A Randomized Clinical Trial to Assess the Efficacy and Safety of Real-Time Continuous Glucose Monitoring in the Management of Type 1 Diabetes in Young Children (4 to <10 Year Olds)

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CHAPTER 1
INTRODUCTION

1.1 Background and Rationale

Tight glycemic control in young children with diabetes is limited by hypoglycemia and the associated risk of impaired cognitive development. There are a number of factors that contribute to the risk of hypoglycemia in this age group, including irregular patterns of eating, inability to recognize and report hypoglycemia, inability to self manage a low blood glucose, and unpredictable peaks and valleys in long acting basal insulins. Young children are also very sensitive to small changes in insulin doses and the inability to deliver insulin by very small increments can only be possible via pump therapy. Night time is the most vulnerable period for hypoglycemia in youth with T1DM, since sleep blunts the counterregulatory responses to hypoglycemia even in non-diabetic children (1). In the 1st funding cycle of the Diabetes Research in Children Network (DirecNet), we studied overnight counterregulatory responses to spontaneous hypoglycemia in young (3-8y/o) vs. older (12-18y/o) children with T1DM and observed that the catecholamine response to spontaneous hypoglycemia is blunted, even in young children (2; 3).

Nocturnal hypoglycemia in the past has been partly attributed to the overnight peaking of the NPH insulin effect when it is given at dinner or at bedtime. It was thought that this effect could be dramatically reduced by the use of insulin infusion pumps and one study showed a significant reduction in hypoglycemia when switching from multiple daily injections to pump therapy (4). Recent studies, however, using continuous glucose sensors have failed to demonstrate a lower rate of hypoglycemia in children wearing insulin infusion pumps when compared to children using multiple daily injections (5-9). These concerns have caused parents of children with diabetes to welcome the possibility of using continuous glucose monitoring with real-time hypoglycemic alarms. Direcnet previously investigated the use of the Abbot Navigator CGM in 8-18 y/o patients with T1DM (see section 1.2.1). A large, multicenter study funded by JDRF is presently exploring the use of CGM technology further in a much larger cohort for an entire year; however, young children (<8y/o) were not included. Hence, it remains to be seen whether CGM technology can be used safely, whether it is tolerable and useful in very young children with T1DM, and whether it can improve glycemic control without increasing hypoglycemia.

Acute hypoglycemia has deleterious transient effects on multiple aspects of cognition, (10-12) it is quite plausible that recurrent mild to moderate hypoglycemia (13; 14) or episodic severe hypoglycemia (15-22) during early childhood, when the brain is undergoing rapid developmental changes plays an etiologic role in these more static cognitive changes. Along with the many other valid reasons for avoidance of hypoglycemia, this observation has generated even greater concern about minimizing hypoglycemia among young children with T1DM due to their potential vulnerability to CNS insult. In addition, chronic hyperglycemia may also affect the developing brain, although this is less well studied (23). Hence the avoidance of large glycemic excursions may well be critical, not only for the avoidance of diabetes complications, but for normal brain function. This underscores the critical need of technology that allows the near-continuous monitoring of plasma glucose with CGM systems, particularly in very young children with diabetes.

1.2 CGM Systems to be Used

This study will use the FreeStyle Navigator® CGM made by Abbott Diabetes Care, the Guardian-REAL Time CGM made by Medtronic MiniMed and the DexCom SEVEN PLUS CGM made by

DexCom Inc. For subjects who are using a 522 or 722 Paradigm insulin pump, there may be an option to use the Paradigm CGM system also made by Medtronic MiniMed. The Guardian REAL-Time and the Paradigm systems use the same sensor and transmitter and calculate the glucose result using the same algorithm, but the Guardian REAL-Time is strictly a CGM receiver and not an insulin pump. All of these CGM systems measure interstitial glucose. Each system consists of a glucose oxidase based electrochemical sensor placed subcutaneously and a receiver to which the glucose measurements (or signal) are sent wirelessly and stored. In human studies the interstitial glucose levels generally lag behind the blood glucose by 3 to 13 minutes.(24; 25)

The version of the Navigator to be used in this study is different than the currently FDA approved version in that it has a 1-hour warm-up period rather than the FDA-approved version which has a 10-hour warm-up period.

Features of these CGM systems are summarized in the table below

	FreeStyle Navigator	**Paradigm/Guardian**	**DexCom SEVEN PLUS**
Range of glucose values	20 to 500 mg/dL	40 to 400 mg/dL	40 to 400 mg/dL
Frequency of glucose values	Every minute (saved every 10 minutes)	Every 5 minutes	Every 5 minutes
Lifespan of sensor	120 hours	72 hours	168 hours
Warm up period	1 hour	2 hours	2 hours
Calibration frequency	4 times at approximately 1hr, 12hrs, 24hrs and 72hrs following sensor insertion	2 times a day (every 12hrs)	2 times a day (every 12hrs)
Home Glucose Meter (HGM) for Calibration	FreeStyle (built in)	One Touch Ultra Link (connected via radiofrequency); can also enter manual calibrations from any HGM	One Touch Ultra (connected via a cable); can also enter manual calibrations from any HGM
Alarms	Hypo, hyper (adjustable); Predicted alarms based on rate of change	Hypo, hyper (adjustable) No predicted alarms on the Paradigm; Guardian has predicted alarms based on rate of change	Hypo, hyper (adjustable) No predicted alarms
Trend Arrows on Receiver Display	Yes	Yes	Yes
Entering of events	Insulin, meals, exercise, health, other	Insulin, meals, exercise	Insulin, meals, exercise, other

1.2.1 Prior Studies on CGMs

Most studies and clinical experience using CGM devices have been in adults.(26-28) In children, DirecNet conducted a prospective long-term follow-up study using the Navigator in 57 children with T1D aged 4 to 17 years, 14 of whom were <8 years old (29; 30). Navigator use was well tolerated by the subjects. Many incorporated it into their daily diabetes management and continued to use it during an optional continuation phase of the study while a minority discontinued use. Parental satisfaction measured on a questionnaire was generally high.

1.3 Study Objective

The primary objective is to determine the efficacy, tolerability, safety, and effect on quality of life of CGM in young children with T1D.

1.3.1 Hypotheses

1. CGM wear in this patient population will be well tolerated and safe.
2. The group wearing CGM will have a greater reduction in HbA1c without an increased rate of severe hypoglycemic events than the comparison group using a home glucose meter.

1.4 Synopsis of Study Protocol

Subjects with T1D who are 4.0 to <10.0 years old will be enrolled into the multi-center protocol which consists of two phases:

(1) A 6-month randomized trial comparing a CGM group with a control group that will use home glucose meter (HGM) monitoring and have the same number of scheduled phone contacts and visits as the CGM group, followed by:

(2) A 6-month period during which the CGM Group continues to use CGM and CGM is initiated in the control group. This 2nd phase of the study will evaluate whether any beneficial effect seen in the first 6 months can be sustained with longer-term use and less intensive contact. As the control group will initiate CGM use with less intensive contact after the first month than was provided at initiation of CGM use in the CGM group in phase 1, this will also allow us to assess if beneficial effects of CGM use can be obtained with more practical personnel intervention.

1.4.1 Summary of Design of Randomized Trial

A. Major Eligibility Criteria

- Clinical diagnosis of T1D
- Age 4 to <10 years
- Insulin therapy for at least twelve months
- HbA1c $\geq$ 7.0%

B. Sample Size

The study will include approximately 140 subjects.

C. Treatment Groups

Subjects will be randomly assigned with equal probability to the following 2 groups:

- CGM for 12 months
- Control Group using HGM monitoring for 6 months followed by CGM use for 6 months

D. Duration of Follow-up

- RCT outcome at 6 months
- Final study outcome at 1 year

E. Main Outcome Measures

RCT – 1st 6 months

Treatment group comparisons of the following:

- HbA1c
- Episodes of severe hypoglycemia
- Percentage of sensor values in range (71 mg/dL to 180 mg/dL)*

- Biochemical hypoglycemia (percentage of sensor values ≤70 mg/dL)*
- Measures of variability: mean amplitude of glycemic excursions (MAGE), SD, mean absolute rate of change*
- Parental quality of life measures

*based on one week of sensor values (both groups will use a blinded sensor for 2 weeks at baseline; the control group will use a blinded sensor for one week at 3 months and 6 months while the CGM group will use an unblinded sensor)

Post-RCT Observational Study – 2nd 6 months

The same outcome measures will be evaluated in within-group analyses.

- For the CGM group, comparisons will be made with both the RCT baseline and the observational phase baseline
- For the control group, comparisons will be made with the observational study baseline

F. Flow Chart of Study

Screening

- Assess eligibility and sign informed consent form

Run-in Phase:

- Optimization of glycemic control for six weeks, with use of a home glucose meter and phone calls weekly for 3 weeks and then once between weeks 4 and 6 from the nurse coordinator
- *This phase is included in order to reduce the study effect on glycemic control in the control group post-randomization.*

Blinded CGM Use:

- Visit to initiate blinded CGM use to obtain a minimum of 96 hours of CGM glucose data, which will serve as a baseline assessment of glycemic control

Randomization Visit

- 14 to 28 days after visit to initiate blinded CGM
- Assess CGM use
- Randomization if CGM use successful and no contraindications

Randomized Trial Phase (0-26 weeks)

- Visits at 1,4,8,13,19,26 weeks

Post-RCT Observation Phase (27-52 weeks)

- Visits at 13 and 26 weeks
- Additional follow-up visits for the control group after starting CGM at weeks 1 and 4, and phone contacts at 3 days and 2 weeks.

G. Schedule of Study Visits/Phone Contacts and Examination Procedures

Phase 1

Visit (V) or Phone (P)	Enr* V	CGM V	0 V	3d P	1w V	2w P	4w V	6w P	8 w V	10 w P	13 w V	16 w P	19 w V	22 w P	26 w V
Blinded CGM**		X									X**				X**

Pre-randomization compliance assessment			X												
HbA1c-DCA2000	X		X				X		X		X		X		X
HbA1c-lab			X								X				X
Skin Assessment			X		X		X		X		X		X		X
Data download					X		X		X		X		X		X
Review diabetes management	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Parental QOL Questionnaires		X													X

*After enrollment, there is a six-week period for optimization of glycemic control during which phone contacts will occur weekly for first three weeks and then once between weeks 4 and 6.

**Both groups will use a blinded CGM at baseline. At 13 and 26 weeks, the Control group will use a blinded CGM and will return it a week later.

Phase 2

	Control Group				Both Groups	
Visit (V) or Phone (P)	**3d P**	**1w V**	**2w P**	**4w V**	**13w V**	**26w V**
HbA1c-DCA2000				X	X	X
HbA1c-lab					X	X
Skin Assessment		X		X	X	X
Data download		X		X	X	X
Review diabetes management	X	X	X	X	X	X
Parental QOL Questionnaires						X

1.5 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.

There is no restriction on the number of subjects to be enrolled by a site.

CHAPTER 2
SUBJECT ENROLLMENT AND STUDY INITIATION

2.1 Study Population

Approximately 140 subjects are expected to be enrolled in the study.

A goal of recruitment will be to enroll a minimum of 10% minorities.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

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

1) Clinical diagnosis of type 1 diabetes and using daily insulin therapy for at least twelve months
   The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not needed.
2) Age ≥4.0 to <10.0 years
   - *A goal for recruitment will be to have approximately 1/3 of subjects age 4-5, 1/3 age 6-7 and 1/3 age 8-9.*
3) HbA1c ≥ 7.0% (measured with DCA2000 or other local point-of-care device)
   - *In order to assure a broad range of baseline HbA1cs, if after randomization of the first two-thirds of subjects, more than half of the subjects have baseline HbA1c <7.5% (central laboratory measurement from sample obtained at time of randomization after run-in period), then the remaining subjects will need to have enrollment HbA1c ≥7.5%.*
4) Current insulin regimen involves either use of an insulin pump or multiple daily injections of insulin (at least 3 shots per day) for the last three months, with no plans to switch the modality of insulin administration during the next 6 months (e.g., injection user switching to a pump, pump user switching to injections, or the addition of Lantus (Glargine) insulin)
   - *Subjects using premixed fixed doses of insulin at the time of enrollment will not be eligible*
   - *If a subject is switched to a pump, eligibility can be reassessed after 3 months of pump use*
5) Parent/guardian understands the study protocol and agrees to comply with it
   - *Subjects with a parent/Guardian who speaks only Spanish will be enrolled only if a CGM device is being used in the study that functions in Spanish and has a User Guide in Spanish.*
6) Investigator believes that subject/parent is likely to comply with the protocol
7) No expectation that subject will be moving out of the area of the clinical center during the next 12 months, unless the move will be to an area served by another study center.
8) Informed Consent Form signed by the parent/guardian.

2.2.2 Exclusion

Subjects who meet any of the following criteria are not eligible for the study:

1) Diabetes diagnosed <6 months of age

2) Use of a medication such as oral/inhaled glucocorticoids that in the judgment of the investigator will affect the wearing of the sensors or the completion of any aspect of the protocol.

3) The presence of any of the following diseases or another disease that the investigator believes to be a contraindication to participation in the protocol:

- Asthma if treated with systemic or daily inhaled corticosteroids in the last 6 months
  - *Intermittent treatment with inhaled corticosteroids does not exclude subjects from enrollment*
- Cystic fibrosis
  - *Celiac disease and adequately treated thyroid disease do not exclude subjects from enrollment*

4) Home use of CGM in past 6 months.

5) Participation in an intervention study (including psychological studies) in past 6 weeks.
   - Subjects may participate in other nonintervention protocols during the course of this protocol
   - Another member of the same household is participating in this study.

2.3 Subject Enrollment and Baseline Data Collection

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

2.3.1 Informed Consent

For eligible subjects, the study will be discussed with the parent/legal guardian (referred to subsequently as 'parent'). The parent will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. A copy of the consent form will be provided to the parent and another copy will be added to the subject's clinic chart.

Written informed consent must be obtained from the subject (and parent for minors) prior to performing any study-specific procedures that are not part of the subject's routine care.

2.3.1.1 Authorization Procedures

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

2.3.1.2 Special Consent Issues

The study population for this study includes children. The consent form and study procedures will be discussed with these subjects at a level at which they can understand. The study staff will ask questions of each minor subject to assess the autonomy and understanding of the study.

2.3.2 Historical Information and Physical Exam

A history will be elicited from the subject/parent and extracted from available medical records with regard to the subject's diabetes history and current diabetes management. A standard physical exam (including vital signs and height and weight measurements) will be performed by

the study investigator or his or her designee. The physical exam will include inspection of the skin.

2.3.3 HbA1c

HbA1c level will be measured using the DCA2000 or comparable local point of care device. The measurement must be made within 2 weeks prior to enrollment.

This HbA1c measurement can be performed as part of usual clinical care prior to obtaining informed consent for participation in the trial.

2.3.4 Diabetes Management

The first part of the study is to optimize current glycemic control. This is being done in order to reduce the study effect on glycemic control in the control group post-randomization.

At the enrollment visit, the investigative team will discuss with the parent, the subject's insulin dosing, meals, and other aspects of diabetes management.

The parent will be instructed to perform glucose testing with a study-provided HGM at least 4 times a day. The test strips to be used during the study are called the FreeStyle Omni. These tests strips are currently not approved by the Food and Drug Administration but have been submitted to the FDA for review.

The nurse coordinator will call the parent weekly for the first three weeks and then once between weeks four and six to review the diabetes management and make adjustments as indicated in the insulin dosing. HGM glucose may be downloaded and transmitted to the clinic at intervals during this part of the study.

CHAPTER 3
BASELINE CGM VISIT

3.1 Clinic Visit

The subject will have a clinic visit after the 6 weeks of optimizing glycemic control.

At the visit, quality of life questionnaires will be completed and a CGM sensor will be inserted. The parent will be instructed on insertion, calibration, and care of the CGM.

Subjects who will use a Medtronic system will use the Guardian Clinical device which is the same as the Guardian REAL-Time but does not display the glucose results. Those who will use the Navigator or the DexCom will get that device, but it will be programmed by a computer in the clinic to not display the glucose results.

3.2 Questionnaires

The parent will complete the following questionnaires (described in chapter 7):

- Blood Glucose Monitoring System Rating Questionnaire
- Problem Areas in Diabetes (PAID-Parent version)
- Hypoglycemia Fear Survey

3.3 Instructions for Home Use of the Blinded CGM

The parent will be instructed to have the child use the CGM on a daily basis and will be instructed in the use of the device.

- Blood glucose testing using the HGM (unblinded) should continue to be at least 4 times a day.
- The parent will be informed that to be eligible for the randomized trial, the CGM must be used on a minimum of 7 out of 14 days, at least 96 hours of CGM glucose values including at least 24 hours of glucose values during the hours of 10 p.m. and 6 a.m. must be obtained, and a minimum of 3 HGM glucose measurements must be made each day.

CHAPTER 4
RANDOMIZATION VISIT

4.1 Timing of Visit

Enrolled subjects will return 14 to 28 days after the blinded CGM use was initiated.

The purpose of the visit will include the following:

- Assessment of compliance with the use of the CGM and HGM
- Assessment of skin reaction in areas where a CGM sensor was worn
- Randomization to the CGM Group or the Control Group
- For subjects in the CGM Group, initiation of unblinded CGM use
- Instruction on downloading of glucose data for those with a home computer
- Collection of blood sample to send to the central laboratory for baseline HbA1c determination

4.2 Review of CGM and HGM Data

The HGM and CGM data will be downloaded and reviewed by personnel not involved with treatment of the subject to assess whether the subject has been compliant.

- To be continued in the study, it will be necessary that the subject has completed at least 3 HGM measurements a day since the baseline CGM visit, has used the CGM on at least 7 out of 14 days prior to the visit, and obtained at least 96 hours of CGM glucose values with at least 24 hours of glucose values during the hours of 10 p.m. and 6 a.m.

Subjects not meeting these criteria may be given a second opportunity at investigator discretion to complete the CGM and HGM requirements.

Subjects who are unable to meet the CGM and HGM compliance requirements will be withdrawn from the study and not randomized.

4.3 Skin Assessment

The skin in areas where the sensor was inserted will be inspected to assure that there are no serious skin reactions that would preclude extended use of a sensor in the study.

4.4 Assessment of Parent's Willingness and Ability to Complete the Protocol

The protocol again will be discussed with the parent to be sure the parent has a good understanding of the protocol and is committed to accepting randomization to either group and to following and completing the protocol.

4.5 Randomization

Subjects who have been compliant with home glucose monitoring and use of the CGM will be randomized to one of two treatment groups:

1. CGM Group
2. Control Group

The subject'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, stratified by clinical center and HbA1c (<8.0% and >=8.0%).

Once a subject is randomized that subject will be included in the data analysis regardless of whether or not the protocol for the assigned randomization group is followed. Thus, the investigator must not randomize a subject until he/she is convinced that the subject/parent will accept assignment to either of the two groups.

4.6 HbA1c

For randomized subjects, a blood sample will be drawn to send to the central laboratory at the University of Minnesota for the baseline HbA1c determination. The HbA1c will also be measured using the DCA2000 or similar point of care device at this visit.

4.7 Procedures for the CGM Group

The CGM will be unblinded and the parent will be provided with sensors, a HGM and test strips. The parent will be instructed to use the CGM on a daily basis and will be instructed in the use of the device including calibration of the device using a study HGM and downloading the device (if the parent has access to a home computer). The parent will be instructed to continue testing with the HGM at least 4 times each day. In addition, the parent will be asked to test using the HGM one night per week at approximately 3 a.m. Those with email access will be asked to email the downloaded data to the clinical center before each scheduled phone call.

The parent will be observed placing the sensor. A guide booklet will be provided for the parent to take home. The parent will be instructed to contact the site staff if any appreciable skin reaction occurs.

During the visit, the CGM, insulin pump (if the subject uses an insulin pump), and HGM data from the pre-randomization visit week will be reviewed with the parent. The parent will be provided with algorithms to use to make changes to the diabetes management based on the data from the CGM and HGM.

4.8 Procedures for the Control Group

For subjects in the Control Group, changes will be made in the insulin dosing based on the HbA1c and the HGM data downloaded at this visit, and the investigator's prior experience in treating the subject.

The parent will be provided with a HGM and test strips and will be asked to perform at least 4 fingerstick blood glucose measurements per day. In addition, the parent will be asked to test using the HGM one night per week at 3 a.m.

The parent will be provided with algorithms to use to modify diabetes management based on the HGM glucose readings.

Parents with access to a home computer will be provided with the software to download the HGM and will be asked to do so weekly. Those with email access will be asked to email the downloaded data to the clinical center prior to each scheduled phone call.

CHAPTER 5
RANDOMIZED TRIAL PHASE

5.1 Home Procedures and Diabetes Management

5.1.1 CGM Group

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

A study HGM will be used for calibration of the CGM sensor. Additional HGM glucose measurements may be performed by the subject at anytime, particularly prior to making a real-time management decision based on the CGM glucose reading.

At least once a week, subjects who have a home computer will be instructed to download the CGM and HGM data for viewing. Subjects with email access will send the CGM and HGM data to the clinical center prior to each scheduled phone call. The steps to follow will be detailed in the subject instruction manual.

Subjects who discontinue use of the CGM will remain in follow-up though the 26-week visit. These subjects will be discontinued from the study after completion of the 26-week visit.

5.1.2 Control Group

A study HGM will be used for a fingerstick blood glucose check a minimum of four times a day (prior to each meal and bedtime). Subjects will be permitted to check a fingerstick glucose as many times a day as they choose.

Subjects who have a home computer will be asked to download the HGM at least once a week. Data summaries and charts will be available for these subjects to view. Subjects with email access will send the HGM data to the clinical center prior to each scheduled phone call. The steps to follow will be detailed in the subject instruction manual.

5.1.2.1 Use of Blinded CGM by Control Group

After the 13 and 26-week visits, the Control Group will use the same blinded CGM that was used at baseline for approximately one week. Instructions will again be provided for fingerstick testing on the HGM at least 4 times each day and as needed for calibration of the sensor.

Subjects will return one week after each visit to return the CGM. The blinded CGM will be downloaded by personnel not involved with treatment of the subject. Subjects who do not obtain at least 96 hours of CGM glucose values with at least 24 hours of glucose values during the hours of 10 p.m. and 6 a.m. will be asked to repeat use of the blinded CGM so that a sufficient amount of blinded data is obtained. Phase 2 will begin for these subjects once a sufficient amount of data is obtained from the blinded CGM use.

5.2 Follow-up Visits and Phone Contacts

The schedule for follow-up visits and phone contacts is the same for both treatment groups with the exception of a visit following the 13-week and 26-week visits for the Control Group to return the blinded CGM (no study procedures will be completed at these visits).

A primary purpose of the visits and contacts will be to review diabetes management and make adjustments as needed.

5.2.1 Follow-up Visits

Follow-up visits will occur at

- 1 week (± 2 days)
- 4 weeks (±1 week)
- 8 weeks (±1 week)
- 13 weeks (±1 week)
- 19 weeks (±1 week)
- 26 weeks (±1 week)

5.2.1.1 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 HGM use
- Skin assessment (CGM Group)
- Review of glucose data and pump data (if available) and recommendations for changes in diabetes management
- HbA1c determination using the DCA2000 or similar point of care device for management decisions (4 weeks, 8 weeks, 13 weeks, 19 weeks and 26 weeks)
- Collection of a blood sample to send to the central laboratory for HbA1c determination (13 weeks, 26 weeks)
- Completion of questionnaires by parent (26 weeks)
    - Blood Glucose Monitoring System Rating Questionnaire
    - Problem Areas in Diabetes (PAID-Parent version)
    - Hypoglycemia Fear Survey
    - CGM Satisfaction Scale (CGM Group Only)

5.2.2 Phone Contacts

A phone contact will be made between each protocol visit at the following times:

- 3 days (± 1 day)
- 18 days (±3 days)
- 6 weeks (±1 week)
- 10 weeks (±1 week)
- 16 weeks (±1 week)
- 22 weeks (±1 week)

CHAPTER 6
POST-RANDOMIZED TRIAL OBSERVATION PHASE

6.1 CGM Group

Subjects in the CGM Group will continue using the CGM and will be given additional sensors and instructed to use the sensors as often as they would like. Subjects will return for visits 13 weeks (± 1 week) and 26 weeks (±1 week) following the 26-week visit.

- Subjects who have discontinued the use of the CGM will have a final study visit and then be discontinued from the study.

6.2 Control Group

Subjects in the Control Group will be provided with a CGM and sensors.

- Parents will be instructed on use of the CGM and how to use the glucose and HGM data to adjust diabetes management.
- Subjects who discontinue the use of the CGM will have a final study visit and will be discontinued from the study.

Follow-up visits will occur during phase 2 after 1 week (±2 days), 4 weeks (±1 week), 13 weeks (±1 week), and 26 weeks (±1 week).

Phone contacts will occur during phase 2 at 3 days (±1 day) and 2 weeks (±4 days).

6.3 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 HGM use
- Skin assessment
- Review of glucose data and pump data (if available) and recommendations for changes in diabetes management
- HbA1c determination using the DCA2000 or similar point of care device for management decisions (phase 2-4 weeks (control group only), 13 weeks, 26 weeks)
- Collection of a blood sample to send to the central laboratory for HbA1c determination (phase 2-13 weeks, 26 weeks)
- Completion of parental questionnaires parent (phase 2 visit at 26 weeks)
    - Blood Glucose Monitoring System Rating Questionnaire
    - Problem Areas in Diabetes (PAID - Parent version)
    - Hypoglycemia Fear Survey
    - CGM Satisfaction Scale

CHAPTER 7
PARENTAL QUESTIONNAIRES

7.1 Introduction

The following questionnaires will be completed during the study by the parent:

- Blood Glucose Monitoring System Rating Questionnaire
- Problem Areas in Diabetes (PAID - Parent version)
- Hypoglycemia Fear Survey
- CGM Satisfaction Scale

All of the questionnaires are completed at baseline and 26 weeks during phase 1 and at the end of phase 2, with the exception of the Continuous Glucose Monitor Satisfaction Scale, which is completed by the CGM Group at 26 weeks and during the post-RCT observation phase by both groups at phase 2-26 weeks.

Each questionnaire is described briefly below. The procedures for administration are described in the study procedures manual.

7.2 Blood Glucose Monitoring System Rating Questionnaire

The Blood Glucose Monitoring System Rating Questionnaire was designed to assess subjects' rating of their current method of blood glucose monitoring. At baseline, all subjects will answer the questions as they relate to the home glucose meter being used prior to enrollment in the study. At the phase 1 and 2 26 weekvisits, the CGM group will answer the questions as they relate to the CGM. The Control Group will answer the questions related to the HGM at 26 weeks and to the CGM at phase 2-26 weeks. Administration time is approximately 10 minutes.

7.3 Hypoglycemia Fear Survey

The original Hypoglycemia Fear Survey measured several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consisted of a 10-item Behavior subscale that measured behaviors involved in avoidance and over-treatment of hypoglycemia and a 13-item Worry subscale that measured anxiety and fear surrounding hypoglycemia. The instrument has since been revised to create a parent version and a child version of the original instrument. The Worry Scale for these latter two versions consists of items with a 5-choice Likert response format. Administration time is approximately 10 minutes.

7.4 Problem Areas in Diabetes (PAID – Parent Version)

This questionnaire is administered to the parents of youth with diabetes to assess diabetes-specific quality of life of parents. Administration time is approximately 10 minutes.

7.5 Continuous Glucose Monitor Satisfaction Scale

This questionnaire was designed for this study to measure the impact of using a CGM on family diabetes management, general family relationships, and individual emotional, behavioral and cognitive reactions to use of the device. Administration time is approximately 10-20 minutes.

CHAPTER 8
ADVERSE EVENTS

8.1 Definition

A reportable adverse event in this study is defined as any untoward medical occurrence that meets criteria for a serious adverse event or any unexpected medical occurrence in a study subject that is study or device-related.

8.2 Recording of Adverse Events

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

The investigator will elicit reports of adverse events from the subject at each visit and phone call and complete all adverse event forms online. Each adverse event form is reviewed by 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 device or study procedures.

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.

Definitions of relationship and intensity are listed on the website data entry form.

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

8.3 Reporting Serious 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 significant disability/incapacity
- Is a congenital anomaly/birth defect

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 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 both serious and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB.

8.4 Risks And Discomforts

The investigators have determined that this protocol meets the criteria 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.

It is the assessment of the investigators that this protocol falls under DHHS 46.404 which is not involving greater than minimal risk. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the subjects as described in Section 9.1.

8.4.1 CGM

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.

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

8.4.2 Fingerstick Blood Glucose Measurements

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

8.4.3 Psychosocial Questionnaires

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

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

8.5 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled adverse event data at periodic intervals.

CHAPTER 9
MISCELLANEOUS CONSIDERATIONS

9.1 Benefits

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

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

9.2 Subject/Parent Reimbursement

The study will provide the CGM and related supplies, and the study HGM and test strips.

The study will be paying the subject $25 per completed protocol-required visit to cover travel and other visit-related expenses. Additional travel expenses will be paid in select cases for subjects with higher expenses. There will be no compensation for completing telephone calls.

Subjects who complete the study will be able to keep the study HGM. Test strips for the HGM to be used after the study will be the subject's responsibility. The CGM device and all components will need to be returned.

9.3 Subject Withdrawal

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

9.4 Confidentiality

For security purposes, subjects 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 A_{1C} results, continuous glucose monitor results, blood work results, HGM blood glucose measurements, information pertaining to hypoglycemic excursions and the treatment given, as well as all other study related data gathered during study visits and phone calls.

During each visit, the study devices will be downloaded to a computer that is secured and password protected, the files will be sent directly to the coordinating center via email. All files will include only the subject's identifier; no names or personal information will be included.

Laboratory specimens will be sent to the University of Minnesota which serves as the central lab for the study. As needed to comply with site-specific HIPAA policies, the Jaeb Center will enter into a Data Use Agreement with local study sites.

During the study, subjects with a home computer will be asked to download the CGM and study HGM data to their home computer. The downloaded data for the CGM may be provided to the company that makes the CGM as well as the data collected for the study during visits and phone

calls. The data provided to the company will include only the subject's identifier; no names or personal information will be included.

9.5 Early Discontinuation of the Study

The study may be discontinued prior to its planned completion by decision of the Steering Committee, with concurrence by the Data and Safety Monitoring Committee.

CHAPTER 10
STATISTICAL CONSIDERATIONS

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, which will supersede these sections when it is finalized.

10.1 Sample Size Estimation

Sample size was estimated for the primary outcome of "success", defined as a decrease in HbA1c $\geq$0.5% from baseline to 26 weeks and no severe hypoglycemic events.

- For purposes of analysis, a severe hypoglycemic event will be defined as an event, confirmed by a glucose level <60 mg/dL and characterized by at least one of the following: 1) seizure or coma, 2) glucagon given, 3) symptoms of acute and significant change in alertness status, loss or near-loss of consciousness, or 4) emergency medical personnel provided treatment. 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.

From the JDRF CGM RCT, the control group success proportion has been estimated to be 10%.

A survey of investigators indicated that the expected success proportion in the CGM group, if it is beneficial, would be 35%.

For 90% power with a type 1 error rate of 5% (2-sided), the sample size is computed to be 65 per group (130 total). This has been increased to a total of 140 to account for losses to follow up.

10.2 Statistical Analysis

10.2.1 Phase 1: Randomized Trial Phase

Analyses will follow a modified intent-to-treat principle with all subjects analyzed in the group to which they were randomized, regardless of actual sensor use. The exception to full intent-to-treat is that only subjects with a baseline HbA1c ($\geq$6.8%) will be included in the primary analysis (the baseline HbA1c is measured at a central laboratory and will not be available until after the subject is randomized). Data from subjects with a baseline HbA1c <6.8% will be analyzed separately.

Primary Outcome

As noted above, success is defined as improvement in HbA1c from baseline to 26 weeks $\geq$0.5%, with no severe hypoglycemic events (as described below). Randomization groups will be compared using logistic regression adjusting for baseline HbA1c. If there is >5% missing data, multiple imputation will be used based on Rubin's method.

Secondary HbA1c Analysis

As a secondary analysis, the mean ± SD values for the 26 week HbA1c value with 95% confidence intervals or percentiles appropriate to the distribution will be given for each randomization group. Randomization groups will be compared using an ANCOVA model adjusting for baseline HbA1c. 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. A 95% confidence interval will also be given for the difference of the randomization groups based on the ANCOVA model.

Glycemic Indices

The percentage of sensor values in the target range of 71-180 mg/dL at 13 and 26 weeks (separate outcome measures) will be compared between the two randomization groups. The percentage of sensor values in the hypoglycemic range (≤70 mg/dL) also will be compared.

Percentages of sensor values in the target and hypoglycemic ranges will be calculated giving equal weight to each of the 24 hours of the day for each subject. Comparisons of the two randomization groups will be performed using analogous ANCOVA models as described above for HbA1c. 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.

Randomization groups will also be compared for the total amount of sensor data available for this analysis at 13 and 26 weeks, amount of data between 10 p.m. – 6 a.m. and the percentage of subjects requiring a second week of sensor wear.

Hypoglycemia

Severe hypoglycemic events will be tabulated in each treatment group. The cumulative probabilities of a hypoglycemic event in each treatment group were compared using a log rank test and the incidences of hypoglycemic events compared using a permutation test.

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. For questionnaires administered to both randomization groups (i.e., excluding the CGM Satisfaction Scale) comparisons will be made using similar ANCOVA models as described above for HbA1c. No formal adjustment will be made for multiple comparisons.

Skin Assessments

For each scheduled visit and any unscheduled visits during which an assessment was performed tabulations will be given for percentage of subjects with dry skin, scabbing and scarring and for adverse events due to skin reaction.

Other Adverse Events

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

Subgroup Analyses

Exploratory subgroup analyses will be performed for subgroups based on age (4-5, 6-7, 8-9 years), HbA1c (≤8.0%, ≥8.0%) and type of insulin delivery (pump, MDI).

10.2.2 Phase 2: Post-RCT Observation Phase

For the CGM group, the primary outcome for phase 1 will be computed through phase 2 using the phase 1 baseline. The full distribution of changes in HbA1c in phase 2 will be tabulated and the

mean±SD of the change during phase 2 will be computed as will the other measures described above for phase 1.

For the Control Group, the proportion of subjects with an improvement in HbA1c ≥0.5%, without a severe hypoglycemic event, during phase 2 will be computed. The distribution of changes in HbA1c will be tabulated. Mean ± SD (or percentiles appropriate to the distribution) HbA1c values will be given at baseline, 13 and 26 weeks of phase 2. The paired t-test will be used to compare the phase 2 26-week HbA1c with the phase 2 baseline HbA1c.

In both groups, similar analyses will be performed for the percentage of sensor values in the target and hypoglycemia ranges and questionnaires. The number of hours of sensor data obtained in the week prior to the 13 and 26 week visits of phase 2 will be tabulated. Any adverse events will be summarized as described above.

CHAPTER 11
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