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JDRF Randomized Clinical Trial to Assess the Efficacy of Real-Time Continuous Glucose Monitoring in the Management of Type 1 Diabetes: Research Design and Methods

JDRF CGM Study Group

Abstract

Background: While real-time (RT) continuous glucose monitoring (CGM) systems may revolutionize treatment of type 1 diabetes (T1D), there is insufficient evidence currently available to support widespread utilization of these devices. The Juvenile Diabetes Research Foundation (JDRF) CGM Study Group developed a randomized clinical trial to determine if RT-CGM can improve glycemic control and quality of life in children and adults with T1D. This paper presents the research design and methods that are being employed in this study.
Methods: The JDRF CGM Study Group trial is a randomized, parallel group, efficacy and safety study. Subjects with T1DM who meet eligibility criteria are randomized to either standard self-monitoring of blood glucose (SMBG) alone or use of any of the three current RT-CGM systems as a supplement to SMBG. After the 6-month randomized period, the Control Group is offered use of RT-CGM, and both groups are studied for an additional 6 months. Subjects are divided into two cohorts: the Main Study Cohort includes subjects with baseline glycosylated hemoglobin (HbA1c) 7.0–10.0% inclusive, and the Exploratory Pilot Study Cohort includes subjects with HbA1c <7.0%. Difference in HbA1c is the primary outcome in the Main Study. Other outcomes include the percentage of sensor glucose values within the 70–180 mg/dL range, scores on questionnaires that assess the impact of RT-CGM on living with T1D, and the cost-effectiveness of RT-CGM.
Results: Recruitment for the study was completed on December 15, 2007.
Conclusion: Results of this clinical trial should help establish whether or not current RT-CGM devices are beneficial to patients with T1D.

Introduction

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)[1–3] but at the cost of a threefold increase in the frequency of severe hypoglycemia and a twofold increase in the frequency of excessive weight gain. Despite increased use of insulin pumps and multiple injection regimens and the introduction of rapid- and long-acting insulin analogs, many individuals with T1D across all age groups fail to achieve target glycosylated hemoglobin (HbA1c) levels recommended by the DCCT more than 12 years ago. While self-monitoring of blood glucose (SMBG) plays an important role in achieving target HbA1c levels, most patients infrequently measure glucose levels immediately after meals and during the overnight period. Consequently, postprandial hyperglycemia and nocturnal hypoglycemia are commonly observed even in well-controlled individuals with T1D.[4–7] Even in individuals with T1D who measure glucose levels consistently before and after meals, rates of glucose change are elevated compared to those without diabetes and thus may render even vigilant individuals susceptible to unexpected glucose excursions.[8] In addition, the fear of hypoglycemia is a major obstacle to successful intensive insulin therapy.

The introduction of sensors for the continuous monitoring of interstitial glucose offered the potential to lower glycosylated hemoglobin (HbA1c) levels more safely (i.e., with less rather than more hypoglycemia). Nevertheless, the original devices were either used for short-term retrospective analysis (the Medtronic MiniMed [Northridge, CA] CGMS®) or

A listing of the JDRF CGM Study Group appears in Appendix A.

were too difficult and uncomfortable to use and not very accurate (the GlucoWatch® Biographer™ [Animas Corp., West Chester, PA]).[9] More recently, several new, real-time (RT) continuous glucose monitoring (CGM) systems have been introduced that have improved accuracy, functionality, and tolerance. However, sufficient evidence has not yet been accumulated to justify the widespread utilization of these devices, even for children with T1D who are so difficult to treat with standard methods of management. Clinical trials of RT-CGM technology are also critically important to demonstrate how this technology should be implemented and used.

In 2006, the Juvenile Diabetes Research Foundation (JDRF) issued a Request for Applications from leading adult and pediatric diabetes research centers in the United States to participate in a consortium to develop a randomized clinical trial to fill the gaps in knowledge related to the efficacy and effectiveness of the new RT-CGM systems. Ultimately, 10 clinical centers, a coordinating center, and a health economics follow-on team were selected, operating procedures for the JDRF CGM Study Group were established, a randomized clinical trial protocol was developed, and subjects began to be enrolled in the study in early 2007. In this paper, we present and discuss the research design and methods that are being employed in this large-scale, multicenter study.

Research Design and Methods

Study design

The JDRF CGM study is a randomized, parallel group, efficacy and safety study. As shown in Figure 1, subjects with T1D who meet eligibility criteria are randomized 1:1 to either standard SMBG alone or use of RT-CGM as a supplement to SMBG. At completion of the 6-month RCT, subjects in the RT-CGM group continue to use RT-CGM for another 6 months to examine the durability of any beneficial effects of RT-CGM that are seen in the first 6 months. In addition, subjects in the SMBG control group are offered use of RT-CGM for 6 months with less intensive contact than was provided at initiation of RT-CGM use in the RT-CGM group. This crossover extension period is being offered to the SMBG control group both as incentive to participate in the RCT and as a means to examine whether RT-CGM is effective, even in the face of less intense clinic follow-up. It should also be noted that the JDRF CGM study actually includes two, separate study cohorts who differ with respect to baseline HbA1c levels. The Main Study Cohort comprises patients with T1D who have a baseline HbA1c of 7.0–10.0% inclusive. The Exploratory Pilot Study Cohort includes subjects who meet the same eligibility criteria but have a baseline HbA1c of $<7.0\%$.

The separation into two cohorts and two separate studies according to baseline HbA1c level was done because the investigators concluded that there was no single widely accepted primary outcome that could be used across the full range of HbA1c values. A difference in HbA1c levels between the two study groups at end point is a meaningful primary outcome for individuals who enter the study with HbA1c $\geq 7.0\%$ that would be acceptable to the scientific, clinical, and insurance communities. On the other hand, change in HbA1c is not a satisfactory primary outcome for individuals with HbA1c $<7.0\%$ at baseline. In this group of patients, successful use of RT-CGM to reduce the frequency of hypoglycemic events may be associated with either no change or a small increase of HbA1c levels. Including such individuals in the Main Study (with HbA1c as the primary outcome) would have reduced that study's statistical power to lower HbA1c and give the mistaken appearance of lack of effectiveness.

Reduction in the frequency of severe hypoglycemia is perhaps a plausible and appealing primary outcome in subjects with HbA1c levels $<7.0\%$. Fortunately, the frequency of severe hypoglycemia, as defined by the DCCT, appears to be decreasing with the more widespread use of insulin pumps and insulin analogs.[6,10–16] Since the RCT is relatively short in duration, an impractically large sample size would be needed to evaluate whether RT-CGM use can reduce the incidence of severe hypoglycemic events in either cohort. 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 sensor glucose level is known. Therefore, subjects with baseline HbA1c $<7.0\%$ are enrolled in an Exploratory Pilot Study that is examining

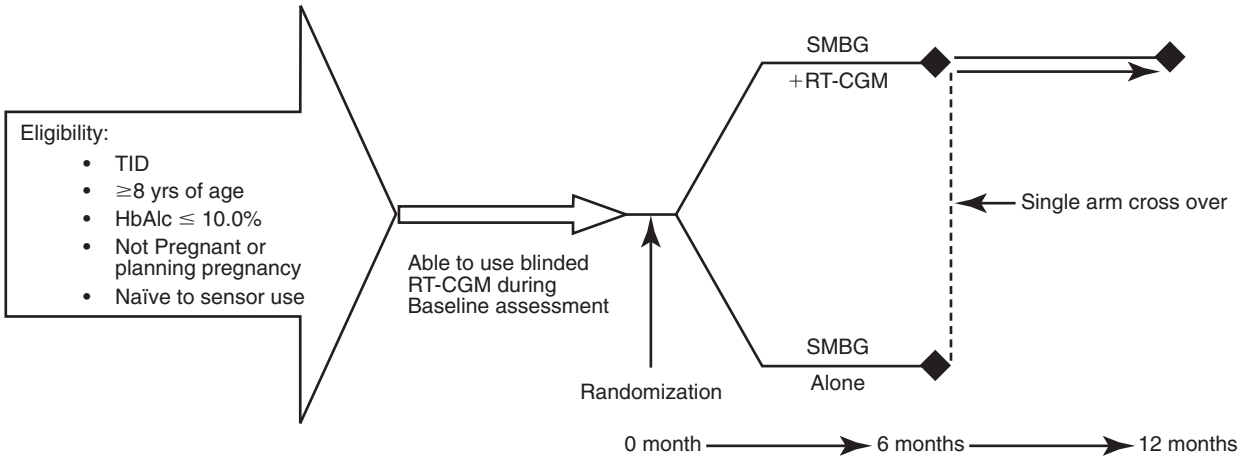

FIG. 1. Study design.

outcomes that would be appropriate to use to evaluate the value of RT-CGM in subjects with HbA1c already in the adult target range. Examples of beneficial outcomes in this study include an increase in the percentage of glucose values within the target range, a decrease in glucose levels in the hypoglycemic range, a reduction in glucose variability, and improvements in psychosocial well-being.

RT-CGM systems used in the trial

Since the objective of the study is to determine whether using RT-CGM technology is beneficial in the management of T1D and not whether a specific RT-CGM system is beneficial over another, subjects are allowed to choose among the Medtronic, DexCom (San Diego, CA), or Abbott Diabetes Care (Alameda, CA) RT-CGM systems on enrollment in the study. The Study Group elected to take this approach because the technology involved with the three RT-CGM systems and the accuracy of the devices are similar (Table 1). It was anticipated that allowing the subject to select one system over another, based on personal preferences, would enhance compliance with using the system and mimic clinical practice with use of such devices. Moreover, subjects can switch from one system to another if there is reason to believe that they would be more successful with a different system. This approach is very similar to the flexible approach to intensive insulin treatment that was utilized in the DCCT.[17]

Study populations

As shown in Figure 1, the general eligibility criteria for both the Main and Exploratory Study cohorts were similar. Subjects with HbA1c levels >10.0% were excluded because it was believed that such patients were at high risk for not using the sensor consistently and not complying with treatment algorithms. Other exclusion criteria included:

- Presence of a significant psychiatric or medical disorder that in the judgment of the investigator would adversely affect metabolic control of diabetes, wearing of the sensors, or completion of the protocol.
- Home use of one of the three RT-CGM systems in the past 6 months.
- Participation in another intervention study in the past 6 weeks.

Table 1. Features of the Three RT-CGM Devices That Are Being Used in the Trial

	Abbott Diabetes	*DexCom*	*Medtronic*
Range of glucose values	20–500 mg/dL	40–400 mg/dL	40–400 mg/dL
Frequency of glucose values	Every minute (saved every 10 min)	Every 5 min	Every 5 min
Lifespan of sensor	120 h	168 h	72 h
Warm-up period	10 h	2 h	2 h
Calibration frequency	4 times a day (at approximately 10 h, 12 h 24 h, and 72 h following sensor insertion)	2 times a day (every 12 h)	2 times a day (every 12 h)
HGM for calibration	FreeStyle (built-in)	One Touch® Ultra® (can enter manually)	BD Logic (connected via radiofrequency; can also enter manually)
Alarms	Hypo- and hyperglycemia (adjustable); predicted alarms based on rate of change	Hypo- and hyperglycemia (adjustable); no predicted alarms	Hypo- and hyperglycemia (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
Software	Provides modal day, trends, data list, and daily details	Provides trends graph	Provides integration of pump data with sensor data: daily details, trend graphs, modal day graphs and pre-/postprandial profiles by meal
Other features			Can be combined with a Medtronic pump in a single device
Food and Drug Administration status	Approved for ≥18-year-olds as adjunct to HGM	Approved for ≥18-year-olds as adjunct to HGM	Approved for ≥7-year-olds as adjunct to HGM

HGM, home glucose monitor.

- Another member of the same household is participating in this study.
- For females, pregnant or intending to become pregnant during the next year.

Although it was reasonable to believe that continuous subcutaneous insulin infusion (CSII) pump patients might more readily adapt to wearing a sensor than patients receiving multiple daily injection (MDI) therapy, the JDRF Study Group thought that it was important to include both CSII- and MDI-treated subjects in the study to increase the generalizability of the study results. Subjects in the Main Study Cohort ($n = \sim 330$) and the Exploratory Study Cohort ($n = \sim 120$) are divided approximately equally across each of the following three age groups: 8 to <15 years old, 15 to <25 years old, and ≥25 years old.

Outcome measures

HbA1c. The primary outcome of the Main Study is between group differences in HbA1c levels, measured at the DCCT/Epidemiology of Diabetes Interventions and Complications Study HbA1c Central Laboratory at the University of Minnesota (Minneapolis).[18] HbA1c levels are also measured locally using the DCA2000 (Bayer Diagnostics, Tarrytown, NY) or comparable point-of-care device to assess eligibility.

CGM profiles. All subjects wear and use a blinded RT-CGM system of their choice for 1 week prior to randomization. To qualify for randomization, subjects must have used the RT-CGM system for at least 6 out of the 7 days, have a total of at least 96 h of RT-CGM glucose values with at least 24 h between the hours of 10 p.m. and 6 a.m., and have performed at least three meter glucose tests each day. SMBG control group subjects in both cohorts are blinded to baseline, and subsequent blinded CGM profiles that are obtained at 3 and 6 months post-randomization. These data will be compared with unblinded sensor data obtained in the RT-CGM group at the same time points of study. Outcomes of interest include indices of glucose variability such as the mean amplitude of glycemic excursions[19] and SD scores.

Hypoglycemia. Data regarding hypoglycemia, including the circumstances surrounding severe hypoglycemic events, are obtained during each patient contact. A severe hypoglycemic event is defined as one that requires the assistance of another person to treat. Whether such severe events caused seizures or coma is also ascertained.

Questionnaires to assess the impact of RT-CGM on living with T1D. Several questionnaires were administered to assess the impact of RT-CGM on living with T1D:

- Pediatric Quality of Life Inventory (PedsQL)[20]
- Hypoglycemia Fear Survey[21]
- Problem Areas in Diabetes (PAID—Adult Subject Version)[22]
- Problem Areas in Diabetes (PAID—Parent Version)[23]
- SF-12 measure of health status[24]
- The Continuous Glucose Monitor Satisfaction Scale[25]
- Blood Glucose Monitoring System Rating Questionnaire. This questionnaire was developed for this study by the investigators to assess subjects' rating of their current method of blood glucose monitoring, be it meter or CGM device.

Questionnaires to assess the cost-effectiveness of RT-CGM. Several questionnaires were administered to assess the cost-effectiveness of RT-CGM:

- Health Utilities Index Mark 3 (HUI3)[26]
- Time-tradeoff experience utility questionnaire[27]
- Complication Utilities[28]
- Treatment Utilities[28]
- Willingness to Pay Questionnaire[29]
- Caregiving Time
- Health Services Utilization Questionnaire
- Health Insurance Coverage Questionnaire

Diabetes management

Since the trial is designed as an efficacy study, subjects in both treatment groups are seen in clinic for follow-up visits and contacted between clinic visits by telephone frequently during the randomized phase of the study (Tables 2 and 3). For subjects randomized to the RT-CGM group, the RT-CGM, SMBG, and pump data (if subject uses an insulin pump) are reviewed, and changes are made to diabetes management as needed during each scheduled contact. Subjects and parents are taught to use protocol-developed algorithms to make changes in diabetes management in RT based on RT-CGM and SMBG data. The treatment algorithms for use of RT-CGM data are very similar to those previously employed by several of the pediatric centers participating in this trial in a recent Diabetes Research in Children Network (DirecNet) pilot study of the FreeStyle Navigator® system (Abbott Diabetes Care).[30] Examples of the algorithms that are being employed in both treatment groups can be reviewed in Appendix B.

For subjects randomized to the SMBG control group, glucose meter and pump data (if the subject uses an insulin pump) are reviewed, and changes are made in diabetes management as needed. The blinded RT-CGM data are downloaded but are not reviewed by study personnel until the end of the first 6 months of the study. Subjects and parents are taught to use the protocol-developed algorithms for how to make changes to diabetes management based on SMBG data. SMBG data from both groups are downloaded and transmitted to the Data Coordinating Center for future analyses. The downloaded SMBG and corresponding sensor data will also be used to assess the accuracy of the sensors, as previously described.[31]

Sample size estimation for Main Study Cohort

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 the sample size 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,

Table 2. Schedule of Study Visits, Phone Contacts, and Outcome Assessments in Randomized Trial Phase

	Randomized trial phase													
	Enrollment	*0*	*3 days*	*1 week*	*2 weeks*	*4 weeks*	*6 weeks*	*8 weeks*	*10 weeks*	*13 weeks*	*16 weeks*	*19 weeks*	*22 weeks*	*26 weeks*
Visit (V) or phone (P) contact	V	V	P	V	P	V	P	V	P	V	P	V	P	V
Blinded RT-CGM[a]	X									X[a]				X[a]
Pre-randomization compliance assessment		X												
HbA1c														
DCA2000	X	X				X		X		X		X		X
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 years and parent)	X													X
Hypoglycemia Fear Survey	X													X
PAID Survey (subjects ≥18 years and parents of subjects <18 years)	X													X
SF-12 (subjects ≥ 18 years)	X													X
CGM Satisfaction Scale[b]														X
Cost-effectiveness data	X			X		X		X		X		X		X

[a]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.
[b]RT-CGM Group only.

Table 3. Schedule of Study Visits, Phone Contacts, and Outcome Assessments in Post-Randomized Control Trial Observation Phase (Following 6-Month Follow-Up Visit)

	Control group				*Both groups*	
	3 days	*1 week*	*2 weeks*	*4 weeks*	*13 weeks*	*26 weeks*
Visit (V) or phone (P) contact	P	V	P	V	V	V
HbA1c						
DCA2000				X	X	X
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 years and parent)						X
Hypoglycemia Fear Survey						X
PAID Survey (subjects ≥18 years and parents of subjects <18 years)						X
SF-12 (subjects ≥ 18 years)						X
CGM Satisfaction Scale						X
Algorithm Satifaction Questionnaire[a]				X		X
Cost-effectiveness data		X		X	X	X

[a]Control Group only.

15 to <25 years old, and ≥25 years old) for a total of 330 subjects (165 in each randomization group).

Statistical analysis

Main Study Cohort, Randomized Trial. The primary 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 Main Study 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. The primary outcome for this cohort is the HbA1c value at 26 weeks. 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 analysis of covariance (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.

Cost-effectiveness analysis. The main study analysis will be accompanied by a within-trial and lifetime cost-effectiveness analysis of RT-CGM compared with standard care. For both analyses, the effectiveness parameter will be expressed in terms of quality-adjusted life-years. 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 National Institutes of Health model of T1D that was developed to analyze the long-term implications of the initial DCCT results. 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 utilization and costs, household income, employment, and caregiver time.

Exploratory Pilot Study 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.

Timeline

Recruitment for the study began in January 2007, and enrollment in both cohorts was completed on December 15, 2007. Consequently, analyses of the randomized control trial data should begin in June or July 2008.

Appendix A

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Appendix B

Dose adjustment guidelines—retrospective log review (Control Group): pump therapy

You have been given this set of insulin dosage adjustment guidelines because you use insulin pump therapy. Pump therapy consists of two components: "basal" insulin and "bolus" insulin. The basal insulin is supposed to cover your body's needs in between meals and overnight, and the bolus insulin is supposed to cover your meals; it is also used to correct for high blood sugars.

To use these dose adjustment guidelines, you will need to check your blood sugar levels in the morning, before each meal, and before bedtime.

Your target glucose values are:

- Pre-meal: 70–130 mg/dL
- Peak post-meal: <180 mg/dL
- Bedtime/overnight: 100–150 mg/dL

For the meal bolus you will use your current insulin-to-carbohydrate (I/C) ratio.

For the correction dose you will correct to these target blood glucose levels:

Day: _____ mg/dL (1 unit per_____ over _____mg/dL)
Night: _____ mg/dL (1 unit per ____ over _____ mg/dL)

- Use your I/C ratio for every meal and a correction factor to "correct" for the high and bring it down into range.
- If you don't use I/C ratios or correction factors, then you will need to instead increase or decrease the bolus (short-acting) insulin doses by small steps (1–2 units).

Example:

- Your I/C ratio = 1 unit for 10 g of carbohydrate.
- Your target blood glucose = 100 mg/dL.
- Your high glucose correction is 1 unit per 50 mg/dL over your target.
- Your current blood glucose is 200 mg/dL, and you are about to eat 60 g of carbohydrate.

Calculate: 6 units of insulin (for the 60 g of carbohydrate) + 2 units (to lower blood glucose by 100) = 8 units.

- You can also use a correction for high blood sugar at other times besides meals if your blood sugar is high (in the example above, take 2 units of short-acting insulin for the high blood sugar). However, you should be careful that you wait at least 2–3 h before taking more insulin.

Using the logs to adjust your doses: for subjects on pump therapy

If you have access to a home computer, the study staff can give you software to download your home glucose meter and look at the data on your computer. You can use this to make adjustments to your insulin:

- Download your meter.
- In your software program, examine the report that shows the blood sugar information grouped according to meal or time of day (before breakfast, after breakfast, before lunch, after lunch, before dinner, after dinner, before bed, and overnight).
- Look for patterns that occur 2 out of 3 days. If there are no patterns, don't make any changes.

If you don't have a computer to download your meter, you can still use your blood sugar logs to make changes. Collect at least 3 days' worth of blood sugar records from your log:

- Draw a CIRCLE around all the glucose levels OVER your target.
- Draw a BOX around all the glucose levels UNDER your target.
- Look down the columns (corresponding to meals or times of the day) and look for consistent patterns over 2–3 days.
- If there are no patterns, don't make any changes.

Glucose pattern (2–3 days)	*Suggested changes*
Blood glucose in morning	High • Look at your bedtime blood glucose, and if that is out of range work on correcting that before trying to change the overnight insulin. • Increase the basal insulin rate by 0.05–0.1 units/h starting 3 h before your morning sugar check. • Check blood glucose at 3:00 am. If high at that time, increase the basal rate by 0.05–0.1 units/h from midnight to 2 a.m. • Consider eating fewer carbs in your bedtime snack or increase I/C ratio (example: if 1:15, change to 1:12 or 1:10)
	Low • Look at your bedtime blood glucose, and if that is out of range work on correcting that before trying to change the overnight insulin. • Decrease basal insulin rate by 0.05–0.1 units/h starting 3 h before your morning sugar check. • Check blood glucose at 3:00 a.m. If low at that time, decrease the basal rate by 0.05–0.1 units/h from midnight to 2 a.m. • Consider eating more carbs in your bedtime snack or decrease I/C ratio (example: if 1:15, change to 1:17 or 1:20). • Consider adding protein or fat to your bedtime snack.
Blood glucose pre-lunch	High • Breakfast I/C ratio: increase ratio by 2–5 (example: if 1:15, change to 1:12 or 1:10). • Cut out or decrease midmorning snack. • Increase basal rate by 0.05–0.1 units/h from 8 to 10 a.m.
	Low • Breakfast I/C ratio: decrease ratio by 2–5 (example: if 1:15, change to 1:17 or 1:20). • Consider adding or increasing a morning snack. • Decrease basal rate by 0.05–0.1 units/h from 8 to 10 a.m.
Blood glucose pre-dinner	High • Lunch I/C ratio: increase ratio by 2–5 (example: if 1:15, change to 1:12 or 1:10). • Consider cutting down or reducing the afternoon snack. • Increase the basal rate by 0.05–0.1 units/h between lunch and 3 p.m.

Glucose pattern (2–3 days)	*Suggested changes*
	Low • Lunch I/C ratio: decrease ratio by 2–5 (example: if 1:15, change to 1:17 or 1:20). • Consider adding or increasing the afternoon snack. • Decrease the basal rate by 0.05–0.1 units/h between lunch and 3 p.m.
Bedtime	High • Dinner I/C ratio: increase ratio by 2–5 (example: if 1:15, change to 1:12 or 1:10). • Increase the basal rate by 0.05–0.1 units/h between dinner and 8 p.m.
	Low • Dinner I/C ratio: decrease ratio by 2–5 (example: if 1:15, change to 1:17 or 1:20). • Decrease the basal rate by 0.05–0.1 units/h between dinner and 8 p.m.

Insulin dose adjustment guidelines—Minimed Paradigm® REAL-Time sensor use for subjects on pump therapy

In addition to using the blood sugar logs to adjust your insulin doses every week, you should also use your continuous glucose sensor and home glucose meter to make changes to your insulin doses in "real time," that is, whenever you are about to take a pre-meal dose of insulin, or whenever the sensor is alerting you for a high or low blood sugar.

Your target glucose values are:

- Pre-meal: 70–130 mg/dL
- Peak post-meal: <180 mg/dL
- Bedtime/overnight: 100–150 mg/dL

For the meal bolus use your current I/C ratio.

For the correction dose you will correct to these target blood glucose levels:

Day: _____ mg/dL (1 unit per_____ over _____mg/dL)
Night: _____ mg/dL (1 unit per ____ over _____ mg/dL)

For the meal bolus calculation:

- Look at the RT-CGM and home glucose meter to determine what your blood glucose level is.
- If your blood sugar is 70 mg/dL or lower: take 15 g of simple carbohydrate, and once your glucose is above 70 mg/dL, then begin to eat your meal, and take your usual insulin bolus to cover all of the carbohydrates in the meal.
- If your blood sugar is above 70 mg/dL: do your usual calculation of the amount of rapid-acting insulin needed to cover the carbohydrates in the meal and the correction for high blood sugar.
- Now look at the receiver screen on your RT-CGM. See if there are any up or down arrows adjacent to your glucose reading. Make the following adjustment to the amount of rapid acting insulin that you just calculated for your meal:

Glucose rising >40 mg/dL, (↑↑) two up arrows	Increase meal dose by 20%
Glucose rising 20–40 mg/dL, (↑) up arrow	Increase meal dose by 10%
Glucose rising or falling by <20 mg/dL, no arrows	No change in meal dose of rapid-acting insulin
Glucose falling 20–40 mg/dL, (↓) down arrow	Decrease meal dose by 10%
Glucose falling by >40 mg/dL, (↓↓) down arrows	Decrease meal dose by 20%

Example for meal:

- Your I/C ratio = 1 unit for 10 g of carbohydrate.
- Your target blood glucose = 100 mg/dL.
- Your high glucose correction is 1 unit per 50 mg/dL over your target.
- Your current blood glucose is 200 mg/dL, and you are about to eat 60 g of carbohydrate.
- Your sensor indicates (↑ ↑) two up arrows.

Calculate: 6 units of insulin (for the 60 g of carbohydrate) + 2 units insulin (for the high glucose correction of 1 unit for each 50 mg/dL over target) + 1.6 units trend arrow correction (20% of 8 units = 1.6) for a total of 9.6 units. Infuse 9.6 units.

The following is for correction bolus calculation at times other than meals:

- Do your usual calculation of the amount of rapid-acting insulin needed to correct for the high blood sugar.
- Look at the RT-CGM arrow and make the following adjustments to the amount of rapid-acting insulin that you just calculated to cover the high blood glucose:

Glucose rising >40 mg/dL, (↑↑) two up arrows	**Increase dose by 20%**
Glucose rising 20–40 mg/dL, (↑) up arrow	Increase dose by 10%
Glucose rising or falling by < 20 mg/dL, no arrows	No change in dose of rapid-acting insulin
Glucose falling 20–40 mg/dL, (↓) down arrow	Decrease dose by 10%
Glucose falling by >40 mg/dL, (↓↓) down arrows	Decrease dose by 20%

Example for time other than meal:

- Using the example above (without the meal), you would correct for a high blood sugar of 200 mg/dL with (↑) one up arrow.

Calculate: 2 units for the high glucose correction (1 unit for each 50 mg/dL over target) + 0.2 units trend arrow correction (10% of 2 units = 0.2) for a total of 2.2 units. Infuse 2.2 units.

If you are doing a correction for high blood sugar outside of a meal, you should wait at least 2–3 h before taking any more insulin.

When to check your blood sugar with the study home glucose meter:

1. Whenever the RT-CGM calls for a calibration to be entered.
2. When you are going to make an insulin management decision.
3. You have symptoms that are not consistent with the RT-CGM values (for example, you feel low, but the RT-CGM do not show that you are low).
4. Anytime a high or low alarm/event goes off (high or low event is considered first alarm in a 1-h period).

High alert_____ mg/dL	❑ Did you take your pre-meal insulin dose? **NO**—Take the amount of insulin that you should have, as shown above, using your pre-meal blood sugar. **YES—Wait at least 2 h after the last dose before taking a correction dose,** since there may be a lot of insulin left over from your last injection. ❑ Make sure you correct to the targets shown at the beginning of these instructions(_____ during the day and _____ during the night)
Low alert_____ mg/dL	❑ Treat with 15 g of carbohydrate

Using the RT-CGM downloads and blood sugar logs to adjust your doses for subjects on pump therapy

If you have access to a home computer, the study staff can give you software to download your RT-CGM and look at the data on your computer. You can use this to make adjustments to your insulin in a different way from examining blood glucose logs:

- Download your RT-CGM.
- In your software program, examine the report that shows several days of sensor tracings all overlapping on top of each other. It may be called "glucose modal day," "sensor daily overlay," or "modal day." Choose 3 days to examine at one time.
- Look for patterns that occur 2 out of 3 days. If there are no patterns, don't make any changes.

If you don't have a computer to download your CGM, you can still use your blood sugar logs to make changes. Collect 3–4 days' worth of blood sugar records from your log.

- Draw a CIRCLE around all the glucose levels OVER your target.
- Draw a BOX around all the glucose levels UNDER your target.
- Look down the columns (corresponding to meals or times of the day) and look for consistent patterns over 2–3 days.
- If there are no patterns, don't make any changes.

Glucose pattern (2–3 days)	*Suggested changes*
Blood glucose in morning	High • Look at your bedtime blood glucose, and if that is out of range work on correcting that before trying to change the overnight insulin. • Increase the basal insulin rate by 0.05–0.1 units/h starting 3 h before your morning sugar check • Check blood glucose at 3:00 a.m. If high at that time, increase the basal rate by 0.05–0.1 units/h from midnight to 2 a.m. • Consider eating fewer carbs in your bedtime snack or increase bedtime snack I/C ratio (example: if 1:15, change to 1:12 or 1:10) Low • Look at your bedtime blood glucose, and if that is out of range work on correcting that before trying to change the overnight insulin. • Decrease basal insulin rate by 0.05–0.1 units/h starting 3 h before your morning sugar check. • Check blood glucose at 3:00 a.m. If low at that time, decrease the basal rate by 0.05–0.1 units/h from midnight to 2 a.m. • Consider eating more carbs in your bedtime snack or decrease bedtime snack I/C ratio (example: if 1:15, change to 1:17 or 1:20).

Glucose pattern (2–3 days)	*Suggested changes*
	• Consider adding protein or fat to your bedtime snack.
BG pre-lunch	High • Breakfast I/C ratio: increase ratio by 2–5 (example: if 1:15, change to 1:12 or 1:10). • Cut out or decrease mid-morning snack. • Increase basal rate by 0.05–0.1 units/h from 8 to 10 a.m. Low • Breakfast I/C ratio: decrease ratio by 2–5 (example: if 1:15, change to 1:17 or 1:20). • Consider adding or increasing a morning snack. • Decrease basal rate by 0.05–0.1 units/h from 8 to 10 a.m.
BG pre-dinner	High • Lunch I/C ratio: increase ratio by 2–5 (example: if 1:15, change to 1:12 or 1:10). • Consider cutting down or reducing the afternoon snack. • Increase the basal rate by 0.05–0.1 units/h between lunch and 3 p.m. Low • Lunch I/C ratio: decrease ratio by 2–5 (example: if 1:15, change to 1:17 or 1:20). • Consider adding or increasing the afternoon snack. • Decrease the basal rate by 0.05–0.1 units/h between lunch and 3 p.m.
Bedtime	High • Dinner I/C ratio: increase ratio by 2–5 (example: if 1:15, change to 1:12 or 1:10). • Increase the basal rate by 0.05–0.1 units/h between dinner and 8 p.m. Low • Dinner I/C ratio: decrease ratio by 2–5 (example: if 1:15, change to 1:17 or 1:20). • Decrease the basal rate by 0.05–0.1 units/h between dinner and 8 p.m.

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References

1. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329: 977–986.
2. The Diabetes Control and Complications Trial Research Group: Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. J Pediatr 1994;125:177–188.
3. The Diabetes Control and Complications Trial Research Group: Adverse events and their association with treatment regimens in the diabetes control and complications trial. Diabetes Care 1995;18:1415–1427.
4. Bergada I, Suissa S, Dufresne J, Schiffrin A: Severe hypoglycemia in IDDM children. Diabetes Care 1989;12:239–244.
5. Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV: Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes Care 2001;24:1858–1862.
6. Davis E, Keating B, Byrne G, Russell M, Jones T: Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. Diabetes Care 1997;20:22–25.
7. The DCCT Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 1991;90:450–459.
8. Kovatchev BP: Is glycemic variability important to assessing antidiabetes therapies? Curr Diabetes Rep 2006;6: 350–356.
9. Diabetes Research in Children Network (DirecNet) Study Group: A randomized multicenter trial comparing the GlucoWatch Biographer with standard glucose monitoring in children with type 1 diabetes. Diabetes Care 2005;28: 1101–1106.

10. Bulsara MK, Davis EA, Holman CDJ, Jones TW: The impact of a decade of changing treatment on rates of severe hypoglycemia in a population-based cohort of children with type 1 diabetes. Diabetes Care 2004;27:2293–2298.
11. Craig ME, Handelsman P, Donaghue KC, Chan A, Blades B, Laina R, Bradford D, Middlehurst A, Ambler G, Verge CF, Crock P, Moore P, Silink M; NSW/ACT HbA1c Study Group: Predictors of glycaemic control and hypoglycaemia in children and adolescents with type 1 diabetes from NSW and the ACT. Med J Aust 2002;177:235–238.
12. Davis EA, Keating B, Byrne GC, Russell M, Jones TW: Impact of improved glycaemic control on rates of hypoglycaemia in insulin dependent diabetes mellitus. Arch Dis Child 1998;78:111–115.
13. Rewers A, Chase HP, Mackenzie T, Walravens P, Roback M, Rewers M, Hamman RF, Klingensmith G: Predictors of acute complications in children with type 1 diabetes. JAMA 2002;287:2511–2518.
14. Rosilio M, Cotton JB, Wieliczko MC, Gendrault B, Carel JC, Couvaras O, Ser N, Bougnères PF, Gillet P, Soskin S, Garandeau P, Stuckens C, Le luyer B, Jos J, Bony-Trifunovic H, Bertrand AM, Leturcq F, Lafuma A: Factors associated with glycemic control: a cross-sectional nationwide study in 2,579 French children with type 1 diabetes. Diabetes Care 1998;21:1146–1153.
15. Wagner VM, Grabert M, Holl RW: Severe hypoglycaemia, metabolic control and diabetes management in children with type 1 diabetes in the decade after the Diabetes Control and Complications Trial—a large-scale multicentre study. Eur J Pediatr 2005;164:73–79.
16. Weinzimer SA, Ahern JH, Doyle EA, Vincent MR, Dziura J, Steffen AT, Tamborlane WV: Persistence of benefits of continuous subcutaneous insulin infusion in very young children with type 1 diabetes: a follow-up report. Pediatrics 2004;114:1601–1605.
17. The Diabetes Control and Complications Trial Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes 1997;46:271–286.
18. Diabetes Research in Children Network (DirecNet) Study Group: Comparison of fingerstick hemoglobin A1c levels assayed by DCA 2000 with the DCCT/EDIC central laboratory assay: results of a Diabetes Research in Children Network (DirecNet) Study. Pediatr Diabetes 2005;6:13–16.
19. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF: Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970;19:644–655.
20. Varni JW, Burwinkle TM, Jacobs JR, Gottschalk M, Kaufman F, Jones KL: The PedsQL™ in Type 1 and Type 2 diabetes: reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales and Type 1 Diabetes Module. Diabetes Care 2003;26:631–637.
21. Green LB, Wysocki T, Reineck BM: Fear of hypoglycemia in children and adolescents with diabetes. J Pediatr Psychol 1990;15:633–641.
22. Polonsky WH, Anderson BJ, Lohrer PA, Welch G, Jacobson AM, Aponte JE, Schwartz CE: Assessment of diabetes-related distress. Diabetes Care 1995;18:754–760.
23. Antisdel JE: Diabetes-specific distress among parents of youth with type 1 diabetes [abstract 6123]. Dissertation Abstracts Int 2001;61:1–2.
24. Ware JE, Kosinski M, Keller SD: A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–233.
25. Diabetes Research in Children Network (DirecNet) Study Group: Youth and parent satisfaction with clinical use of the Glucowatch G2 Biographer in the management of pediatric type 1 diabetes. Diabetes Care 2005;28:1929–1935.
26. Horsman J, Furlong W, Feeny D, Torrance G: The Health Utilities Index (HUI®): concepts, measurement properties and applications. Health Qual Life Outcomes 2003;1:54.
27. Neumann P, Goldie S, Weinstein M: Preference-based measures in economic evaluation in health care. Annu Rev Public Health 2000;21:587–611.
28. Huang E, Brown S, Ewigman B, Foley E, Meltzer D: Patient perceptions of quality of life with diabetes-related complications and treatments. Diabetes Care 2007;30:2478–2483.
29. Bala M, Mauskopf J, Wood L: Willingness to pay as a measure of health benefits. Pharmoeconomics 1999;1:9–18.
30. Diabetes Research in Children Network (DirecNet) Study Group: Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the Freestyle Navigator). Pediatr Diabetes 2008;9:142–147.
31. The DirecNet Study Group: The accuracy of the Freestyle Navigator continuous glucose sensor in the inpatient and outpatient setting in children with type 1 diabetes. Diabetes Care 2007;30:59–64.

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