A Pilot Study to Assess the Feasibility of Real-Time Continuous Glucose Monitoring in the Management of Infants and Toddlers with Type 1 Diabetes

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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 ability 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.

DirecNet will be conducting a randomized clinical trial on the safety and efficacy of CGM systems in young children with T1DM between ages 4 to <8yrs. Because of the unique challenges involved in the use of CGM technology in very small children, including unpredictability of

meals, extraordinary sensitivity to very small insulin doses, and very limited body surface area where to place the sensors, to name a few, we hence propose to extend those studies to children less than age 4 yr (i.e., infants and toddlers) as a pilot assessment of the feasibility of the use of these devices in this unique age group.

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	5 times at approximately 1hr, 2hrs, 10hrs, 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 assess the feasibility and safety of CGM use in infants and toddlers with T1D who are <4 years old.

1.4 Synopsis of Study Protocol

Following a run-in period with a blinded CGM, CGM use will be initiated in each enrolled subject. Subjects will remain in the study for up to six months as long as the CGM is still being used. If CGM use is discontinued prior to six months, with no intention to restart it, then a close-out visit will be performed at which the testing listed for the 26 week visitwill be performed.

A. Major Eligibility Criteria

- Clinical diagnosis of T1D
- Age <4 years

B. Sample Size

- Up to 35 subjects.

C. Duration of Follow-up

- Up to six months

D. Outcome Assessments

1) Feasibility

- Proportion of subjects successfully completing the run-in phase and continuing in the study
- Proportion of subjects successfully completing six months of CGM use
- Duration of time of CGM use for subjects discontinuing prior to six months
- Reasons for discontinuation of CGM use

2) Changes from baseline in glycemic control

- HbA1c
- % of sensor values in range (70 mg/dL to 180 mg/dL), <70 mg/dL, <50 mg/dL, >180 mg/dL, and >250 mg/dL
- Measures of variability: mean amplitude of glycemic excursions (MAGE), SD, mean absolute rate of change

3) Other

- Parental quality of life measures
- Episodes of severe hypoglycemia

E. Flow Chart of Study

Screening

- Assess eligibility and sign informed consent form

Run-in Phase:

- Blinded CGM use for 4 out of 7 days to obtain a minimum of 96 hours of CGM glucose data, which will serve as a baseline assessment of glycemic control

Baseline Visit

- 7 to 14 days after visit to initiate blinded CGM
- Assess CGM use
- Continue in study if CGM use successful

Follow up Visits and Phone Contacts

- Visits at 1,4,8,13,19 and 26 weeks with one phone contact between each visit
- If CGM use is discontinued and there is no expectation that it will be restarted, then the subject will have a close-out visit.

G. Schedule of Study Visits and Examination Procedures

	Enr	0	1w	4w	8w	13w	19w	26w
Blinded CGM	X							
Pre-enrollment compliance assessment		X						
HbA1c-DCA2000	X	X		X	X	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
Parental QOL Questionnaires	X							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 35 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
   The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not needed, unless onset of diabetes was prior to 6 months of age in which case positive antibodies are required for eligibility .
2) Age <4.0 years
3) Current insulin regimen involves either use of an insulin pump or multiple daily injections of insulin (at least 2 shots per day) for at least one month
4) 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.*
5) No expectation that subject will be moving out of the area of the clinical center during the next 6 months, unless the move will be to an area served by another study center.
6) Informed Consent Form signed by the parent/guardian.

2.2.2 Exclusion

There are no exclusion criteria for subjects meeting the eligibility criteria.

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 parent 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 young children only.

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 Questionnaire Completion

The parent will complete the following questionnaires (described in chapter 5):

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

2.4 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.

- 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.

- Blood glucose testing using the HGM (unblinded) should continue to be 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 parent will be informed that to be eligible to continue in the study, the CGM must be used on a minimum of 4 out of 7 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 3
BASELINE VISIT

3.1 Timing of Visit

Enrolled subjects will return 7 to 14 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
- Initiation of unblinded CGM use
- Instruction on downloading of glucose data for those with a home computer
- HbA1c measured with DCA2000

3.2 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 enrollment, has used the CGM on at least 4 out of 7 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 continued.

3.3 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.

3.4 HbA1c

HbA1c will be measured using the DCA2000.

3.5 Initiation of Unblinded CGM Use

The CGM will be unblinded (or the unblinded Medtronic device will be provided) and the parent will be provided with sensors. 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 7 to 14 days the CGM was used blinded will be reviewed with the parent. The parent will be provided and will be instructed in the use of algorithms to make changes to the diabetes management based on the data from the CGM and HGM.

CHAPTER 4
HOME PROCEDURES AND FOLLOW UP VISITS

4.1 Home Procedures and Diabetes Management

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. In addition, the parent will be asked to test using the HGM one night per week at 3 a.m.

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.

4.2 Follow-up Visits

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

4.2.1 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)

Additional visits can occur at any time.

Subjects who discontinue CGM use with no intent to restart will have a close out visit that will include the procedures listed for the 26-week visit.

4.2.2 Procedures at Follow-up Visits

The following procedures will be performed 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 (all visits except week 1)
- Completion of questionnaires by parent (26 weeks -see chapter 5 for description)
    - Blood Glucose Monitoring System Rating Questionnaire
    - Problem Areas in Diabetes (PAID-Parent version)
    - Hypoglycemia Fear Survey
    - CGM Satisfaction Scale

4.3 Phone Contacts

One phone contact will be made between each protocol visit. Additional contacts are permissible at any time.

CHAPTER 5
PARENTAL QUESTIONNAIRES

5.1 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, with the exception of the Continuous Glucose Monitor Satisfaction Scale, which is not completed at baseline.

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

5.2 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, parents will answer the questions as they relate to the home glucose meter being used prior to enrollment in the study. At 26 weeks, parents will answer the questions as they relate to the CGM. Administration time is approximately 10 minutes.

5.3 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 of the original instrument. The Worry Scale consists of 15 items, each with a 5-choice Likert response format. Administration time is approximately 10 minutes.

5.4 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. This questionnaire consists of 20 items and administration time is approximately 10 minutes.

5.5 Continuous Glucose Monitor Satisfaction Scale

This 46-item 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. The number of questions may be reduced prior to initiation of its use in the study. Administration time is approximately 10-20 minutes.

CHAPTER 6
ADVERSE EVENTS

6.1 Definition

A reportable adverse event is 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.

6.2 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 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.

6.3 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.

6.4 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.

6.4.1 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.

6.4.2 Fingerstick Blood Glucose Measurements

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

6.4.3 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.

6.5 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 7
MISCELLANEOUS CONSIDERATIONS

7.1 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.

7.2 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.

7.3 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.

7.4 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.

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.

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 may be provided to Abbott Diabetes Care or DexCom Inc. as well as the data collected for the study during the enrollment visit, at follow-up visits, and during phone contacts. The data provided to the companies will include only the subject's identifier; no names or personal information will be included.

7.5 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 8
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.

8.1 Sample Size Estimation

The sample size of 35 is a convenience sample for this pilot study and not based on statistical principals

8.2 Statistical Analysis

Tabulations will be performed for the following:

1) Feasibility

- Proportion of subjects successfully completing the run-in phase and continuing in the study
- Proportion of subjects successfully completing 6 months of CGM use
- Duration of time of CGM use for subjects discontinuing prior to 6 months
- Reasons for discontinuation of CGM use

2) Changes from baseline in glycemic control

- HbA1c
- % of sensor values in range (70 mg/dL to 180 mg/dL), <50 mg/dL, <70 mg/dL, >180 mg/dL, >250 mg/dL
- Measures of variability: mean amplitude of glycemic excursions (MAGE), SD, mean absolute rate of change

3) Other

- Parental quality of life measures
- Episodes of severe hypoglycemia
- Other adverse events

CHAPTER 9
REFERENCES

1. Jones T, Porter P, Sherwin RS, Davis E, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia during sleep. *The New England Journal of Medicine* 338:1657-1662, 1998

2. Diabetes Research in Children Network (DirecNet) Study Group: Impaired overnight counterregulatory hormone responses to spontaneous hypoglycemia in children with type 1 diabetes. . *Pediatric Diabetes* 8:199-205, 2007

3. Diabetes Research in Children Network (DirecNet) Study Group: Impaired counterregulatory hormone responses to hypoglycemia in young children and adolescents with well-controlled type 1 diabetes (T1DM). *Abstract accepted for ADA poster presentation*, 2008

4. Weinzimer SA, Ahern JH, Doyle EA, Vincent MR, Dziura J, Steffen AT, Tamborlane WV: Persistence of benefits of continuous subcutaneous insulin infusion in very young children with type 1 diabetes: a follow-up report. *Pediatrics* 114:1601-1605, 2004

5. DiMeglio LA, Pottorff TM, Boyd SR, France L, Fineberg N, Eugster EA: A randomized, controlled study of insulin pump therapy in diabetic preschoolers. *The Journal of pediatrics* 145:380-384, 2004

6. Fox LA, Buckloh LM, Smith SD, Wysocki T, Mauras N: A Randomized Controlled Trial of Insulin Pump Therapy in Young Children With Type 1 Diabetes. *Diabetes Care* 28:1277-1281, 2005

7. Kaufman FR, Austin J, Neinstein A, Jeng L, Halvorson M, Devoe DJ, Pitukcheewanont P: Nocturnal hypoglycemia detected with the Continuous Glucose Monitoring System in pediatric patients with type 1 diabetes. *J Pediatr* 141:625-630, 2002

8. Weintrob N, Schechter A, Benzaquen H, Shalitin S, Lilos P, Galatzer A, Phillip M: Glycemic Patterns Detected by Continuous Subcutaneous Glucose Sensing in Children and Adolescents

With Type 1 Diabetes Mellitus Treated by Multiple Daily Injections vs Continuous Subcutaneous Insulin Infusion. *Arch Pediatr Adolesc Med* 158:677-684, 2004

9. Wilson DM, Buckingham BA, Kunselman EL, Sullivan MM, Paguntalan HU, Gitelman SE: A Two-Center Randomized Controlled Feasibility Trial of Insulin Pump Therapy in Young Children With Diabetes. *Diabetes Care* 28:15-19, 2005

10. Warren RE, Frier BM: Hypoglycaemia and cognitive function. *Diabetes Obes Metab* 7:493-503, 2005

11. Davis EA, Jones TW: Hypoglycemia in children with diabetes: incidence, counterregulation and cognitive dysfunction. *J Pediatr Endocrinol Metab* 11:177-182, 1998

12. Northam EA, Anderson PJ, Werther GA, Warne GL, Andrewes D: Predictors of change in the neuropsychological profiles of children with type 1diabetes 2 years after disease onset. *Diabetes Care* 22:1438-1444, 1999

13. Northam EA, Anderson PJ, Jacobs R, Hughes M, Warne GL, Werther GA: Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. *Diabetes Care* 24:1541-1546, 2001

14. Hannonen R, Tupola S, Ahonen T, Riikonen R: Neurocognitive functioning in children with type-1 diabetes with and without episodes of severe hypoglycaemia. *Dev Med Child Neurol* 45:262-268, 2003

15. Rovet JF, Ehrlich RM: The effect of hypoglycemic seizures on cognitive function in children with diabetes: A 7-year prospective study. *J Pediatr* 134:503-506, 1999

16. Hershey T, Craft S, Bhargava N, White NH: Memory and insulin dependent diabetes mellitus (IDDM): effects of childhood onset and severe hypoglycemia. *J Int Neuropsychol Soc* 3:509-520, 1997

17. Hershey T, Lillie R, Sadler M, White NH: Severe hypoglycemia and long-term spatial memory in children with type 1 diabetes mellitus: a retrospective study. *J Int Neuropsychol Soc* 9:740-750, 2003

18. Fanelli C, Paramore D, Hershey T, Terkamp C, Ovalle F, Craft S, Cryer P: Impact of nocturnal hypoglycemia on hypoglycemic cognitive dysfunction in type 1 diabetes. *Diabetes* 47:1920-1927, 1998

19. Hershey T, Lillie R, Sadler M, White NH: A prospective study of severe hypoglycemia and long-term spatial memory in children with type 1 diabetes. *Pediatr Diabetes* 5:63-67, 2004

20. Hershey T, Perantie DC, Warren SL, Zimmerman EC, Sadler M, White NH: Frequency and timing of severe hypoglycemia affects spatial memory in children with type 1 diabetes. *Diabetes Care* 10:2372-2377, 2005

21. Bjorgaas M, Gimse R, Vik T, Sand T: Cognitive function in type 1 diabetic children with and without episodes of severe hypoglycaemia. *Acta Paediatr* 86:148-153, 1997

22. Haumont D, Dorchy H, Pelc S: EEG abnormalities in diabetic children: influence of hypoglycemia and vascular complications. *Clin Pediatr* 18:750-753, 1979

23. Perantie DC, Wu J, Koller JM, Lim A, Warren SL, Black KJ, Sadler M, White NH, Hershey T: Regional Brain Volume Differences Associated With Hyperglycemia and Severe Hypoglycemia in Youth With Type 1 Diabetes. *Diabetes Care* 30:2331-2337, 2007

24. Boyne MS, Silver DM, Kaplan J, Saudek CD: Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. *Diabetes* 52:2790-2794, 2003

25. Steil GM, Bernaba B, Saad M, Mastrototaro JJ, Rebrin K: Accurate determination of plasma glucose during hyper- and hypoglycemia with a subcutaneous glucose sensor (Abstract). *Diabetes* 49:A126, 2000

26. Bode BW, Schwartz S, Stubbs HA, Block JE: Glycemic characteristics in continuously monitored patients with type 1 and type 2 diabetes. *Diabetes Care* 28:2361-2366, 2005

27. Garg SK, Schwartz S, Edelman SV: Improved glucose excursions using an implantable real-time continuous glucose sensor in adults with type 1 diabetes. *Diabetes Care* 27:734-738, 2004

28. Bode B, Gross K, Rikalo N, Schwartz S, Wahl T, Page C, Gross T, Mastrototaro J: Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: the Guardian Continuous Monitoring System. *Diabetes Technol Ther* 6:105-113, 2004

29. Diabetes Research in Children Network (DirecNet) Study Group: Continuous Glucose Monitoring in Children With Type 1 Diabetes. *The Journal of Pediatrics* 151:388-393, 2007

30. Diabetes Research in Children Network (DirecNet) Study Group: FreeStyle Navigator Continuous Glucose Monitoring System Use in Children With Type 1 Diabetes Using Glargine-Based Multiple Daily Dose Regimens: Results of a pilot trial Diabetes Research in Children Network (DirecNet) Study Group. *Diabetes Care* 31:525-527, 2008