A Pilot Study to Evaluate the Navigator Continuous Glucose Sensor in the Management of Type 1 Diabetes in Children

Version 1.4
December 3, 2004

Coordinating Center

Jaeb Center for Health Research

Roy W. Beck, M.D., Ph.D. (Director)

Katrina J. Ruedy, M.S.P.H. (Assistant Director)

15310 Amberly Drive, Suite 350

Tampa, FL 33647

Phone (813) 975-8690

Fax (813) 903-8227

Email: direcnet@jaeb.org

Table of Contents

CHAPTER 1
INTRODUCTION

1.1 Introduction and Rationale

Resistance to frequent blood glucose monitoring is a major impediment to attaining good (lower HbA1c level) glucose control. The Diabetes Control and Complications Trial (DCCT) convincingly proved that glucose control closer-to-normal range ("tight" glycemic control) reduced the likelihood of the eye, kidney, and nerve complications of diabetes. Increasing the frequency of glucose monitoring was an important aspect of attaining improved glucose control in the DCCT. As a result of the DCCT, many physicians have attempted to keep children and adults in very "tight" glucose control. Unfortunately, the DCCT study also showed that the incidence of severe hypoglycemia was three times higher in the intensively treated group compared with the standard treatment group. The tools to safely implement tight glycemic control were not available to the DCCT. The Navigator™ by TheraSense has been developed to assist in closer monitoring of glucose levels.

The proper role of the Navigator in the management of type 1 diabetes in children has not been determined. We are planning a randomized clinical trial (RCT) to compare the effect on glycemic control, hypoglycemia, and quality of life of using a Navigator versus standard care. As a prelude to the RCT, we will conduct a pilot study in which subjects will use the Navigator in their home environment. The objectives of the pilot study will include:

- Assessment of the feasibility of using the Navigator continuous glucose sensor on a daily basis
- Development and testing of algorithms for making adjustments to diabetes management based on data from Navigator
- Assessment of accuracy of the Navigator
- Assessment of Navigator function during exercise and during a period of meal-induced hyperglycemia
- Exploratory assessment of the effect of use of the Navigator and algorithms on A1c and frequency of hypoglycemia

1.2 Background on the Navigator

The Navigator was developed by TheraSense, Inc. This sensor uses a glucose oxidase based electrochemical sensor, and is designed to measure blood glucose levels in a range of 20-500 mg/dl. The sensor is inserted subcutaneously and measures interstitial glucose. In human studies the interstitial glucose levels generally lag behind the blood glucose by 3 to13 minutes.[1, 2]

The Navigator, provides a glucose reading every 60 seconds (or 1440 readings a day). Each sensor is designed to provide readings for up to 120 hours. It has alarms for hypoglycemia and hyperglycemia and for projected high and low glucose values. The alarm set points can be adjusted by the user. The Navigator also has a trend arrow indicating the glucose rate of change (>-2 mg/dL/min, -2 to -1 mg/dL/min, -1 to 1 mg/dL/min, 1 to 2 mg/dl/min, and >2 mg/dl/min). Subjects can enter events, such as when they took insulin, ate, or exercised. The sensor requires calibration values to be entered 3 times during the first day of wear at 1hour, 3 hours, and 24 hours and does not require additional calibration values. The values are entered directly into the Navigator which has a TheraSense Freestyle home glucose meter built into the unit. The Navigator has not yet been approved by the FDA. The Navigator currently under review by the FDA will limit sensor wear to 3 days.

1.3 Synopsis of Study Protocol

Study Design/Sample Size: Pilot study with approximately 30 subjects.

Summary of Protocol

1. Informed consent is obtained from eligible subjects (age 3 to <18 years, T1D for ≥1 year, downloadable insulin pump being used, computer with internet access available at home).

2. On the day of enrollment, a hemoglobin A1c is obtained, psychosocial questionnaires are completed, and instructions are given for use of the Navigator sensor. The study personnel will supervise the subject or parent inserting the Navigator sensor in the clinic and will instruct the subject or parent to insert a second sensor at home in 5 days (or sooner if the sensor stops working or is pulled out). To obtain a baseline assessment of glycemic variability, the Navigator used during the first week will be blinded so subjects will not be able to view the data from the sensor. The subject will be instructed to complete at least four glucose measurements a day using the Freestyle meter built into the device.

3. The subject will return for a 24-hour CRC admission approximately one week (7-12 days) after the enrollment visit. An approximately equal number of subjects will insert a new sensor 4, 3, 2, and 1 day prior to the admission to allow for assessment of accuracy over the lifespan of the sensor.

    - Areas where a Navigator sensor was worn during the first week will be assessed by study personnel for any skin irritation.
    - Subjects will continue using the blinded Navigator sensor last inserted at home and a second new sensor will be inserted by the subject or parent with supervision by study personnel.
    - An intravenous catheter will be inserted for reference glucose measurements, which will be drawn every 30 minutes during the admission to send to a central laboratory to assess accuracy of the Navigator.
    - The accuracy of subject/parent blood glucose testing using the Freestyle HGM will be compared with the testing performed by trained study personnel using the same meter.
    - The accuracy of the subject's HGM being used at home may be tested.
    - The accuracy of other commercially-available home glucose meters may also be examined. There will be no additional blood requirements to perform this testing.
    - For subjects ≥7 years old, an exercise session of moderate intensity will be completed in the afternoon. This will allow for assessment of function of the Navigator during exercise and assessment of the accuracy of detecting changes in blood glucose.
    - For subjects of sufficient weight to accommodate the volume of blood required, blood glucose measurements will be made every 10 minutes for one hour after breakfast. This will allow for assessment of the accuracy of the Navigator in detecting change during a period of rising blood glucose.
    - The pre-admission Navigator, HGM, and pump data will be reviewed and changes will be made to diabetes management as needed. Subjects and parents will be provided with extensive teaching to use the protocol-developed algorithms for changes to diabetes management to be used in real time based on Navigator data after the subject leaves the CRC.

4. Each subject will be provided with the instructions for downloading the Navigator.

5. A follow-up visit will be performed at 1, 3, 7, and 13 weeks after the CRC admission. The visit windows will be ±3 days at weeks 1, 3, and 7 and ±1 week for week 13. Subjects may be asked to insert a new sensor 5 days before some of the visits to allow for skin assessments by study personnel after the sensor has been worn for 5 days.

    - At each visit, the Navigator will be downloaded, diabetes management will be reviewed, and compliance with use of the algorithms will be assessed. A study investigator will review the glucose data generated by the Navigator, trends and, in conjunction with the nurse coordinator make treatment recommendations. This will continue until enough collective experience has developed for the nurse coordinator to make the insulin adjustments more autonomously.

    - At each visit, the subject's BG will be tested on his/her Freestyle meter and a Freestyle meter at the clinic to assess the accuracy of the home meters over time.

    - At the 3, 7, and 13-week visits, a psychosocial questionnaire regarding the frequency and convenience of use of the algorithms will be administered.

    - At the 7-week visit, HbA1c will be measured

    - At the 13-week visit, HbA1c will be measured and psychosocial questionnaires will be administered.

6. Phone contacts will be made with the subjects after 3 days (±1 day), then at 2, 4, 8, and 10 weeks (±3 days) following the CRC admission to review their diabetes management and assess compliance with use of the algorithms. Phone contacts will also involve collection of diet data as well as any illnesses, stressful events, and menstrual cycle data for females.

7. At the 13-week visit, subjects who are interested in continuing to use the Navigator will continue in the study for another 13 weeks. Subjects who are not interested will be discontinued from the study.

8. Subjects continuing in the study will be provided with additional sensors and instructed to use them as frequently as they would like. Subjects will also be instructed to continue using the algorithms for diabetes management.

    - At the 26-week visit, psychosocial questionnaires regarding the satisfaction with the Navigator as well as the algorithms will be administered, frequency of use of the sensors and continued compliance with use of algorithms will be assessed, and HbA1c will be measured.

CHAPTER 2
SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Study Population

Approximately 30 subjects will be enrolled in this study at five clinical centers with approximately 6 enrolled at each center.

Enrollment will include approximately 10 subjects in each of the age groups of 3.0 to <7.0 years old, 7.0 to <12.0 years old, and 12.0 to <18.0 years old.

Subjects will include both males and females and an enrollment goal will be to achieve an approximately equal sex distribution in each age group.

A goal of recruitment will be to enroll approximately 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 one year
   The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not needed.
2) Age 3.0 years to less than 18.0 years
3) Subject has used a downloadable insulin pump for at least 6 months
4) Parent/guardian and subject understand the study protocol and agree to comply with it
5) Subjects ≥9.0 years old and primary care giver (i.e., parent or guardian) comprehend written English
   This requirement is due to the fact that the questionnaires to be used as outcome measures do not have validated versions in Spanish or other languages.
6) Subject has a home computer with internet access
7) For females, subject not intending to become pregnant during the next 3 months
8) No expectation that subject will be moving out of the area of the clinical center during the next 3 months
9) Informed Consent Form signed by the parent/guardian and Child Assent Form signed by the subject

2.2.2 Exclusion

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

1) The presence of a significant medical disorder that in the judgment of the investigator will affect the wearing of the sensors or the completion of any aspect of the protocol.
2) The presence of any of the following diseases:
   - Asthma if treated with systemic or inhaled corticosteroids in the last 6 months
   - Cystic fibrosis
   - Other major illness that in the judgment of the investigator might interfere with the completion of the protocol

- *Adequately treated thyroid disease and celiac disease do not exclude subjects from enrollment*

3) Inpatient psychiatric treatment in the past 6 months for either the subject or the subject's primary care giver (i.e., parent or guardian).

4) Current use of oral/inhaled glucocorticoids or other medications, which in the judgment of the investigator would be a contraindication to participation in the study.

2.3 Patient 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 Historical Information and Physical Exam

A history will be elicited from the subject and 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 (a pediatric endocrinologist, pediatric endocrine fellow, or a pediatric endocrine nurse practitioner).

2.3.2 Informed Consent

For eligible subjects, the study will be discussed with the subject and 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. Subjects will either be given the Child Assent Form to read or it will be read to the child. If the parent and child agree to participate, the Informed Consent Form and Child Assent Form will be signed. A copy of the consent form will be provided to the subject and his/her parent and another copy will be added to the subject's clinic chart.

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

2.3.2.1 Authorization Procedures

As part of the informed consent process, each subject 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 subject and their parent, questions will be answered about the details regarding authorization.

2.3.2.2 Special Consent Issues

The study population for this study includes children and adolescents. The consent form and study procedures will be discussed with each subject at a level in which they can understand. The study staff will ask questions of each subject to assess the autonomy and understanding of the study. Each subject will be asked to sign an assent form, if appropriate for the subject's age. Additionally, the parent(s) and/or guardian(s) of each subject will be asked to sign the consent form. They will be given the opportunity to ask questions throughout the study on all study related procedures.

2.3.3 Hemoglobin A1c Determination

The DCA 2000 will be used for baseline measurement of hemoglobin A1c and diabetes management decisions.

2.3.4 Questionnaire Completion

The following questionnaires will be completed. They are described in chapter 6.

- PedsQL Diabetes Module
- Diabetes Self Management Profile (Treatment Adherence Questionnaire)

2.3.5 Instructions for Home Procedures

Each subject will be provided with a Navigator and sensors. The Navigator will be blinded and subjects will not be able to view the Navigator data during the first week of the study. The subject and parent/guardian will be instructed to use the Navigator on a daily basis and will be instructed in the use of the device including calibration of the device using the built-in Freestyle meter. In order to assess accuracy throughout the lifespan of the sensor, approximately 25% of the subjects will be asked to insert a new Navigator sensor four days before the scheduled CRC admission, approximately 25% three days before the admission, approximately 25% two days before the admission, and approximately 25% one day before the scheduled CRC admission.

The subjects will be able to view the results of the Freestyle testing and will be instructed to perform at least 4 blood glucose measurements per day prior to the CRC admission. The measurements will be performed prior to each meal and before bed.

CHAPTER 3
INPATIENT CRC ADMISSION

3.1 Overview

About one week following the enrollment visit, subjects will have an inpatient CRC admission of approximately 24 hours.

- Areas where a Navigator sensor was worn during the first week will be assessed by study personnel for any skin irritation.
- Subjects will continue using the blinded Navigator sensor last inserted at home and a second new sensor will be inserted by the subject or parent with supervision by study personnel.
- An intravenous catheter will be inserted for reference glucose measurements, which will be drawn every 30 minutes during the admission to send to a central laboratory to assess accuracy of the Navigator.
- The accuracy of subject/parent blood glucose testing using the Freestyle HGM will be compared with testing performed using the same meter by study personnel.
- The accuracy of the subject's HGM used at home may be tested.
- The accuracy of other commercially-available home glucose meters may also be examined.
- For subjects $\geq$7 years old, an exercise session of moderate intensity will be completed in the afternoon.
- For subjects of sufficient weight to accommodate the volume of blood required, blood glucose measurements will be made every 10 minutes for one hour after breakfast.
- The preadmission Navigator, HGM, and pump data will be reviewed and changes will be made to diabetes management as needed. Subjects and parents will be provided with extensive teaching to use the protocol-developed algorithms for changes to diabetes management to be used in real time based on Navigator data after the subject leaves the CRC.

3.2 Navigator Management and Procedures

3.2.1 Navigator Placement

At the time of admission, a skin assessment will be made for each area where a sensor was worn in the first week (see section 7.5.1).

Subjects will continue to wear the sensor that was placed at home. If it is not functioning at the time of admission, a new sensor will be inserted.

A second Navigator sensor will be placed by the subject or parent while being supervised by study/CRC personnel. The time of placement and the placement site of each sensor will be recorded. Section 3.5 details the procedures to be followed if a hypoglycemic alarm occurs.

Calibration of the Navigator will be performed by study/CRC personnel. Freestyle readings for calibration will be made to coincide with reference measurements.

3.2.2 Sensor Failure

If a Navigator sensor fails with fewer than 4 hours of reference measurements remaining, it will not be replaced.

3.3 Reference Glucose Measurements

An intravenous catheter will be inserted in an arm vein. The area where the catheter will be inserted may be numbed with Elamax or EMLA cream prior to catheter insertion.

The reference measurements will be timed to be on the half-hour. If the catheter stops functioning, it may be replaced at the discretion of the investigator.

The clinical centers either will use reinfusion of blood or will discard blood with each blood draw, depending on the standard practice at each center's CRC. The blood draws will be performed by the method in standard use at the CRC. The blood samples will be sent to a central lab.

3.3.1 Volume of Blood Draws

Each blood draw will require a blood volume of approximately 1.3 ml per blood draw at the "discard" centers and 0.3 ml per blood draw at the "reinfusion" centers. At the "discard" centers, the maximum number of blood draws based on the subject's weight will be calculated at the time of admission so that the maximum blood volume drawn will not exceed 5% (at reinfusion centers, the maximum blood volume drawn will not approach 5%). Section 7.5.7 provides further details on the blood volume requirements.

3.3.2 Quality Control Specimens

Approximately 5% of the reference blood samples will be collected in duplicate to send to the central lab for quality control purposes.

3.4 Glucose Measurements with the Study Home Glucose Meter

Bedside blood glucose monitoring will be performed using the Freestyle meter built into the Navigator. If the need for a Freestyle blood glucose measurement does not coincide with a reference blood draw, a fingerstick may be done to obtain capillary blood for the glucose measurement. If a fingerstick test is performed, the subject or parent will perform a BG test at the same time study personnel perform the BG test on the Freestyle meter in order to assess the accuracy of subject/parent testing compared with the study personnel. Calibrations for the Navigator will be performed by the CRC staff using fingerstick tests.

3.5 Blood Glucose Testing for Hypoglycemia

If either a subject reports symptoms of hypoglycemia or a Navigator hypoglycemia alarm occurs (for low blood glucose), the blood glucose will be checked on the Freestyle meter.

A reference blood draw will be done if the Freestyle value is $\leq$70 mg/dL. A reference draw will be made every 10 minutes until the BG is >70 mg/dL on the Freestyle meter. For subjects <7, a reference blood draw will be done if the Freestyle value is $\leq$80 mg/dL and additional draws will be made every 10 minutes until the BG is >80 mg/dL.

If an extra reference blood draw falls within 10 minutes of the next scheduled blood draw, then the next scheduled blood draw will be skipped.

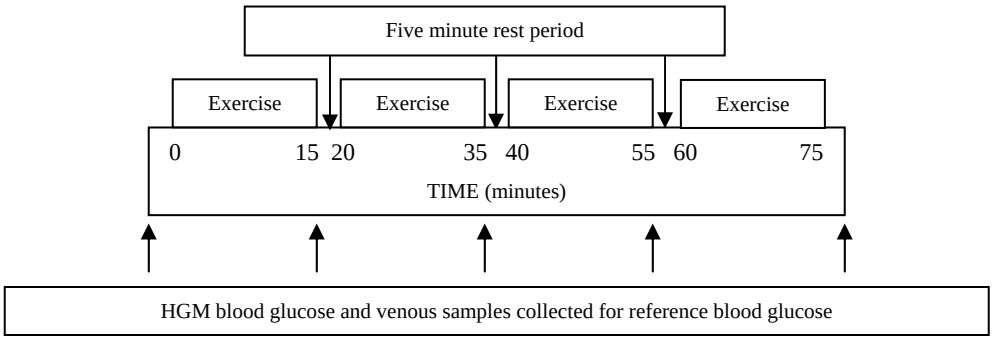
3.6 Exercise Session

For subjects $\geq$7 years of age, the exercise session will be performed in the afternoon. The basal rate normally used at home on a sedentary day will be used by subjects during the CRC admission. In order to enhance the assessment of the Navigator's ability to detect hypoglycemia, the basal rate will be continued during the exercise session.

Approximately 2 hours and again 1 hour before the scheduled start time for the exercise session, the BG will be checked with the Freestyle meter. Insulin or a snack may be given at the discretion of the investigator at either time to try to have the starting BG level between 80 and 200 mg/dL.

Exercise will not begin if the subject's blood glucose is <80 mg/dL as measured by the Freestyle meter. If the blood glucose level is 80 – 120 mg/dL, the subject will be given a snack of 15-30g of carbohydrates and the exercise will begin.

Exercise will consist of 15 minutes on a treadmill at a heart rate of approximately 140 followed by a 5-minute rest period. This cycle will be repeated 3 more times for a total of four 15-minute exercise periods with 5-minute rest periods in between (75 minutes total). Subjects will be encouraged to complete the exercise but will not be coerced to complete any remaining cycles if they are unable. If the 4 cycles are not completed in 2 hours, the exercise will be stopped. A heart rate monitor will be worn throughout the time of exercise to ascertain the effort exerted.



If during exercise the BG drops to <70 mg/dL the subject will be given 15-30g of carbohydrate and after 5-15 minutes, the BG will be rechecked. Exercise will not resume until the BG is >80 mg/dL.

3.7 Post-breakfast Glucose Measurements

In subjects of appropriate weight to accommodate the volume of blood required for testing, the Navigator will be assessed following a physiologic rise in blood glucose after breakfast.

Before starting the post-breakfast glucose measurements, a Freestyle blood glucose level will be obtained. If the blood glucose level is $\geq$250 mg/dl, then the subject's usual insulin correction dose will be given with breakfast. The meal dose (the dose for the carbohydrates to be consumed) will not be given with breakfast, but will be given after the completion of the 10-minute blood draws. The breakfast insulin correction dose (and the meal dose to cover the carbohydrate consumed) will be withheld until after completion of the reference glucose sampling if the blood glucose level is <250 mg/dL.

Reference glucose levels will be obtained at baseline (when the subject finishes breakfast) and every 10 minutes for 60 minutes.

3.8 Diabetes Management

Insulin management will follow the same routine that the subject was following at home prior to the hospitalization. Insulin doses will be determined by parents or subjects in consultation with the study investigator or his/her designee. For management, blood glucose levels from the Freestyle meter will be used.

Standard hypoglycemia treatment will be given for glucose values ≤70 mg/dl in children 7 years of age or older and for glucose values ≤80 mg/dl in children less than 7 years old (approximately 10 grams of carbohydrate--e.g., glucotablets or juice--for children less than age 7 and approximately 15 grams of carbohydrate for children 7 or older; with a recheck of the blood glucose 10 minutes later).

For two consecutive glucose values >300 mg/dl, a urine or serum ketone level will be determined.

3.9 Algorithms for Diabetes Management

During the CRC admission, the Navigator, insulin pump, and HGM data from the pre-admission week will be reviewed with the subject and parent. The subjects and parents will be taught how to make changes to the diabetes management based on the data from the Navigator.

3.10 Daily Activities

Subjects will be permitted to perform their usual indoor activities during the hospitalization.

3.11 Diet

The prescribed diet will be at the discretion of the investigator.

3.12 Hospital Discharge

Prior to discharge, the blinded Navigator sensor will be removed and a CRC nurse and a study nurse or investigator will independently assess the skin in the area of each Navigator sensor insertion (see section 3.2.1).

Subjects will continue wearing the unblinded Navigator inserted at the time of admission and will be provided with additional sensors. The subject and parent/guardian will be instructed to use the Navigator on a daily basis and will be instructed in the use of the device including calibration of the device using the built-in Freestyle meter and downloading the device.

CHAPTER 4
HOME PROCEDURES AND DIABETES MANAGEMENT

4.1 Home Glucose Monitor

Subjects will use the Freestyle as required for calibration of the Navigator sensor. Additional blood glucose measurements may be performed by the subject at anytime.

4.2 Frequency of Use of the Navigator

Each subject will be asked to use a Navigator sensor on a daily basis, inserting a new sensor every 5 days or sooner if the sensor stops working or is pulled out.

Subjects will be instructed to insert a new sensor 5 days before the 3-week and 13-week visits. This will allow for skin assessments to be made following the removal of sensors after 5 days of use.

4.3 Instructions for Use of the Navigator

The subject and parent will be instructed on use of the Navigator and will be provided with a manual describing its calibration and use.

4.4 Downloading the Navigator

At specified intervals, each subject will download the Navigator data, which will be transmitted to the Coordinating Center. The steps to follow will be detailed in the subject instruction manual.

4.5 Self-assessment Using Navigator Download

Instructions will be provided for subjects and parents to download and review the Navigator glucose values.

The goals for blood glucose levels will be as follows:

- Fasting: 70-150 mg/dl
- Premeal: 70-150 mg/dl
- Two hours after each meal: 70-180 mg/dl
- Bedtime: 90-150 mg/dl
- 12a.m. to 4a.m. : 80-150 mg/dl

The aim is to have at least half of the values for each time of day within these ranges.

4.6 Algorithms for Diabetes Management Decisions

The clinical center will provide the subject or primary care giver with algorithms to make management decisions based on real-time data provided by the Navigator and Freestyle meter. The algorithms will be reviewed with the subject and parent during the CRC admission, at each follow-up visit, and during each phone contact.

Compliance with using algorithms will be assessed during phone calls and follow-up visits.

CHAPTER 5
FOLLOW-UP

5.1 Timing of Visits

Follow-up visits will be completed at 1, 3, 7, and 13 weeks following the CRC admission. The visit windows will be ±3 days at weeks 1, 3, and 7 and ±1 week for week 13.

5.2 Overview

The main purpose of the follow-up visits is to review the data from the Navigator, pump, and Freestyle meter, review compliance with use of the algorithms, and make any necessary adjustments for diabetes management. The investigators will review the data and will, in conjunction with the nurse coordinators, implement all insulin adjustments.

At each visit, a skin assessment will be performed where the Navigator has been used. The accuracy of the subject's Freestyle meter will be assessed by comparing a blood glucose result obtained on the subject's meter to a simultaneous test performed on a Freestyle meter in the clinic.

At the 3, 7, and 13-week visits, the Insulin Dose Adjustment Guidelines Satisfaction Questionnaire will be administered (this questionnaire is described in Chapter 6).

At the 7-week follow-up visit, the following also will be done in addition to a standard clinic visit:

- HbA1c determination using the DCA 2000

At the 13-week follow-up visit, the following also will be done in addition to a standard clinic visit:

- HbA1c determination using the DCA 2000
- Completion of questionnaires (the questionnaires are described in Chapter 6)
    - PedsQL Diabetes Module
    - Diabetes Self-Management Profile (Treatment Adherence Questionnaire)
    - Continuous Glucose Monitor Satisfaction Scale
    - Insulin Dose Adjustment Guidelines Satisfaction Questionnaire

5.3 Continued use of the Navigator

At the 13-week visit, subjects not continuing the Navigator will be discontinued from the study.

Subjects willing to continue using the Navigator will be given additional sensors and instructed to use the sensors as often as they would like. These subjects will have a visit at 26 weeks. At the 26-week visit, a skin assessment will be performed where the Navigator has been used and frequency of continued use of the Navigator and algorithms will be assessed. The following will also be done in addition to a standard clinic visit:

- Measurement of HbA1c
- Completion of CGM Satisfaction Scale and Insulin Dose Adjustment Guidelines Satisfaction Questionnaire

5.4 Phone Calls to Subjects

Phone calls will be made from the clinical center to each subject or primary care giver 3 days (±1 day) and 2, 4, 8 and 10 weeks (±3 days) following the CRC admission. The primary purpose of the calls will be to review the subject's diabetes management and make alterations as indicated. During each phone call, the coordinator will review the subject's diabetes management after discussion with a study investigator. The downloaded Navigator data and Freestyle data will be available to

the clinical center for review during the call. Subjects will provide diet data as well as information regarding any illnesses or stressful events. Female subjects will also be asked to provide menstrual cycle information. The Procedure Manual will contain an outline for the clinical center to follow during the call.

CHAPTER 6
QUESTIONNAIRES

6.1 PedsQL Diabetes Module

This is a 28-item scale developed and validated for the measurement of diabetes-specific quality of life. Separate forms have been validated for child self-report (2-4 year old; 5-7 year old; 8-12 year old; and 12-18 year old) and parent report for these same age groups. Participants record the extent to which they (or their child) experienced each of 28 problems related to diabetes in the prior month. This questionnaire will be completed at enrollment and at the 13-week follow-up visit. Administration time is approximately 15 minutes.

6.2 Diabetes Self Management Profile (Treatment Adherence Questionnaire)

This is administered as a structured interview (DSMP) and will be used to determine if changes in diabetes treatment adherence occur during use of the Navigator and to assess whether benefit from use of the Navigator varies with the patient's level of treatment adherence. Parents and younger children will be interviewed together, while parents and children $\geq$9 years old will be interviewed separately. Since administration of the DSMP interview yields the most reliable and valid data if administered by a person not otherwise associated with the diabetes team, all DSMP interviews will be completed via phone by experienced staff at the Nemours Children's Clinic in Jacksonville, FL. The staff completing the interviews will be masked to the assignment group for the subjects. This questionnaire will be completed at enrollment and at the 13-week follow-up visit. Administration time is approximately 20 minutes.

6.3 Continuous Glucose Monitor Satisfaction Scale

This 34-item questionnaire was designed for this study to measure the impact of using the Navigator on family diabetes management, general family relationships, and individual emotional, behavioral and cognitive reactions to use of the device. This questionnaire will be completed at the 13-week and 26-week follow-up visits. Administration time is approximately 15 minutes.

6.4 Insulin Dose Adjustment Guidelines Satisfaction Questionnaire

This questionnaire was developed and will be piloted for this study to measure the frequency and convenience of use of study-developed algorithms and satisfaction with use of the algorithms in conjunction with the Navigator. This questionnaire will be completed at the 3-week, 7-week, 13-week and 26-week follow-up visits. Data from the pilot study will be used to evaluate the measure's psychometric properties including internal consistency, parent-adolescent agreement, associations with study outcomes and descriptive statistics. Administration time is approximately 10 minutes.

CHAPTER 7
ADVERSE EVENTS

7.1 Events To Be Reported

Adverse event reporting will include (1) events that meet criteria for a serious adverse event (SAE), (2) unanticipated adverse device events, (3) events that are considered to have a possible (or greater) relationship to the Navigator or any study procedure, (4) hyperglycemia resulting in diabetic ketoacidosis or hyperosmolar nonketotic coma, and (5) hypoglycemia resulting in seizures or loss of consciousness.

After 7 days following the completion of sensor use and all study procedures, only adverse events with a possible or greater relationship to sensor use or study procedures will be reported.

7.2 Definitions

Adverse events meeting the above reporting criteria will be reported with reference to: time and date of event, relationship to the device, severity, and final outcome.

An adverse event is considered a *Serious Adverse Event* (SAE) when it meets one or more of the following criteria: (1) death, (2) life-threatening, (3) required or prolonged hospitalization, (4) permanent disability, or (5) required intervention to prevent permanent impairment/damage.

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.

The relationship of any adverse event to the device or any other aspect of study participation will be assessed and graded by a study investigator on a four-point scale: (1) not related, (2) possible, (3) probable, and (4) definite. 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.

7.3 Reporting Requirements for Serious and/or Unexpected Adverse Events

Any serious or unexpected adverse event occurring during or within 7 days after completion of the study will be reported to the Coordinating Center within one working day of occurrence. A written report on such an event will be sent to the Coordinating Center within five days of occurrence, stating a description of the reaction, any required intervention, and the outcome. 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. Contact information for the Coordinating Center is located in the front of the protocol as well as in the Study Directory.

7.4 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will approve the protocol prior to its initiation and will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study.

7.5 Risks And Discomforts

7.5.1 Navigator

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. The TheraSense application for FDA approval of the Navigator sensor proposes a 3-day wearing period for each sensor. Nonetheless, TheraSense has indicated to DirecNet that a 5-day wearing period should be safe, effective, and more acceptable to patients. With the 5-day wearing period proposed for this study, the risk of skin reactions may increase. During the CRC admission and at each follow-up visit, each site where the Navigator has been worn will be assessed by study personnel. Both erythema and edema/induration will be scored on a 0 to 4 scale (as described on the case report form and in the Procedures Manual). If the sum of the erythema score and the edema/induration score is 6 or greater, an Adverse Event Form will be completed.

7.5.2 Fingerstick Blood Glucose Measurements

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

7.5.3 Psychosocial Questionnaires

As part of the study, subjects and 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.

7.5.4 IV Risks

A hollow needle/plastic tube will be placed in the arm for taking blood samples or giving fluids during the CRC admission. This will be left in for 24 hours. When the needle goes into a vein, it can cause pain. A special cream (Elamax or EMLA®) may be used to numb the area where the needle will be inserted. The most common risks related to putting the numbing cream on the skin are redness, blanching (temporary whiteness of the skin area), swelling, and itching. There will be the minor discomfort of having the needle/plastic tube taped to the arm. In about one in 10 cases a small amount of bleeding under the skin will produce a bruise. The risk of a blood clot forming in the vein is about one in 100, while the risk of infection or significant blood loss is one in 1000.

7.5.5 Exercise Risks

The exercise session during the CRC admission involves exercising for a short time while pulse and blood sugars are monitored. It is routinely used to diagnose heart and lung problems. Four in 10,000 people get abnormal heartbeats or chest pain while doing this test. One in 100,000 people die. These are usually older people who have a history of heart conditions.

7.5.6 Risk of Hypoglycemia

As with any person having insulin-dependent diabetes, there is always a risk of having a low blood sugar (hypoglycemia) and of ketoacidosis. In this study, hypoglycemia may occur during or following the time the exercise portion of the CRC admission. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and that for a few days the subject may not be as aware of symptoms of low blood sugar. Since we will be closely monitoring subjects during the CRC admission, a serious low blood sugar is not expected to occur. Even if severe low blood sugar does occur, it almost always goes away quickly with treatment to raise the blood sugar.

7.5.7 Post-breakfast Hyperglycemia

The subject’s prebreakfast insulin bolus will be held until the completion of the one-hour postbreakfast blood draws. This is expected to produce a greater rise in the blood glucose than would occur had the prebreakfast bolus been given. Hyperglycemia is usually acutely benign, but may be associated with thirst, glycosuria, ketoacidosis, and hyperosmolar coma. A serious effect from the hyperglycemia is not expected to occur in a single subject as the insulin bolus will be

given after an hour and the subjects will be monitored. Because of the monitoring, the risk is lower than it would be for the subject at home when a premeal bolus is missed (a not infrequent occurrence).

7.5.8 Blood Volume Requirements

At the time of CRC admission, the maximum number of blood draws that can be performed based on a subject's weight will be determined so that the maximum blood volume in the blood draws will not exceed 5% of the subject's blood volume (calculated by multiplying the subject's weight in kilograms by 70 [70cc / kg blood volume] and then multiplying by .05). The maximum number of blood draws is then determined by dividing this maximum blood volume by the amount of blood in each blood draw at the center.

The table below shows the blood volumes for each procedure at the "reinfusion" and "discard" centers, assuming a blood volume of 1.3 ml per blood draw at the "discard" centers and 0.3 ml per blood draw at the "reinfusion" centers. At the "discard" centers, the maximum number of blood draws per subject will be adjusted if the blood draw amount exceeds 1.3 ml.

Table 7.1 Blood Volume Requirements for Study Procedures According to Type of Blood Draw (Reinfusion or Discard)

		Type of Blood Draw Employed at the Clinical Center	
	# of blood draws	**"Reinfusion" (0.3 ml per blood draw)**	**"Discard" (1.3 ml per blood draw)**
Procedure		*blood volume (ml)*	
A. Half-Hourly measurements for 24 hrs	48	14.4	62.4
B. Quality control samples*	3	0.9	3.9
C. Blood draws for hypoglycemia*	3	0.9	3.9
D. Meal-induced hyperglycemia test	6	1.2	5.2
E. Exercise session	5	1.5	6.5

*This is a maximum number; see section 3.3.2 for details on quality control specimens and section 3.5 for details on additional blood draws at times of hypoglycemia

The tables below indicate the procedures to be done based on the age and/or weight of the subjects. At the reinfusion centers, all procedures will be performed on all subjects with the exception of the exercise, which is only completed for subjects $\geq$7 years of age. For discard centers, the procedures performed will be based on the age and weight of the subjects.

Table 7.2: Procedures to Be Done and Blood Volume Required According to Age of Subject

A. "Reinfusion" Centers

	Procedure (*see description in Table 7.1 for each 'letter'*)					
Subject Age	**A**	**B**	**C**	**D**	**E**	**Total Blood Volume***
< 7	14.4	0.9	0.9	1.2	-	17.4
$\geq$ 7	14.4	0.9	0.9	1.2	1.5	18.9

* assumes 0.3 ml per blood draw

B. "Discard" Centers

	Procedure (*see description in Table 7.1 for each 'letter')*					
Subject Age and Weight	**A**	**B**	**C**	**D**	**E**	**Total Blood Volume****
<7, 14.5-<20.1 kg	42.9*	3.9	3.9	-	-	50.7
<7, 20.1-21.5 kg	62.4	3.9	3.9	-	-	70.2
<7, ≥21.6 kg	62.4	3.9	3.9	5.2	-	75.4
≥7, 20.1-21.5 kg	62.4	3.9	3.9	-	-	70.2
≥7, 21.6-23.3 kg	62.4	3.9	3.9	5.2	-	75.4
≥7, ≥ 23.4 kg	62.4	3.9	3.9	5.2	6.5	81.9

* based on adjusted schedule of every 30 min overnight (9PM – 6AM) and hourly at other times

**assumes 1.3 ml per blood draw

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

CHAPTER 8
MISCELLANEOUS CONSIDERATIONS

8.1 Benefits

It is expected that continuous glucose monitors will have an important role in the management of diabetes in children. Therefore, the results of this study are likely to be beneficial for children 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.

8.2 Subject/Parent Reimbursement

The study will provide the Navigator and related supplies, and the Freestyle meter test strips.

Children will be paid $5 for every time the Navigator is downloaded on time and $2 for every time the Navigator is downloaded late during the first 3 months of the study. The amount earned by the child will be recorded and paid in one payment at the end of the study (Maximum of $60 during the study).

The study will be paying $100 for the CRC admission and $25 per completed visit for each of the six required study visits to cover travel and other visit-related expenses. Payment will not be made for missed visits. Payment will be made after the child completes the study.

8.3 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.

8.4 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.

The Diabetes Self-Management Profile, administered at baseline and at the 3-month visit, must be conducted via telephone by trained personnel at the Nemours Children's Clinic in Jacksonville, FL. If the phone interview cannot be conducted during the office visit, the phone number where the subject and parent can be reached may be provided to the staff at Nemours. The interview will be conducted at a time that is convenient for the subject and parent.

During the study, subjects will be asked to download the Navigator and Freestyle data to their home computer. The downloaded data will be emailed to the coordinating center. TheraSense will be provided with the downloaded data as well as the data collected for the study during the CRC

admission, at follow-up visits, and during phone contacts. The data provided to TheraSense will include only the subject's identifier; no names or personal information will be included.

Chapter 9
Statistical Considerations

9.1 Sample Size

The sample size of 30 for this pilot trial is a convenience sample and is not based on statistical principles.

9.2 Analysis Plan

The analysis plan is summarized below and will be detailed in a separate document.

9.2.1 Assessment of the Feasibility of Using the Navigator Continuous Glucose Sensor on a Daily Basis

From baseline through 13 weeks, average weekly values will be given for the following:

- Number of sensors used
- Number of sensors unsuccessfully calibrated
- Hours of sensor use

Use of the sensor on at least 6 of 7 days will be considered a successful week.

Results will also be stratified by week. The bootstrap will be used to account for correlated data from the same subject to test whether weekly hours of sensor use remains stable over time. Similar analyses will be conducted to see whether sensor use is associated with subject demographics such as age, gender or weight.

9.2.2 Development and Testing of Algorithms for Making Adjustments to Diabetes Management Based on Data from Navigator

Downloads from the insulin pump and Freestyle glucose meter will be manually reviewed by study investigators to evaluate the level of subject compliance with the algorithms. Methods for automatically calculating a compliance score based on the expert review will be explored.

9.2.3 Questionnaires

Analysis of total scores from the PedsQL Diabetes Module and the Diabetes Self-Management Profile questionnaires will be analyzed at baseline and 13 weeks separately for patients ($\geq$9 years at enrollment) and parents (all subjects). Paired t-tests will be used to compare baseline vs. 13-week results separately for patients and parents. Correlations between patient and parent scores and baseline and 13-week scores will also be calculated.

9.2.4 Inpatient Accuracy of the Navigator

9.2.4.1 Difference Measures

Navigator glucose measurements from the CRC admission will be paired to glucose values from simultaneous blood draws sent to the central laboratory. For each Navigator-reference glucose pair the following accuracy measurements will be calculated:

- Difference (Navigator glucose minus reference glucose)
- Absolute Difference (absolute value of the Difference)
- Relative Difference (Difference divided by reference glucose, expressed as a percentage)
- Relative Absolute Difference (absolute value of the Relative Difference)
- ISO criteria (binary assessment of accuracy: sensor within ± 15 mg/dL if reference $\leq$ 75 mg/dL or sensor within ± 20% if reference > 75 mg/dL)

The primary assessment of accuracy will exclude glucose values during exercise. Separate analyses for exercise are described in Section 9.2.4.5.

Mean and 95% confidence interval, median and quartile values will be given for the first four accuracy measures listed above as well the percentage of pairs meeting the ISO criteria with 95% confidence interval.

Median relative absolute difference (RAD) and ISO percentages will be explored in subgroups defined by:

- reference glucose level
- sensor age
- day vs. night

Confidence intervals and statistical comparisons will be done using the bootstrap method to account for correlated data from the same subject.

9.2.4.2 Precision

When 2 Navigators are being worn simultaneously during the CRC stay, the glucose values from the devices will be paired to each other. The analyses described in Section 9.2.4.1 will be performed for these pairs to describe the precision of the Navigator.

9.2.4.3 Detection of Hypoglycemia

Hypoglycemic episodes during the CRC stay defined by the reference glucose values will be evaluated for Navigator sensitivity (percentage of episodes successfully detected by the Navigator). The false alarm rate for Navigator defined episodes of hypoglycemia will also be calculated using the reference glucose data.

Analogous calculations of sensitivity and false alarm rates will be calculated for the impending hypoglycemia alarms.

If there are a sufficient number of events, separate analyses will be given for day vs. night.

9.2.4.4 Detection of Hyperglycemia

Analysis will parallel that described for hypoglycemia in Section 9.2.4.2. The definition of hyperglycemia will be $\geq$ 300 mg/dL.

9.2.4.5 Assessment of Navigator Function during Exercise

The analyses described in Section 9.2.4.1 will be run separately for Navigator-reference pairs during exercise. The rate error-grid analysis will also be performed separately.

Sensitivity rates will also be calculated for hypoglycemia (during exercise). The glycemic excursions and rates of change during this period will be compared between reference vs. Navigator glucoses by giving summary statistics for the difference, absolute difference, relative difference and relative absolute difference.

9.2.4.6 Assessment of Navigator Function Post-Breakfast

Analysis of the frequent post-breakfast blood draws described in Section 3.7 will include all pairs from the start of glucose rise until the reference peak. The start of glucose rise will be defined as the first measurement after which the next two values both show a rate of increase $\geq$ 0.5 mg/dL per

minute. Sensitivity rates will be calculated for hyperglycemia defined as a reference glucose ≥ 300 mg/dL. Glycemic excursions and rates of change during this period will be compared between reference vs. Navigator glucoses by giving summary statistics for the difference, absolute difference, relative difference and relative absolute difference.

9.2.5 Outpatient Accuracy of the Navigator

Navigator values from home use will be paired with corresponding Freestyle measurements. Freestyle values used to calibrate the Navigator will be excluded from analysis. The analyses described in Sections 9.2.4.1, 9.2.4.3 and 9.2.4.4 will be repeated for these data to describe Navigator accuracy during outpatient use. Additionally, potential associations of accuracy with subject demographics such as age, gender and weight will be explored.

9.2.6 Comparison of Subject vs. Staff Freestyle Measurements

The difference measures described in Section 9.2.3.1 will be computed for the times when the subject and a CRC staff member made simultaneous Freestyle glucose measurements.

9.2.7 Exploratory Assessment of the Effect of Use of the Navigator and Algorithms on A1c and Frequency of Hypoglycemia

Mean and standard deviation of the A1c values will be given at baseline and 13 weeks. If the distribution of A1c values is suitable for least squares analysis, a paired t-test will be used to compare baseline vs. 13 week values. Otherwise, the Wilcoxon signed-rank test will be used instead. A similar procedure will be used to compare baseline vs. 13 week results for:

- Number of self-reported weekly episodes of symptomatic hypoglycemia
- Number of Navigator defined episodes of hypoglycemia
- Mean glucose (measured by the Navigator)
- Percentage of Navigator measurements in target range 60-180 mg/dL

Mean and standard deviation values for the four measures listed above will also be stratified by baseline A1c values.

9.2.8 Severe Hypoglycemia

All self-reported episodes of severe hypoglycemia defined by seizure or loss of consciousness will be tabulated.

References

1. Boyne, M.S., et al., Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. *Diabetes* 52: 2790-2794, 2003.

2. Steil, G.M., et al., Accurate determination of plasma glucose during hyper- and hypoglycemia with a subcutaneous glucose sensor (Abstract). *Diabetes* 49(Suppl 1): A126, 2000.