted for correlation between baseline and 6 months of 0.48

A noninferiority limit of 7.5% has been selected. Based on the computations in the above table and a standard deviation of 14% (taking into account the correlation of 0.48), to have at least 90% power the total sample size was estimated to be 122. However, in order to have greater exposure to the CGM Only use in the study to better assess safety, it was decided to have 225 participants randomly assigned 2:1 to the CGM Only group or CGM+BGM group.

7.2 Statistical Analysis Plan

Analyses will follow the intent-to-treat principle with all participants analyzed in the group to which they were randomized. The primary analysis will include all participants. A secondary per-protocol analysis will be conducted, the details of which will be included in the SAP.

7.2.1 Outcomes

Primary Outcome

- % time in range of 70 to 180 mg/dl, measured with CGM over the full 6 months of the study

Secondary Outcomes

- Episodes of severe hypoglycemia
- Combined HbA1c and severe hypoglycemia outcome—no worsening of HbA1c by greater than 0.3% AND no severe hypoglycemia event between baseline (randomization) and 6 months
- Change in HbA1c from baseline to 6 months
- Episodes of diabetic ketoacidosis (DKA)
- Other serious adverse events
- Biochemical hypoglycemia (percentage of sensor values <70 mg/dl, <60 mg/dl, and <50 mg/dl)
- Biochemical hyperglycemia (percentage of sensor values >180 mg/dl, >250 mg/dl, and >300 mg/dl)
- Ketotic events not meeting criteria for DKA with blood ketone level $\geq$0.6 mmol/L and $\geq$1.0 mmol/L
- % of days with at least 20 minutes of sensor glucose values <60 mg/dl
- % of days with at least 20 minutes of sensor glucose values >300 mg/dl
- Measures of glycemic variability: coefficient of variation
- Quality of life
- Bolus calculator use frequency

7.2.2 Analytic Methods

Primary Outcome

The relationship between the % time in range and the treatment group will be examined through a least squares regression model adjusting for baseline time in range, CGM user at time of enrollment, and possibly clinical center. If the number of participants per clinical center is too small to include center as a fixed effect (<10 participants/center) then clinical center will be included as a random effect instead. Previous data suggest that the time in range is typically approximately normally distributed so a transformation should not be necessary. However, this will be explored and a transformation or nonparametric analyses will be used instead if the data are highly skewed. A one-sided 95% confidence interval for the difference in treatment groups (CGM+BGM group minus CGM Only group) will be computed.

Secondary Outcomes

For CGM measures, separate analyses will be performed overall and for daytime and nighttime. Continuous variables will be examined in a manner similar to the primary outcome. For categorical variables, the frequencies and percentages for each category will be tabulated separately for each treatment group and the relationship between the treatment group and the outcome will be studied via Fisher's exact test or logistic regression.

Primary analysis will be a single comparison and no attempt will be formally made to control the overall type I error rate for the secondary analyses including subgroup analyses for injection and pump users. Inclusion of sensor data and imputation of missing data will be as described in sections 7.2.3 and 7.2.4.

7.2.3 Missing Data

The CGM data analyses will include all data available during the randomized trial. Therefore, there will not be imputation for missing data.

For HbA1c, if the central laboratory value is unavailable then the local point of care or local laboratory value at 26 weeks will be used. If neither measurement is available then the value will be imputed based on available previous lab and/or local HbA1c measurements using multiple imputation methods.(10)

7.2.4 CGM Use

CGM use will be tabulated as (1) the number of days in which CGM was used and (2) the proportion of time with CGM glucose values. Each will be tabulated overall and by month for each treatment group.

7.2.5 Clinical Severe Hypoglycemic Events

Clinical severe hypoglycemic events will be tabulated in each treatment group and reported as the number of events per 100 person-years. A treatment group comparison will be made using a permutation test, and the proportion with of at least one event will be examined using Fisher's exact test or logistic regression.

- For purposes of analysis, a severe hypoglycemic event will be defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. 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.

7.2.6 Subgroups

Separate analyses will be conducted for prior CGM users and nonusers using similar methods as for the primary analysis above. The interaction between prior CGM use and treatment group will be assessed by including an interaction term in the least squares model.

7.2.7 Questionnaires

Mean ± SD values or percentiles appropriate to the distribution will be given by randomization group for the total score and each subscale for each questionnaire at 26 weeks.

7.2.8 Adverse Events

Adverse events will be tabulated by treatment group and appropriate statistical tests will be performed.

For each case of severe hypoglycemia or DKA, the CGM and BGM (blinded and standard) data for the prior 24 hours will be assessed along with any available insulin data and knowledge of precipitating factors to make a determination as to whether the event appeared to be related to reliance on the CGM.

7.2.9 Frequency of CGM Use

CGM use in both groups will be tabulated with respect to the number of days CGM was used and the percentage of maximum possible time of CGM use. The results will be compared between treatment groups.

7.2.10 Frequency of Standard BGM Measurements

Standard BGM frequency per day will be computed for each participant in both groups. Excluding calibration values, the number of standard BGM measurements per day will be compared between treatment groups.

7.2.11 Blinded BGM Measurements in the CGM Only Group

For the CGM Only group, the frequency of blinded BGM measurements will be tabulated over the course of the study.

The blinded BGM values will be compared with corresponding CGM values. The use by the CGM Only group of a blinded BGM meter at times that a standard BGM measurement is not made will provide the opportunity to assess the frequency of discordance between CGM and BGM glucose measurements and the clinical outcome of each of these events. The data will be explored to identify cases where the difference

could be clinically meaningful (without knowledge of the subsequent course) and then an assessment as to the outcome clinically. In addition, for cases of SH, DKA, biochemical hypoglycemic events, and biochemical hyperglycemic events, the available data will be explored to determine if reliance on the CGM glucose values could have contributed to the event.

7.2.12 Other Tabulations

Other tabulations will include

1) Baseline characteristics
2) Visit and phone contact completion/Missed and out-of-window visits and phone contact
3) Protocol deviations

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APPENDIX 1

A Randomized Trial Comparing Use of Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Adults with Type 1 Diabetes

DEVICE RISK ANALYSIS

Scope: The Risk Analysis assesses risks to the individual who participates in the study if assigned to the experimental treatment group (CGM Only group) over and above the risks associated with having type 1 diabetes and using CGM according to its approved label, which is assessed by having a control group that uses CGM according to the approved label of the Dexcom G4 Platinum Continuous Glucose Monitoring System (CGM+BGM group).

Discussion of Risk Analysis: The risk of using CGM alone for insulin dosing, without a confirmatory BGM measurement, relates to the accuracy of the sensor and the possibility of an adverse event if the CGM glucose value substantially deviates from the true glucose level, particularly when an insulin bolus is given. Thus, average sensor accuracy is not the relevant issue. It is the extremes of inaccuracy that are most relevant as such instances could have an adverse clinical effect on the study participant. The protocol has been designed to mitigate these risks.

There are essentially two hazards requiring mitigation:

1) CGM glucose reading erroneously substantially higher than the true glucose level such that a larger bolus is given than should have been given. This has the potential to result in severe hypoglycemia.
2) CGM glucose reading erroneously substantially lower than the true glucose level such that a smaller bolus is given than should have been given. This has the potential to result in hyperglycemia.

Although these events are expected to be very uncommon occurrences, the protocol is taking a conservative approach by defining a patient population for the study that has demonstrated diabetes management competency and is at reduced risk for severe hypoglycemia and hyperglycemia. Risks for both hypoglycemia and hyperglycemia are further mitigated by defining circumstances when participants in the CGM Only group should not rely solely on the CGM glucose value and a standard BGM measurement should be made.

The risk of severe hyperglycemia which results in DKA over and above the risk in day-to-day life, as will be estimated from the control group, is virtually eliminated by the mitigations that are described below. The risk of severe hypoglycemia is substantially reduced by the mitigations described below with respect to the eligibility/exclusion criteria for study participation and the protocol requirements but cannot be totally eliminated, and there are no additional mitigations that could be put in place that could reduce the risk further. Nevertheless, the very small risk of severe hypoglycemia occurring due to sensor inaccuracy is deemed acceptable.

Risk Analysis

Our Risk Analysis is based on **Likelihood** of an event occurring and the potential **Severity** if it does occur. The **Risk Level** of an event occurring is the product of the severity and likelihood risk factors.

Potential Severity Level

Severity Number	Severity Classification	Severity Description
1	Negligible	Little or no potential of injury, pain or discomfort
2	Low	Potential of minor injury, pain, or user discomfort
3	Moderate	Potential of non-life threatening injury, pain, or direct or indirect exacerbation of existing non-life threatening condition
4	High	Major requiring medical intervention
5	Very High	Potential of imminent death or serious injury

Likelihood Level

Likelihood Number	Likelihood of Occurrence	Description
1	Improbable	Unlikely to ever occur
2	Remote	Slight probability of occurrence
3	Occasional	Occurring at irregular or infrequent intervals
4	Probable	Likely to happen or to become real
5	Frequent	Occurring at short intervals

Risk Level

The Risk Level is the product of the Likelihood of the event with the risk mitigations in place and the potential Severity. This value is used to prioritize the risks. A total score less than 9 was determined to be acceptable. This breakdown of the scoring is shown in the matrix below: "A" = acceptable risk and "U" = unacceptable risk.

		Potential Severity of the Risk				
Likelihood of Occurrence		Negligible(1)	Low (2)	Moderate(3)	High (4)	Very high(5)
	Improbable (1)	A	A	A	A	A
	Remote (2)	A	A	A	A	U
	Occasional (3)	A	A	U	U	U
	Probable (4)	A	A	U	U	U
	Frequent (5)	A	U	U	U	U

Description of Risks and Risk Mitigations

Risk 1: Hypoglycemia

Hypoglycemia resulting from an inappropriately large insulin bolus due to the CGM glucose reading being erroneously higher than the true glucose level such that a larger bolus is given than should have been given.

Mitigation

Restrictions on Patient Population

1) Exclude individuals with substantial hypoglycemia unawareness if any of the following is present on the Clark Hypoglycemia Unawareness Survey:
   - Survey score >2
   - Survey Q1 is answered as 'I no longer have symptoms when my blood sugar is low'
   - Survey Q7 response indicates that symptoms of hypoglycemia are not felt until glucose level is <50 mg/dl
   - Survey Q8 response is 'never' or 'rarely' to the question 'to what extent can you tell by your symptoms that your blood sugar is low'
2) Exclude individuals with a severe hypoglycemic event requiring assistance in the past 12 months and severe hypoglycemia resulting in severe/loss of consciousness within 3 years since prior severe hypoglycemia is an indicator of greater risk of future severe hypoglycemia
3) Restrict age to be ≥18 years old since adults are more likely to adhere to protocol
4) Exclude HbA1c >9.0% as an indirect indicator of possible poor self-management compliance
5) Exclude individuals who are at greater risk for being harmed by hypoglycemia—such as history of seizures, myocardial infarction in past 6 months, or stroke in past 6 months
6) Exclude if during run-in phase compliance with CGM and BGM instructions is not demonstrated
7) Exclude if during run-in phase, CGM glucose values are <60 mg/dl for more than 10.0% of the time since prior biochemical hypoglycemia increases the risk of a severe hypoglycemic event
8) Non-CGM users will use standard CGM for 8 weeks prior to entering the randomized trial to ensure that the participant is well trained on using CGM and all participants will be required to demonstrate a good understanding of CGM on an assessment of CGM knowledge at end of run-in phase
9) Exclude if using a beta blocker since it can mask the symptoms of hypoglycemia
10) Exclude if there is need to use acetaminophen since it can produce sensor inaccuracy
11) Exclude if known to be pregnant or intending to try to become pregnant during time period of the study since it can lead to glucose fluctuations

Protocol/Procedural Stipulations

1) The CGM will be used as adjunctive for the first 12 hours of a new sensor, since initial accuracy may not be as good after a new sensor is inserted.
2) If it has been 12 hours since the initial calibration and the difference between the CGM glucose reading and BGM glucose value is greater than 20% of the BGM glucose value for CGM readings >80mg/dL or greater than 20 points for CGM readings <80mg/dL, the participant will be instructed to wash his or her hands and perform another BGM glucose measurement.
   a. If the difference between this second BGM measurement and the CGM is still greater than 20% of the BGM value for CGM readings >80mg/dL, or greater than 20 points for CGM readings <80mg/dL, the second BGM value will be entered into the CGM to recalibrate the sensor.
   b. If a recalibration was done, the participant will wash his or her hands and perform a standard BGM measurement prior to the next meal. If the CGM and BGM measurements still differ by greater than 20% of the BGM glucose value for CGM readings >80mg/dL, or greater than 20 points for CGM readings <80mg/dL, the sensor will be replaced.
3) On a sick day (nausea and vomiting), CGM will be used as adjunctive and require a standard BGM measurement for all diabetes management decisions.

4) A standard BGM measurement will be performed if any symptoms are suggestive of hypoglycemia but the CGM glucose is not low.

5) A standard BGM measurement can be performed if the participant has any concern about CGM accuracy.

6) A standard BGM measurement will be performed if 20 minutes after treating a low CGM glucose, the CGM glucose has not begun to rise according to participant's expectation based on past experience.

7) A standard BGM will be available at all times in case a BGM measurement is needed.

8) The CGM will not be used to make diabetes management decisions for 4 hours if acetaminophen is taken for any reason.

Post-mitigation Risk Level

Severity Classification: 4 (major event requiring medical intervention)

Likelihood: 2-Remote –slight probability of occurrence at a frequency higher than expected in the control group due to sensor inaccuracy

Risk level: 8 (acceptable risk)

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Risk 2: Hyperglycemia

Hyperglycemia resulting from an insufficient insulin bolus due to the CGM glucose reading being erroneously lower than the true glucose level such that a smaller bolus is given than should have been given

Mitigation

Restrictions on Patient Population

1) Restrict age to be ≥18 years old since adults are more likely to adhere to protocol

2) Exclude HbA1c >9.0% as an indirect indicator of possible poor self-management compliance

3) Exclude if diabetic ketoacidosis occurred more than once in the past 12 months

4) Exclude if during run-in phase compliance with CGM and BGM instructions is not demonstrated

5) Non-CGM users will use standard CGM for 8 weeks prior to entering the randomized trial to ensure that the participant is well trained on using CGM and all participants will be required to demonstrate a good understanding of CGM on an assessment of CGM knowledge at end of run-in phase

6) Exclude if there is a need to use acetaminophen since it can produce sensor inaccuracy

7) Exclude if known to be pregnant or intending to try to become pregnant during time period of the study since it can lead to glucose fluctuations

Protocol Stipulations

1) The CGM will be used as adjunctive for first 12 hours of a new sensor, since initial accuracy may not be as good after a new sensor is inserted.

2) On a sick day, CGM will be used as adjunctive and require a standard BGM measurement for all diabetes management decisions.

3) A standard BGM measurement will be performed prior to giving an insulin bolus if the CGM glucose is >250 mg/dl.

4) A standard BGM measurement will be performed if the CGM fasting glucose is >300 mg/dl. A blood ketone measurement will be made if the BGM measurement confirms that the glucose level is >300 mg/dl.

5) A standard BGM measurement will be performed if the CGM glucose level during the day is >300 for one hour. A blood ketone measurement will be made if the BGM measurement confirms that the glucose level is >300 mg/dl.

6) A standard BGM measurement will be performed if at least one hour after treating a high CGM glucose with an insulin bolus, the CGM glucose has not begun to decrease according to the participant's expectation based on past experience.

7) If it has been 12 hours since the initial calibration and the difference between the CGM glucose reading and BGM glucose value is greater than 20% of the BGM glucose value for CGM readings >80mg/dL or greater than 20 points for CGM readings <80mg/dL, the participant will be instructed to wash his or her hands and perform another BGM glucose measurement.
    a. If the difference between this second BGM measurement and the CGM is still greater than 20% of the BGM value for CGM readings >80mg/dL, or greater than 20 points for CGM readings <80mg/dL, the second BGM value will be entered into the CGM to recalibrate the sensor.
    b. If a recalibration was done, the participant will wash his or her hands and perform a standard BGM measurement prior to the next meal. If the CGM and BGM measurements still differ by greater than 20% of the BGM glucose value for CGM readings >80mg/dL, or greater than 20 points for CGM readings <80mg/dL, the sensor will be replaced.

8) A standard BGM will be available at all times in case a BGM measurement is needed.

9) The CGM will not be used to make diabetes management decisions for 4 hours if acetaminophen is taken for any reason.

Post-mitigation Risk Level

Severity Classification: 4 (major event requiring medical intervention)

Likelihood: 1-Negligible –with the risk mitigations in the protocol to check the blood glucose and, if confirmed,ketones when the fasting CGM glucose is >300 mg/dl and when the CGM glucose level is>300 mg/dl during the day for one hour, there should be no increased risk of DKA compared with the control group.

Risk level: 4 (acceptable risk)

ABBREVIATIONS

Abbreviation	Meaning
BGM	Blood Glucose Monitoring
CGM	Continuous Glucose Monitoring
CMS	Centers for Medicare and Medicaid Services
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
IRB	Institutional Review Board
JDRF	Juvenile Diabetes Research Foundation
LOC	Loss of Consciousness
MDI	Multiple Daily Injections
MedDRA	Medical Dictionary for Regulatory Activities
NPH	Humulin® N or Novolin® N
PBMC	Peripheral Blood Mononuclear Cells
RNA	Ribonucleic Acid
SH	Severe Hypoglycemia
T1D	Type 1 diabetes