A Randomized Clinical Trial to Assess the Efficacy of Real-Time Continuous Glucose Monitoring in the Management of Type 1 Diabetes

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CHAPTER 1
INTRODUCTION

1.1 Introduction and Rationale

The Diabetes Control and Complications Trial (DCCT) clearly demonstrated the importance of glycemic control in preventing and delaying the microvascular complications of type 1 diabetes (T1D)[1, 2] but at the cost of a 3-fold increase in the frequency of severe hypoglycemia and a 2-fold increase in the frequency of excessive weight gain. The DCCT also demonstrated that achieving and maintaining target glucose and HbA1c levels was more difficult in adolescents than adults with T1D. Compared with intensively treated adults, intensively treated adolescents in the DCCT had higher HbA1c levels, a 60% increase in the risk of severe hypoglycemia, and the same 2-fold increase in the rate of obesity.[3]

Despite increased use of insulin pumps and multiple injection regimens and the introduction of rapid and long-acting insulin analogs, the majority of individuals with T1D fail to achieve target HbA1c levels recommended by the DCCT more than 12 years ago. While self-monitoring of blood glucose plays an important role in achieving target HbA1c levels, most patients measure glucose levels infrequently immediately after meals and during the overnight period. Consequently, post-prandial hyperglycemia and asymptomatic nocturnal hypoglycemia are commonly observed even in well-controlled individuals with T1D.[4] In addition, the fear of hypoglycemia by patients, and for children's parents, is a major obstacle to successful intensive insulin therapy, and the lack of overnight monitoring is a problem since more than 50% of severe hypoglycemic events occur during sleep.[5-7]

Increasing the frequency of glucose monitoring was an important aspect of attaining improved glucose control in the DCCT. However, resistance to frequent blood glucose monitoring is a major impediment to attaining good (lower HbA1c level) glucose control. Real-time continuous glucose monitoring (RT-CGM) offers the opportunity to improve glycemic control, including reducing rather than increasing the incidence of severe hypoglycemia as control is "tightened." The GlucoWatch Biographer™ was the first "real-time" glucose sensor made available for daily use by patients. Unfortunately, it was not tolerated well and few children found it to have long-term utility.[8] Recently several RT-CGM systems were approved by the FDA: the DexCom STS Continuous Glucose Monitoring System™ (DexCom, Inc., San Diego, CA) and the Paradigm® and Guardian® REAL-Time Continuous Glucose Monitoring Systems (Medtronic Minimed, Northridge, CA). The same sensor is used by the Paradigm and Guardian systems. Therefore, for this protocol we are considering the Paradigm and Guardian devices as the same device. An additional RT-CGM system, the FreeStyle Navigator™ Continuous Glucose Monitoring System (Abbott Diabetes Care, Inc.) has been evaluated by the Diabetes Research in Children Network (DirecNet) and is expected to receive FDA approval shortly.

The proper role of the RT-CGM in the management of T1D has not been determined. Clinical trials of RT-CGM technology are critically important to demonstrate that this technology is effective and to provide information on how it should be implemented and used.

1.2 Current RT-CGM Systems

All three of these RT-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.[9, 10]

Features of the three RT-CGMS are summarized in the table below

	Navigator	DexCom	Paradigm/Guardian
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	72 hours
Warm up period	10 hours	2 hours	2 hours
Calibration frequency	4 times at approximately 10hrs, 12hrs, 24hrs and 72hrs following sensor insertion	2 times a day (every 12hrs)	2 times a day (every 12hrs)
Home Glucose Meter (HGM) for Calibration	FreeStyle (built in)	One Touch Ultra (connected via a cable)	BD Logic (connected via radiofrequency); 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	Hypo, hyper (adjustable) No predicted alarms
Trend Arrows on Receiver Display	Yes	No	Yes
Entering of events	Insulin, meals, exercise, health, other	Not available	Insulin, meals, exercise
Other features			Can be combined with a Medtronic pump in a single device (functioning separately)
FDA status	Pending for adults	Approved for >=18 year olds as adjunct to HGM	Approved for >=18 year olds as adjunct to HGM

1.2.1 Studies on the Three RT-CGMs

FreeStyle Navigator

Bode et al. [11] reported on adults with type 1 (N=60) or type 2 (N=41) diabetes who wore a blinded Navigator sensor for an average of 287h. Patients spent an average 8% of time in the hypoglycemic range (<70 mg/dL), 63% time in euglycemia (70-180 mg/dL) and 29% time in the hyperglycemic range (>180 mg/dL). The sensor detected an average of 1.6 hypoglycemic episodes per day each lasting an average of 0.9h. No accuracy data were reported.

DexCom STS

Garg et al. [12] studied 15 adults with T1D. The mean relative absolute difference (RAD) was 16% during a 12h inpatient session compared to a home glucose meter reference and 25% compared to a YSI reference. The bias difference compared to a home glucose meter was <15% in each glucose range studied. Patients wore a blinded sensor at home for a mean of 50 days followed by a period of unblinded home use (mean 44 days). Patients spent a median 47% less time below 3.1 mmol/L and 25% less time above 13.3 mmol/L (both $P < 0.05$) when the sensor was unblinded. No adverse events were reported as a result of sensor use.

The DexCom users guide reports a median RAD of 20% pooling inpatient and outpatient data.[13]

Guardian

Bode et al. [14] randomized 71 adults with T1D to wear the Guardian sensor with either the hypo-/hyperglycemia alarms turned on or off. The median RAD value was 17% with a median bias of –8 mg/dL compared to a home glucose meter. Both randomization groups wore two sensors (median sensor life 72h) with the alarms turned off during the first period. During the second period each subject wore two more sensors with the alarms activated (set to 70 and 250 mg/dL) in those randomized to the alarm group. The median duration of hypoglycemic excursions dropped significantly more between the two periods in the alert group (27.8 vs. 4.5 minutes; P = 0.03), but the median number of hypoglycemic events increased slightly more in the alert group (+0.5 vs. +0.03 per day; P = 0.18). No significant differences in the incidence or duration of hyperglycemia. Eleven adverse events were reported from 7 subjects including 7 instances of mild skin irritation, 2 instances of excessive bleeding (moderate intensity), 1 instance of hematoma and 1 instance of moderate discomfort.

Piper et al. [15] reported a mean RAD of 18% compared to a laboratory reference in 20 children <3y of age undergoing cardiac bypass surgery. Within range of 23.1 to 37.5^{o} C, no affect of temperature on accuracy was detected. Mean glucose concentrations were 84, 157, 137 and 114 mg/dL preoperatively, on the day of surgery, postoperative days 1 and postoperative day 2, respectively. Subjects wore the sensor for a mean 48h and no instances of adverse events related to the sensor were reported.

1.3 DirecNet Pilot Study

The Diabetes Research in Children Network (DirecNet) conducted a pilot study using the Navigator. The study included 30 children with T1D aged 4 to 17 years who were using an insulin pump. On the day of enrollment, HbA1c was measured, psychosocial questionnaires were completed, and instructions were given for use of the Navigator. To obtain a baseline assessment of glycemic control, the Navigator was blinded during the first week so subjects were not able to view the sensor data. Subjects returned for a 24-hour admission in a clinical research center approximately one week after the enrollment visit to assess the accuracy of the Navigator and to be instructed on how to use the Navigator glucose data in daily diabetes management. Follow-up visits were performed after 1, 3, 7, and 13 weeks. At the 13-week visit, subjects who were interested in continuing to use the Navigator were provided with additional supplies to continue in the study for another 13 weeks.

Results: During inpatient use, the median RAD was 12% compared to a laboratory reference and 74% of Navigator-reference pairs met the ISO criteria (sensor within ±15 mg/dL if reference <75 mg/dL or sensor within ±20% if reference ≥75 mg/dL). During hypoglycemia (reference ≤70 mg/dL), the median absolute difference was 14 mg/dL and the median RAD was 13% and 10% when the reference was 71-180 and >180 mg/dL, respectively. There was no tendency for the Navigator to read systematically higher or lower than the reference (median difference –2 mg/dL; P = 0.34). Accuracy was similar during outpatient use with the built in Freestyle meter as the reference.

Twenty-eight of the 30 subjects completed the planned 13-week duration of the pilot study. Subjects averaged 149 hrs/wk of Navigator use during the first 4 weeks and 134 hrs/wk during wks 9-13. Two subjects withdrew prior to the 13-week visit and 2 subjects had a severe skin reaction but continued to use the Navigator after the reaction resolved.

For the 28 subjects completing the 13-week visit, HbA1c decreased from a mean at baseline of 7.1% to 6.8% at 13 weeks (P=0.02) despite the fact that 75% of the subjects started with an A1c <7.5%. There was an immediate increase in the percentage of glucose values in the target range that then remained steady during the 13 weeks (52% at baseline, 60% during weeks 1-4, and 60% during weeks 9-13, P= 0.01 comparing baseline to weeks 9-13). Glycemic variation as measured by the SD and the mean

amplitude of glycemic excursions (MAGE), which quantifies glucose stability by taking the average change in glucose over each excursion from peak to nadir (or nadir to peak),[16] also decreased during the study period, but this did not achieve statistical significance. Both subjects (≥9y) and their parents reported high overall satisfaction with the Navigator on the CGM Satisfaction Scale at 13 weeks with average item scores of 3.6 and 3.9, respectively, on a 5-point Likert scale. At 13 weeks, none of the patients and only 1 parent disagreed that the DirecNet Applied Treatment Algorithm (DATA) gave good clear directions for how much insulin to give.

Twenty-six of 28 subjects elected to continue to use the Navigator beyond 13 weeks. Navigator use decreased during this period, during which there were no protocol-specified visits or phone contacts. One subject dropped from the study prior to the 26 week visit. At the 26-week visit, 7 others reported that they had not used the Navigator in the previous 7 days. Among the other 18 subjects, Navigator use which averaged 139 hours/week in weeks 9-13 decreased to 108 hours/week in weeks 22-26. HbA1c at 26 weeks averaged 7.0% overall, which was not significantly better than the baseline A1c (P=0.64), but remained lower among the N=12 subjects whose baseline HbA1c was >7.0% (7.2% at 26 weeks vs. 7.6% at baseline; P=0.02). Despite the decrease in use, both subjects (≥9y) and their parents continued to report high overall satisfaction with the Navigator on the CGM Satisfaction Scale at 26 weeks with average item scores of 3.7 and 4.1, respectively, on a 5-point Likert scale.

Since all of the subjects enrolled in this study were on insulin pump therapy, a second pilot study evaluating the use of the Navigator is being conducted for subjects on multiple daily injection therapy using glargine as basal insulin.

The positive results in this pilot study using the Navigator are encouraging in indicating that incorporating RT-CGM into the daily management of T1D in children is feasible and viewed extremely positively by both patients and parents. However, the results must be viewed cautiously since the study did not include a concurrent control group and the data suggested a drop off in use after the first 13 weeks. Nevertheless, the results provide a compelling rationale for a larger scale randomized trial.

1.4 Study Objective

The primary objective of the study is to determine if RT-CGM can improve glycemic control and quality of life in children and adults with T1D. In addition, an evaluation of the cost-effectiveness of RT-CGM will be conducted.

1.5 RT-CGM Systems to Use in the Trial

The technology involved with the three RT-CGM systems is similar. Therefore, the objective of the study involves whether the diabetes management strategy using RT-CGM technology is beneficial and not whether a specific RT-CGM system is beneficial. As a result, one, two, or all three of the RT-CGM systems described earlier may be used in the trial depending on availability of the RT-CGM systems, costs, feasibility aspects of use, and cooperation of the companies to provide whatever modifications are needed to the systems for the conduct of the trial (such as blinding the readouts during parts of the study and retrieval of the data for the project's database). Shortly before enrollment of the first subject, the study group will decide which RT-CGM system(s) will be used in the study. This may change as the study progresses based on availability of RT-CGM systems, development of enhancements, and experience with the different systems. When more than one RT-CGM system is available for assignment, the selection for a new subject will be made by the investigator.

During the course of the study, subjects may receive upgraded RT-CGM systems as they become available and could be switched from one system to another if their use of one system was not successful and there was reason to believe that they might be successful with a different system.

1.6 Synopsis of Study Protocol

Subjects with T1D who are at least 8 years old will be enrolled into the multi-center protocol which consists of two phases:

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

(2) a 6-month observational study during which the RT-CGM Group continues to use RT-CGM to evaluate whether any beneficial effect seen in the first 6 months is sustained with longer-term use and less intensive contact and the control group initiates RT-CGM use with less intensive contact after the first month than was provided at initiation of RT-CGM use in the RT-CGM group in phase 1.

The protocol will include two sub-studies with identical protocols.

- The primary study will include subjects with a HbA1c of 7.0% to 10.0% inclusive.
- The secondary study will include subjects with HbA1c <7.0%.

This separation into two sub-studies according to baseline HbA1c level was done because there is not a widely accepted primary outcome that can be used across the full range of HbA1c values.

- For individuals with HbA1c ≥7.0%, HbA1c is a meaningful outcome measure that is likely to detect any beneficial effect of RT-CGM intervention in a randomized trial.
- For individuals with HbA1c <7.0%, neither HbA1c nor incidence of hypoglycemia is a satisfactory outcome. With successful RT-CGM use, HbA1c may not change or may even rise slightly. Therefore, HbA1c is not an appropriate endpoint for this group. Including such individuals in the primary study (with HbA1c as the outcome) would likely reduce the study's statistical power. In individuals with HbA1c <7.0%, a major goal of RT-CGM is to reduce the incidence of severe hypoglycemia. However, this is a problematic endpoint for a randomized trial because the frequency of episodes of severe hypoglycemia in the control group is expected to be low, and as a result, an unfeasibly large sample size would be needed to evaluate whether RT-CGM use can reduce the incidence. A definition of hypoglycemia that included less severe events (such as confirmed symptomatic episodes in which assistance was not needed) probably would be biased against the RT-CGM group, since the use of the RT-CGM is likely to identify more events merely because the glucose level is known. Therefore, this cohort of subjects will be included as a secondary pilot study to explore outcomes that could be appropriate to use to evaluate the value of RT-CGM in subjects with HbA1c in the excellent range.

1.6.1 Summary of Design of Randomized Trial

A. Major Eligibility Criteria

- Clinical diagnosis of T1D
- Age ≥8 years
- Insulin regimen includes either an insulin pump or multiple daily injections

B. Sample Size

The primary study (HbA1c ≥7.0%) will include a minimum of 330 subjects, with approximately 110 in each of three age groups of 8 to <15 years old, 15 to <25 years old, and ≥25 years old. Depending on the results of an interim analysis (see section 9.1.3) this may be increased up to 450 subjects.

The secondary study (HbA1c <7.0%) will include a minimum of 120 subjects, with approximately 40 in each of three age groups of 8 to <15 years old, 15 to <25 years old, and ≥25 years old. If the goal of 120 subjects is reached prior to completion of recruitment of the primary cohort, recruitment may be continued up to 240 subjects.

Enrollment will include approximately 50% of subjects using an insulin pump and approximately 50% of subjects using multiple daily injections of insulin (at least 3 shots per day).

C. Treatment Groups

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

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

D. Duration of Follow-up

- RCT outcome at 6 months
- Subsequent observational study outcome at 1 year
- Total duration – 1 year

E. Main Outcome Measures

RCT – 1st 6 months

Treatment group comparisons of the following:

- HbA1c
- Episodes of severe hypoglycemia
- Percentage of sensor values in range (70 mg/dL to 180 mg/dL)*
- Biochemical hypoglycemia (percentage of sensor values <70 mg/dL)*
- Quality of life measures
- Measures of variability: mean amplitude of glycemic excursions (MAGE), SD, mean absolute rate of change*

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

Post-RCT Observational Study – 2nd 6 months

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

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

A cost-effectiveness analysis will be included in the analysis plan of the study.

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

Randomized Trial Phase

Visit or Phone	Enr V	0 V	3d P	1w V	2w P	4w V	6w P	8w V	10 w P	13 w V	16 w P	19 w V	22 w P	26 w V
Blinded RT-CGM*	X									X*				X*
Pre-randomization compliance assessment		X												
HbA1c-DCA2000	X	X				X		X		X		X		X
HbA1c-lab		X								X				X
Skin Assessment		X		X		X		X		X		X		X
Data download				X		X		X		X		X		X
Review diabetes management		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Glucose Monitoring System Rating Questionnaire	X													X
PedsQL Questionnaire (Subjects <18 yrs & Parent)	X													X
Hypoglycemia Fear Survey	X													X
PAID Survey (Subjects ≥18 yrs and Parents of subjects <18 yrs)	X													X
SF-12 (Subjects ≥18 yrs)	X													X
CGM Satisfaction Scale**														X
Algorithm Satisfaction Questionnaire						X				X				
Cost-effectiveness data	X			X		X		X		X		X		X

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

**RT-CGM Group only.

Post-RCT Observation Phase (*following 6 month follow-up visit*)

	Control Group				Both Groups	
	3d	1w	2w	4w	13w	26w
Visit or Phone	**P**	**V**	**P**	**V**	**V**	**V**
HbA1c-DCA2000				X	X	X
HbA1c-lab					X	X
Skin Assessment		X		X	X	X
Data download		X		X	X	X
Review diabetes management	X	X	X	X	X	X
Blood Glucose Monitoring System Rating Questionnaire						X
PedsQL Questionnaire (Subjects <18 yrs & Parent)						X
Hypoglycemia Fear Survey						X
PAID Survey (Subjects ≥18 yrs and Parents of subjects <18 yrs)						X
SF-12 (Subjects ≥18 yrs)						X
CGM Satisfaction Scale						X
Algorithm Satisfaction Questionnaire*				X		
Cost-effectiveness data		X		X	X	X

*Control Group only

1.6.2 Summary of Protocol

1. Informed consent and assent (if applicable) will be obtained from eligible subjects and their parent/guardian if <18 years of age in compliance with local IRB policies.

2. On the day of enrollment, a HbA1c will be obtained, psychosocial questionnaires will be completed, and instructions will be given for use of the RT-CGM. The study personnel will supervise the subject or parent inserting the RT-CGM sensor in the clinic and will instruct the subject or parent to insert a second sensor at home as needed. To obtain a baseline assessment of glycemic control and variability, the RT-CGM 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 study HGM to calibrate the RT-CGM.

3. The subject will return for the randomization visit 10±3 days after the enrollment visit.
   - Subjects who have been compliant with use of the RT-CGM and HGM will be randomized to one of two treatment groups: RT-CGM Group or Control Group.
     - Compliance will be defined as use of the RT-CGM for at least 6 out of the 7 days prior to the randomization visit, at least 96 hours of RT-CGM glucose values obtained with at least 24 hours between the hours of 10 p.m. and 6 a.m., and use of the HGM for testing at least 3 times each day prior to the randomization visit.

- Subjects who are not compliant will be given another opportunity to complete the baseline requirements at the discretion of the investigator.

- For the RT-CGM Group, the RT-CGM, HGM, and pump data (if subject uses an insulin pump) will be reviewed and changes will be made to diabetes management as needed. Subjects/parents will be taught to use the protocol-developed algorithms for changes to diabetes management to be used in real time based on RT-CGM and HGM data. Instructions for downloading the RT-CGM and HGM will be provided to subjects with a home computer.

- For the Control Group, a HGM and test strips will be provided. The HGM and pump data (if subject uses an insulin pump) will be reviewed and changes made in diabetes management as needed. The blinded RT-CGM data will be downloaded but will not be reviewed by study personnel until the end of the first 6 months of the study. Subjects and parents will be taught to use the protocol-developed algorithms for how to make changes to diabetes management based on HGM data.

4. Both groups will have follow-up visits at 1, 4, 8, 13, 19, and 26 weeks ($\pm$1 week) plus one phone contact between each visit (including one phone contact between randomization and the one week visit) to review their diabetes management.
   - Both groups will download device data on a weekly basis (if the subject has a computer). Subjects with email access will be instructed to email the downloaded data to the clinical center prior to each phone contact.

   - For both groups, at each visit, the HGM and pump (if subject uses an insulin pump) will be downloaded and for the RT-CGM Group, the RT-CGM will be downloaded.

6. In the 13th and 26th weeks, the Control Group will use a blinded RT-CGM for one week. The RT-CGM Group will continue to use the unblinded RT-CGM. The Control Group will return the blinded RT-CGM to the clinic after a week. The data will be reviewed by personnel who are not involved in the care of the subject to determine if additional blinded sensor data are needed. The blinded data will not be reviewed by study personnel for management decisions until the end of the first 6 months of the study.

7. Following the 26-week visit:
   - Subjects in the RT-CGM Group will continue to use the RT-CGM.

   - Subjects in the Control Group will be provided with a RT-CGM and sensors after the week of blinded use and will have visits after 1 week and 4 weeks, with a phone contact during the first and third weeks.

   - Both groups will have visits after 13 weeks and 26 weeks (study time 9 and 12 months).
     - At the 26-week visit (study time 12 months), subjects using the FreeStyle Navigator will be given the choice to continue in the study until the device is approved by the FDA or until Abbott Diabetes Care can no longer provide supplies for the study. Subjects who agree to continue in the study will sign an addendum to the informed consent.
       - Subjects who continue in the study will return to the clinic every 3 months for a standard clinic visit.

1.7 General Considerations

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

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

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

CHAPTER 2
SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Study Population

Approximately 450 subjects are expected to be enrolled in the study (see section 1.6.1, B). Some centers will be enrolling children, some adults, and some both.

- Approximately one-third of the subjects will be enrolled in each of the following three age groups: 8 to <15 years old, 15 to <25 years old, and ≥25 years old.
- Enrollment is expected to include approximately 50% of subjects using an insulin pump and approximately 50% of subjects using multiple daily injections of insulin (at least 3 shots per day).
- Enrollment is expected to include approximately 330 individuals with HbA1c ≥7.0% and 120 with a HbA1c <7.0%.

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 a minimum of 10% minorities.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

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

1) Clinical diagnosis of type 1 diabetes and using daily insulin therapy for at least 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 ≥8 years
3) HbA1c less than or equal to 10.0%
   - *The DCA2000 or comparable point of care device will be used to assess eligibility.*
4) Insulin regimen involves either use of an insulin pump or multiple daily injections of insulin (at least 3 shots per day) and has been stable for the last two months, with no plans to switch the modality of insulin administration during the next 6 months (e.g., injection user switching to a pump, pump user switching to injections, or the addition of Lantus (Glargine) insulin)
   - *Subjects using premixed fixed doses of insulin at the time of enrollment will not be eligible*
5) Subject (and parent/guardian for children) understands the study protocol and agrees to comply with it
6) Subjects ≥9 years old and primary care giver (i.e., parent or guardian if subject is a minor) comprehend written English or Spanish
   - *This requirement is due to the fact that the questionnaires to be used as outcome measures do not have validated versions in other languages.*
   - *Spanish-speaking subjects will be enrolled only if a RT-CGM device that functions in Spanish and has a User Guide in Spanish is available.*
7) No expectation that subject will be moving out of the area of the clinical center during the next year, unless the move will be to an area served by another study center.
8) Informed Consent Form signed by the subject (or parent/guardian if subject is a minor, with subject signing the Child Assent Form)

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

2) The presence of any of the following diseases:
   - Asthma if treated with systemic or daily inhaled corticosteroids in the last 6 months
     - *Intermittent treatment with inhaled corticosteroids does not exclude subjects from enrollment*
   - Cystic fibrosis
     - *Adequately treated thyroid disease and celiac disease do not exclude subjects from enrollment*

3) Inpatient psychiatric treatment in the past 6 months (if the subject is a minor, for either the subject or the subject's primary care giver).

4) Home use of RT-CGM in past 6 months.
   - *Use of a CGMS or GlucoWatch does not exclude subjects from enrollment*

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

6) Another member of the same household is participating in this study.

7) For females, pregnant or intending to become pregnant during the next year
   Pregnancy is an exclusion because of uncertainty about the lag between interstitial fluid glucose and blood glucose during pregnancy, which might affect the accuracy of the sensor. Subjects who become pregnant during the study will be discontinued from the study.

2.3 Subject Enrollment and Baseline Data Collection

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

2.3.1 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.

2.3.2 HbA1c

HbA1c level measured using the DCA2000 or comparable point of care device will be used to assess eligibility. 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.

2.3.3 Informed Consent

For eligible subjects, the study will be discussed with the subject (and parent/legal guardian if the subject is a minor, referred to subsequently as 'parent'). The subject/parent will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Subjects of appropriate age (per IRB requirements) will either be given the Child Assent Form to read or it will be read to the child. If the subject (and parent for minors) agrees to participate, the Informed Consent Form and Child Assent Form

(if applicable) will be signed. A copy of the consent form will be provided to the subject and another copy will be added to the subject's clinic chart.

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

2.3.3.1 Authorization Procedures

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

2.3.3.2 Special Consent Issues

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

2.3.4 Questionnaire Completion

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

Subjects <18 Years Old

- Blood Glucose Monitoring System Rating Questionnaire
- Peds-QL (combined sections of generic / diabetes modules)
- Hypoglycemia Fear Survey

Parents of Minor Subject

- Blood Glucose Monitoring System Rating Questionnaire
- Peds-QL (combined sections of generic / diabetes modules)
- Problem Areas in Diabetes (PAID - Parent version)
- Hypoglycemia Fear Survey

Subjects 18 Years and Older

- Blood Glucose Monitoring System Rating Questionnaire
- Problem Areas in Diabetes (PAID)
- SF-12
- Hypoglycemia Fear Survey

2.3.5 Instructions for Home Procedures

Each subject will be provided with a RT-CGM and sensors. The RT-CGM to be used will be decided upon by the investigator if more than one is available for assignment. The RT-CGM will be blinded and subjects will not be able to view the RT-CGM data. The subject will be instructed to use the RT-CGM on a daily basis and will be instructed in the use of the device.

- Subjects will be advised to use the RT-CGM daily and to measure the blood glucose using the HGM (unblinded) at least 4 times a day.

- Subjects will be informed that to be eligible for the randomized trial, the RT-CGM must be used on a minimum of 6 out of 7 days, at least 96 hours of RT-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
RANDOMIZATION VISIT

3.1 Timing of Visit

Enrolled subjects will return 10 (±3) days after enrollment for baseline testing and randomization. The purpose of the visit will include the following:

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

3.2 Review of RT-CGM and HGM Data

The HGM and RT-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 RT-CGM on at least 6 out of 7 days prior to the visit, and obtained at least 96 hours of RT-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 RT-CGM and HGM requirements.

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

3.3 Randomization

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

1. RT-CGM Group
2. Control Group

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

- The Jaeb Center will construct a Master Randomization List using a permuted block design.
- For subjects with baseline HbA1c ≥7.0%, the randomization will be stratified by clinical center, age (8-<15, 15-<25, >=25) and HbA1c (7.0-8.0, 8.1-10.0).
- For subjects with baseline HbA1c <7.0%, the randomization will be stratified by clinical center only.

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

3.4 Procedures for the RT-CGM Group

The RT-CGM provided at enrollment will be unblinded and the subject will be provided with sensors. The subject will be instructed to use the RT-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 subject has a home computer). Those with email access will be asked to email the downloaded data to the clinical center before each scheduled phone call.

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

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

3.5 Procedures for the Control Group

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

Subjects will be provided with a HGM and test strips and will be asked to perform at least 4 fingerstick blood glucose measurements per day.

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

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

3.6 HbA1c

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

CHAPTER 4
RANDOMIZED TRIAL PHASE

4.1 Home Procedures and Diabetes Management

4.1.1 RT-CGM Group

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

A study HGM will be used for calibration of the RT-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 RT-CGM glucose reading.

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

Subjects who are not successfully using the assigned RT-CGM may be switched to a different RT-CGM if more than one is in use in the study. Criteria to be used in deciding whether a switch is to be made will be provided in the site procedures manual.

4.1.2 Control Group

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

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

4.1.2.1 Use of Blinded RT-CGM by Control Group

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

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

4.2 Follow-up Visits and Phone Contacts

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

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

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)

4.2.1.1 Procedures at Follow-up Visits

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

- Assessment of compliance with RT-CGM and HGM use
- Skin assessment (RT-CGM Group)
- Review of glucose data and pump data (if available) and recommendations for changes in diabetes management
- Collection of data for cost-effectiveness analysis
- HbA1c determination using the DCA2000 or similar point of care device for management decisions (4 weeks, 8 weeks, 13 weeks, 19 weeks and 26 weeks)
- Collection of a blood sample to send to the central laboratory for HbA1c determination (13 weeks, 26 weeks)
- Completion of Algorithm Satisfaction Questionnaire (4 weeks and 13 weeks)
- Completion of questionnaires (26 weeks)
    - **Subjects <18 Years Old**
        - Blood Glucose Monitoring System Rating Questionnaire
        - Peds-QL (combined sections of generic / diabetes modules)
        - Hypoglycemia Fear Survey
        - CGM Satisfaction Scale (RT-CGM Group Only)
    - **Parents of Minor Subject**
        - Blood Glucose Monitoring System Rating Questionnaire
        - Peds-QL (combined sections of generic / diabetes modules)
        - Problem Areas in Diabetes (PAID - Parent version)
        - Hypoglycemia Fear Survey
        - CGM Satisfaction Scale (RT-CGM Group Only)
    - **Subjects >=18 Years Old**
        - Blood Glucose Monitoring System Rating Questionnaire
        - Problem Areas in Diabetes (PAID)
        - SF-12
        - Hypoglycemia Fear Survey
        - CGM Satisfaction Scale (RT-CGM Group Only)

4.2.2 Phone Contacts

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

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

794 • 22 weeks (±1 week)

CHAPTER 5
POST-RANDOMIZED TRIAL OBSERVATION PHASE

5.1 RT-CGM Group

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

- Subjects who have discontinued the use of the RT-CGM or are unwilling to continue using it will remain in follow-up though 12 months, without using RT-CGM.
- Subjects who are not successful using the assigned RT-CGM may be switched to a different RT-CGM if more than one is in use in the study.

5.2 Control Group

Subjects in the Control Group will be provided with a RT-CGM and sensors. The same RT-CGM system used during the blinded periods in the first 6 months will be used unless the investigator believes there is a reason to change.

- Subjects will be instructed on use of the RT-CGM and how to use the glucose and HGM data to adjust diabetes management.
- Subjects who discontinue the use of the RT-CGM or are unwilling to continue using it will remain in follow-up through 12 months, without using RT-CGM.
- Subjects who are not successful using the assigned RT-CGM may be switched to a different RT-CGM if more than one is in use in the study. Criteria to be used in deciding whether a switch is to be made will be provided in the site procedures manual.

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

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

5.3 Procedures at Follow-up Visits

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

- Assessment of compliance with RT-CGM and HGM use
- Skin assessment
- Review of glucose data and pump data (if available) and recommendations for changes in diabetes management
- Collection of data for cost-effectiveness evaluation
- HbA1c determination using the DCA2000 or similar point of care device for management decisions (13 weeks, 26 weeks)
- Collection of a blood sample to send to the central laboratory for HbA1c determination (13 weeks, 26 weeks)
- Completion of Algorithm Satisfaction Questionnaire (4 weeks for Control Group Only)
- Completion of questionnaires (26 weeks)
    - **Subjects <18 Years Old**
        - Blood Glucose Monitoring System Rating Questionnaire
        - Peds-QL (combined sections of generic / diabetes modules)
        - Hypoglycemia Fear Survey
        - CGM Satisfaction Scale

- **Parents of Minor Subject**
  - Blood Glucose Monitoring System Rating Questionnaire
  - Peds-QL (combined sections of generic / diabetes modules)
  - Problem Areas in Diabetes (PAID - Parent version)
  - Hypoglycemia Fear Survey
  - CGM Satisfaction Scale

- **Subjects ≥18 Years Old**
  - Blood Glucose Monitoring System Rating Questionnaire
  - Problem Areas in Diabetes (PAID)
  - SF-12
  - Hypoglycemia Fear Survey
  - CGM Satisfaction Scale

5.4 Optional Continuation of Study for Subjects Using the FreeStyle Navigator

At the 26-week visit, subjects using the FreeStyle Navigator will be given the opportunity to continue in the study until the device has FDA approval or until Abbott Diabetes Care can no longer provide supplies for the study. Subjects who continue in the study will sign an addendum to the consent form and will return to the clinic for a standard visit every 3 months.

CHAPTER 6
QUESTIONNAIRES

6.1 Introduction

All of the questionnaires are completed at baseline and 26 weeks during the randomized trial phase and at 26 weeks during the post-RCT observation phase, with the exception of the Algorithm Satisfaction Questionnaire which is completed at 4 weeks and 13 weeks during the RCT and at 4 weeks by the Control Group in the post-RCT observation phase and the Continuous Glucose Monitor Satisfaction Scale, which is completed during the RCT by the RT-CGM Group at 13 weeks and 26 weeks and during the post-RCT observation phase by both groups after 13 weeks and 26 weeks.

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

6.2 Blood Glucose Monitoring System Rating Questionnaire

The Blood Glucose Monitoring System Rating Questionnaire was designed for this study to assess subjects' rating of their current method of blood glucose monitoring. At baseline, all subjects will answer the questions as they relate to the home glucose meter being used prior to enrollment in the study. At 26 weeks and 52 weeks, the RT-CGM group will answer the questions as they relate to the RT-CGM. The Control Group will answer the questions related to the HGM at 26 weeks and to the RT-CGM at 52 weeks. A separate parent version of the questionnaire will be completed at each timepoint for subjects <18 years old. Administration time is approximately 10 minutes.

6.3 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL (Pediatric Quality of Life Inventory) is a modular instrument for measuring health-related quality of life (HRQOL) in children and adolescents ages 2-18. The PedsQL 4.0 Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL Disease-Specific Modules. The proposed version for this study will consist of 29 items. The appropriate version of this questionnaire will be completed by subjects <18 yrs of age and their parents at baseline and 26 weeks of the RCT and at 26 weeks of the post-RCT observational phase. Administration time is approximately 10 minutes.

6.4 Hypoglycemia Fear Survey

The original Hypoglycemia Fear Survey measured several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consisted of a 10-item Behavior subscale that measured behaviors involved in avoidance and over-treatment of hypoglycemia and a 13-item Worry subscale that measured anxiety and fear surrounding hypoglycemia. The instrument has since been revised to create a parent version and a child version of the original instrument. The Worry Scale for these latter two versions consists of 15 items, each with a 5-choice Likert response format. The appropriate version of this questionnaire will be completed by all subjects and the parents of subjects <18 yrs of age at baseline and 26 weeks of the RCT and at 26 weeks of the post-RCT observational phase. Administration time is approximately 10 minutes.

6.5 Problem Areas in Diabetes (PAID – Adult Subject Version)

The Problem Areas in Diabetes (PAID) is a measure of diabetes-specific emotional distress that was developed by the Joslin Diabetes Center, Boston. This self-administered questionnaire consists of 23 items that cover a range of emotional problems frequently reported in type 1 and type 2 diabetes. Each item is scored 0 to 4 ("Not a problem" to "Serious Problem"). This questionnaire will be completed by subjects ≥18 yrs of age at baseline and 26 weeks of the RCT and at 26 weeks of the post-RCT observational phase. Administration time is approximately 10 minutes.

6.6 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 will be completed by parents of subjects <18 years of age at baseline and 26 weeks of the RCT and at 26 weeks of the post-RCT observational phase. It consists of 20 items and administration time is approximately 10 minutes.

6.7 SF-12

The SF-12 is a multipurpose short-form (SF) generic measure of health status. The 12 items in the SF-12 are a subset of those in the SF-36. SF-12 includes on or items from each of the eight health concepts. Therefore, the SF-12 measures eight concepts of health status: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and psychological well being). The first four health concepts indicate physical health status and the others indicate mental health status. This questionnaire will be completed by subjects $\geq$18 yrs of age baseline and 26 weeks of the RCT and at 26 weeks of the post-RCT observational phase. Administration time is approximately 5 minutes.

6.8 Continuous Glucose Monitor Satisfaction Scale

This 46-item questionnaire was designed for this study to measure the impact of using a RT-CGM 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 26-week follow-up visit during the RCT by the RT-CGM Group and by both groups at the 26-week follow-up visits in the post-RCT observational phase. The number of questions may be reduced prior to initiation of its use in the study. A version of this questionnaire will also be completed by the spouses of adult subjects in the RT-CGM group following the 26-week visit of the RCT and by spouses of adult subjects in both groups following the 26-week visit of the post-RCT observational phase. For spouses, the questionnaire will be completed on paper at home and mailed back to the clinical center. Administration time is approximately 10-20 minutes.

6.9 Algorithm Satisfaction Questionnaire

This questionnaire was developed to measure the frequency and convenience of use of study-developed algorithms and satisfaction with use of the algorithms developed for the protocol. A separate questionnaire will be completed by the RT-CGM Group and the Control Group at 4 weeks and 13 weeks. The Control Group will complete the RT-CGM Algorithm Satisfaction Questionnaire at 4 weeks in the post-RCT observational phase. Data from this 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 5 minutes.

CHAPTER 7
ADVERSE EVENTS

7.1 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.

7.2 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.

7.3 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.

7.4 Risks And Discomforts

7.4.1 Skin Reactions

There is a low risk for developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies.

During each follow-up visit, each site where a RT-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 observation 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.

7.4.2 Fingerstick Blood Glucose Measurements

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

7.4.3 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.

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

7.5 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 8
MISCELLANEOUS CONSIDERATIONS

8.1 Benefits

It is expected that RT-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.

8.2 Subject/Parent Reimbursement

The study will provide the RT-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 and if the device is approved by the FDA, the subject will also be able to keep the RT-CGM. Test strips for the HGM and sensors for the RT-CGM to be used after the study will be the subject's responsibility.

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

Some of the cost effectiveness data being collected at enrollment at follow-up visits must be conducted via telephone by trained personnel for the study. If the phone interview cannot be conducted during the office visit, the phone number where the subject can be reached may be provided to the trained personnel for the study. The interview will be conducted at a time that is convenient for the subject (and parent if the subject is a minor).

During the study, subjects with a home computer will be asked to download the RT-CGM and study HGM data to their home computer. The downloaded data may be provided to Abbott Diabetes Care, DexCom, Inc., Medtronic Minimed or LifeScan, Inc. (depending on which types of RT-CGM and HGM are used) 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.

CHAPTER 9
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.

9.1 Sample Size Estimation

9.1.1 Primary Cohort

In the Direcnet randomized trial of the Glucowatch, there were 174 subjects (ages 7-<18) whose baseline HbA1c was between 7.0 and 10.0 (mean 8.0). The standard deviation of the 6 month HbA1c values was 0.9 and the correlation between baseline and 6 month values was 0.58. Data from adults with diabetes indicate a standard deviation of similar magnitude.

Assuming a two-tailed test with type I error rate of 5% and adjustment for baseline HbA1c, a sample size of 94 (47 per group) would give 90% power to detect a mean difference of 0.5 in HbA1c. Increasing by approximately 15% to account for any dropouts or noncompliant subjects gives a sample size of 110.

Preplanned subgroup analyses will be done by age, so 110 subjects will be enrolled for each of the three strata (8 to <15 years old, 15 to <25 years old, and ≥25 years old) for a total of 330 subjects (165 in each randomization group).

9.1.2 Secondary Cohort

From a pilot study conducted by DirecNet using the Navigator, the mean ± SD percentage of sensor values ≤70 mg/dL was 3.5% ± 4.1%, with a correlation between baseline and Week 13 percentages of 0.66.

Assuming a two-tailed test with type I error rate of 5% and adjustment for the baseline percentage ≤70 mg/dL, a sample size of 102 (51 per group) would give 90% power to detect a mean difference of 2% (e.g., 5% vs. 3%) in the hypoglycemic range. Increasing by approximately 15% to account for any dropouts or noncompliant subjects gives a sample size of 120.

Analysis will be pooled across age groups so the total sample size will be a minimum of 120.

9.1.3 Interim Sample Size Re-estimation

Before recruitment ends and after approximately 75-100 subjects from the primary cohort (baseline HbA1c ≥7.0) have completed their 6 month visit, an interim analysis will be performed to re-evaluate the necessary sample size. To ensure that this interim analysis does not materially inflate the probability of a type I error, only the estimated variance will be used to re-calculate sample size. No estimate of the treatment effect itself will be used. The estimated variance of the treatment effect after adjustment for baseline HbA1c will be calculated pooling across age strata. If this variance is larger than originally anticipated, the sample size will be increased to up to 450 patients (150 per age stratum) in order to achieve the desired 90% power.

It is anticipated that by the time 75-100 patients complete the 6 month visit that most or all of the targeted 330 patients will have already been recruited. Results of this interim analysis will therefore not be used to reduce the sample size if the observed variance is smaller than originally expected.

9.2 Statistical Analysis

9.2.1 Primary Cohort

9.2.1.1 Randomized Trial

Analysis will follow the intent-to-treat principle with all subjects analyzed in the group to which they were randomized, regardless of actual sensor wear. The primary analysis will include all subjects in the primary cohort. Preplanned subgroup analyses will be performed separately for each of the age strata: 8 to <15 years old, 15 to <25 years old, and ≥25 years old.

- **HbA1c**

The primary outcome for this cohort is the HbA1c value at 26 weeks measured in the central laboratory. If the laboratory value is unavailable then the DCA2000 value at 26 weeks will be imputed. If neither measurement is available then the value will be imputed based on available previous lab and/or DCA2000 HbA1c measurements (baseline, 4, 8, 13 and/or 19 weeks) using Rubin's method.[17]

Mean ± SD values for the 26 week HbA1c value with 95% confidence intervals or percentiles appropriate to the distribution will be given for each randomization group. Randomization groups will be compared using an ANCOVA model adjusting for baseline HbA1c and factors used to stratify the randomization. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or non-parametric methods will be used instead. However, previous experience suggests that HbA1c values will follow an approximate normal distribution. A 95% confidence interval will also be given for the difference of the randomization groups based on the ANCOVA model.

Improvement of at least 0.5% from baseline to 26 weeks will be analyzed as a secondary (binary) outcome. Randomization groups will be compared using logistic regression adjusting for the same factors mentioned above in the ANCOVA model.

- **Glycemic Indices**

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

Percentages of sensor values in the target and hypoglycemic ranges will be calculated giving equal weight to each of the 24 hours of the day for each subject. Comparisons of the two randomization groups will be performed using analogous ANCOVA models as described above for HbA1c. Residual values will be examined for an approximate normal distribution. If values are highly skewed, then a transformation or non-parametric methods will be used instead.

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

- **Hypoglycemia**

Clinical hypoglycemic events will be tabulated in each treatment group, which will be compared using Fisher's exact test. For purposes of analysis, a hypoglycemic event will be defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the

restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

- **Questionnaires**

Mean ± SD values or percentiles appropriate to the distribution will be given by randomization group for the total score and each subscale for each questionnaire at 26 weeks. Results will be given separately for patient (for those old enough to fill out the questionnaire) and parent responses. For questionnaires administered to both randomization groups (i.e., excluding the CGM Satisfaction Scale comparisons will be made using similar ANCOVA models as described above for HbA1c. No formal adjustment will be made for multiple comparisons.

- **Skin Assessments**

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

- **Adverse Events**

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

9.2.1.2 Post-RCT Observation Phase

Mean ± SD (or percentiles appropriate to the distribution) HbA1c values will be given by randomization group at baseline, 13 and 26 weeks of phase 2. The paired t-test will be used to compare the original control group at baseline vs. 26 weeks of phase 2. A similar t-test will be used to compare the group originally randomized to the sensor at 26 weeks of phase 2 vs. baseline of phase 1 and vs. baseline of phase 2 to see if any benefit was sustained through 1 year. Similar analyses will be performed for the percentage of sensor values in the target and hypoglycemia ranges and questionnaires. The number of hours of sensor data obtained in the week prior to the 13 and 26 week visits of phase 2 will be tabulated. Any adverse events will be summarized as described above.

9.2.2 Secondary Cohort

Analyses in the secondary cohort (HbA1c <7.0% at baseline) will parallel those described for the primary cohort. The percentage of sensor values ≤70 mg/dL at 26 weeks of phase 1 will be considered the primary outcome with HbA1c treated as a secondary outcome. Analysis will follow the intent-to-treat principle with all subjects analyzed in the group to which they were randomized, regardless of actual sensor wear.

9.3.3 Cost-effectiveness Analysis

The cost-effectiveness analysis will be detailed in a separate document and is summarized below.

The analyses will address the following objectives:

- To collect utilities for T1D-related health states for patients and their caregivers and to measure health care utilization and economic consequences attributable to RT-CGM.
- To evaluate the within-trial cost-effectiveness of RT-CGM compared with standard care.
- To evaluate the lifetime cost-effectiveness of RT-CGM utilizing a simulation model of the complications of diabetes.
- To compare the lifetime cost-effectiveness of RT-CGM with perfect self-selection with lifetime cost-effectiveness based on traditional cost-effectiveness analysis.

For all analyses, the effectiveness parameter will be expressed in terms of quality-adjusted life-years (QALYS). Cost accounting will vary according to the time-frame and perspective of the analysis. The within-trial health system perspective will include all the direct costs associated with the program and all direct and indirect medical costs accrued by the subjects during the course of the trial. On the other hand, the societal perspective for the within-trial analysis will also account for the time costs for parents of pediatric subjects and for the adult subjects enrolled in the study.

For the lifetime analysis, investigators will modify and utilize the original NIH model of T1D that was developed to analyze the long-term implications of the initial DCCT results. The model will be modified to incorporate recent changes in our understanding of the impact of glucose control on the development of complications.

Data to be collected from study subjects at baseline and during the study will include utilities for current health, utilities for complication health states, utilities for treatment-related experiences, medical care costs, household income, employment, and caregiver time.

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