A Randomized Clinical Trial to Assess the Effectiveness of the GlucoWatch Biographer in the Management of Type 1 Diabetes in Children

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CHAPTER 1
INTRODUCTION

1.1 Introduction and Rationale

Resistance to frequent blood glucose monitoring is a major impediment to attaining "good" (lower HbA1c level) glucose control. The Diabetes Control and Complications Trial (DCCT) convincingly proved that glucose control "closer-to-normal" range ("tight" glycemic control) reduced the likelihood of the eye, kidney, and nerve complications of diabetes. Increasing the frequency of glucose monitoring was an important aspect of attaining improved glucose control in the DCCT. As a result of the DCCT, many physicians have attempted to keep children and adults in very "tight" glucose control. Unfortunately, the DCCT study also showed that the incidence of severe hypoglycemia was three times higher in the intensively treated group compared with the standard treatment group. The tools to safely implement tight glycemic control were not available to the DCCT. The GlucoWatch® G2™ Biographer (GWB) by Cygnus Inc. and the Continuous Glucose Monitoring System (CGMS) by Medtronics Minimed, Inc. have both been developed to assist in closer monitoring of glucose levels.

The proper role of the GWB in the management of type 1 diabetes in children has not been determined. We are conducting a randomized clinical trial (RCT) to compare the effect on glycemic control, hypoglycemia, and quality of life of using a GWB versus standard care.

1.2 Background on the GlucoWatch Biographer

The GWB is the first non-invasive glucose-monitoring device. The Food and Drug Administration (FDA) has approved the GWB for use in adults and in children. Although the accuracy of the device has been demonstrated, [1-6] the FDA approval does not permit changes in insulin doses to be made based on the GWB values. Thus, a capillary blood glucose level must be done every time an alarm is given for a low or high blood sugar.

The GWB technology is based on reverse iontophoresis where interstitial glucose molecules are extracted from underneath the skin and electrochemically converted to a proportional glucose value. The device is worn on the arm, at least three inches away from the wrist or elbow joint. A replaceable unit called the Autosensor attaches to the skin for glucose extraction and detection. The AutoSensor consists of two hydrogel discs that contain the enzyme glucose oxidase. A single triple 'A' battery operates the device. Thus, the maximum current sent through the skin for glucose extraction is that of a triple 'A' battery. The process of extraction and detection takes 10 minutes. The GWB II model to be used in the study gives up to 6 readings per hour for 13 hours. The subjects can read glucose values displayed on the GWB II. It also has a high and low glucose alarm that can be set by the user for certain glucose levels of their choice (e.g., less than 60 mg/dl and/or more than 300 mg/dl). A two-hour warm-up time followed by a single finger stick value is needed to calibrate the device. The GWB II is the identical mechanical device as the GWB I, but the software has been changed to allow for a 2-hour instead of a 3-hour warm up, and readings are made every 10 minutes instead of every 20 minutes.

The use of the GWB has been demonstrated to be safe. Potential skin reactions are described in chapter 10.

Our study group conducted an inpatient study in which the GWB glucose values were compared with gold standard blood glucose values in children 1 to <18 years old who were wearing two GWBs over a 24-hour period. There were no serious skin reactions in the more than 100 subjects

who participated in the study. Based on the accrued data, the GWB is considered to be sufficiently accurate to assess its merits in the outpatient setting.

1.3 Literature on the Use of the GlucoWatch Biographer in Children

An initial accuracy study of the GWB1 was done on 66 subjects in two clinics.[5] Glucose levels were compared with the HemoCue® (Aktiebolaget Leo, Helsingborg, Sweden) Photometer using a blood glucose sample obtained by fingerstick. Thereafter, blood glucose was measured on samples obtained by fingerstick using the same photometer at hourly intervals for up to 12h. Blood samples were obtained 20±5 min before the biographer reading was calculated, to adjust for the 20-min lag time between the biographer readings and blood glucose.

There were 732 paired points from biographers worn on the forearm, 202 from those worn on the upper arm, 229 from those worn on the leg, and 150 from those worn on the torso. These paired points were used to analyze the accuracy of the device compared with blood glucose measurements.

The mean absolute relative difference (MARD) between forearm biographer readings and BG readings 20 min earlier was 21.0% and ranged from 21.2 to 21.8% for biographers worn at alternative sites. The percentage of points within 20 mg/dl or 30% of the comparative glucose values was 76% for forearm biographers and ranged from 72 to 75% for biographers worn at alternative sites. The mean absolute difference was <18 mg/dL at all of the regions where the biographer was worn, and the mean relative difference (MRD) ranged from 7.5% on the forearm to 4.3% on the torso. The slope, intercept, correlation coefficient, and root mean square difference (RMSD) were similar for all anatomic wear sites.

The region assignments made using the consensus grid and the Clarke grid were stratified by BG range (2.3-4.4, 4.5-6.7, 6.8-13.3 and 13.4-22.2 mmol). For the Clarke grid the low and high glucose ranges had fewer A + B points and more D points than the euglycemic glucose ranges. For the consensus grid, the results in each BG range were similar; 92.8-100% points fell in the A + B regions, and 0-7.2% in the C region. No points were assigned to the D or E regions of the consensus grid in any BG range.

Of the 1313 measurements made by the biographer, 97% were in the clinically acceptable A and B regions of the consensus grid. Only 3% of the readings differed enough from the reference method to fall in the C region. Points in this region of the consensus grid, if used to guide therapy, would indicate altered clinical action that would be likely to affect clinical outcome. No points fell in the D region, where therapeutic action could lead to significant medical risk, and none were assigned to the E region, where clinical action could lead to dangerous consequences.

Mild erythema was observed at the glucose extraction sites in two-thirds of the patients. Erythema was less frequent at the adhesive sites. Two strong erythema reactions were seen at adhesive sites (one forearm site and one leg site). Seventy-four percent of skin lesions resolved within 24h, and 93% of all lesions resolved within 48h. All but one lesion resolved by 1 wk. In no subject was the study terminated prematurely because of irritation at the biographer wear sites. One subject with a family history of atopic dermatitis experienced skin irritation at a biographer wear site on the leg that persisted for 10 wk after the study. Because of prolonged recovery, this was classified as an adverse event of mild severity. No other adverse events occurred.

A second study using the GWB1 in children was done by Chase et al.[7] This was a 3 month pilot trial in which 40 children, ages 7 through 17 years, were randomized to wear at least 4 GWB1 devices

per week (20 children) or to serve as controls (20 children). All 40 subjects were asked to do at least 4 capillary glucose levels/day as well as levels anytime the high (16.7 mmol/L) or low (<3.9 mmol/L) alarms sounded. They brought meters or transmitted glucose values (both groups) and GWB1 devices (test group) to the center weekly, and all 40 subjects were called weekly regarding dose adjustments.

The test subjects averaged 3.5 wears of the GWB1 per week over the 3-month period. HbA1c levels showed a significant ($p<0.05$) reduction in the test group but not in the control group. After the 3-month study period, the control subjects were also given GWB1 devices to wear. In the following 3 months the control group also showed a decline in HbA1c levels (9.0 vs. 8.4%), which remained lower after 6 months (in both groups). The GWB1 group detected significantly more hypoglycemia (capillary blood glucose <70 mg/dl), particularly during the night. There were no severe hypoglycemic events in either group.

1.4 Background on the CGMS

The CGMS was developed and is distributed by Medtronics Minimed, Inc.[8] This sensor uses a glucose oxidase based electrochemical sensor which generates 2 electrons for each glucose molecule oxidized. The current generated from measuring glucose is called the ISIG (Input SIGnal). The CGMS system is designed to measure blood glucose levels in a range of 40-400 mg/dl. The sensor is inserted subcutaneously and measures interstitial glucose. Lag times between changes in the serum glucose and changes in sensor output are generally between 4-9 minutes in animal studies.[9] In human studies the interstitial glucose levels generally lag behind the blood glucose by 3 to13 minutes.[10, 11] When functioning properly, the CGMS acquires glucose values every 10 seconds and these values are averaged in the monitor to provide a reading every 5 minutes (or 288 readings a day). Each sensor is designed to measure readings over 72 hours. The sensor can be inserted with equal success by patients and health care professionals, has been able to work in a broad age rage (from 2 weeks to 74 years old), and sex, race and duration of diabetes do not appear to influence sensor function.[12, 13] The sensor is well tolerated with the only side effect being mild to moderate site irritation in 2% of patients.[12]

The present version of the CGMS, which has been approved by the FDA, provides data in a retrospective analysis, much like a Holter monitor. The sensor does not display the glucose in "real time" and does not have alarms to warn of hypo or hyperglycemia. The sensor requires at least 3 capillary glucose readings each day to validate sensor function and allow for development of a calibration equation. These calibration measurements are performed with a home glucose meter, and calibration is dependent upon the subject entering glucose values correctly into the sensor. The sensor cannot be worn in the water and must be kept dry. The sensor is designed to provide glucose information for 72 hours.

1.5 Synopsis of the Protocol

Study Design/Sample Size: Randomized trial with approximately 200 subjects

Major Eligibility Criteria

- Age 7 to <18 years
- Duration of diabetes $\geq$1 year, using daily insulin therapy (pump or at least 2 injections/day)
- Diagnosis of type 1 diabetes by investigator judgment

- Subject on stable insulin regimen and not expected to make change in administration modality within the next 6 months (e.g., injection user switching to pump, pump user switching to injections, or the addition of Lantus (Glargine) insulin)
- HbA1c 7.0 to 11.0% inclusive

Major Outcome Measures

Timing of Primary Outcome Assessment: 6 months

- Change in HbA1c from baseline
- Change in frequency of hypoglycemia as measured with a weekly home questionnaire
- Change in biochemical hypoglycemia as measured with the CGMS after 3 mos and 6 mos
- Psychosocial questionnaires: Diabetes-related anxiety questionnaire, PedsQL Diabetes Module, sensor satisfaction scale (for GWB group)

Summary of Protocol

1. Informed consent is obtained from eligible subjects.
2. On the day of enrollment, psychosocial questionnaires are completed and a CGMS is inserted to establish a baseline for biochemical hypoglycemia. Instructions are given for completion of 8-point blood glucose testing on at least 2 days while the CGMS is worn and completion of the study home diary.
3. Following completion of the baseline CGMS use, the subject will return for a visit 4 to 14 days after enrollment. If CGMS use, HGM use, and 8-point testing have been successfully completed, a blood sample will be obtained for the baseline HbA1c.
   - Subjects who are noncompliant in using the CGMS or HGM will not be continued in the study.
   - Subjects who have been compliant will be randomized to either the GWB Group or the Usual Care Group.
   - For the GWB Group, GWB use will be initiated.
4. Each subject will be provided with a PC for downloading of GWB and HGM and to serve as a resource for diabetes self-management.
5. For the GWB Group, the GWB will be used a minimum of two times per week, with at least one day and one night of sensor wear.
6. For both groups, downloaded data will be submitted to the coordinating center once each week.
7. Phone contacts will be made with the subjects after 1, 2, and 4 weeks and then every 4 weeks to review their diabetes management.
8. A follow-up visit will be performed at 3 months.
   - HbA1c will be measured
9. A follow-up visit will be performed at 6 months.
   - HbA1c will be measured
   - Psychosocial questionnaires will be administered
10. A CGMS will be used at baseline, after 3 months, and after 6 months to assess hypoglycemia.
    - 8-point blood glucose testing will be performed on at least 2 days of each CGMS wear.
    - For the GWB group, the GWB will be initiated at each visit and the GWB will not be used again by the patient for the duration of the CGMS use period or on days of 8-point testing.

- An attempt will be made to obtain at least 72 hours of sensor glucose measurements during each use period.

CHAPTER 2
SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Study Population

Approximately 200 subjects will be enrolled in this study at five clinical centers with approximately 40 enrolled at each center.

Enrollment will include approximately 100 subjects in each of the age groups of 7.0 to <12.0 years old and 12.0 to <18.0 years old.

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

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

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

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

1) Clinical diagnosis of type 1 diabetes and using insulin therapy (either a pump or at least 2 injections per day) 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 7.0 years to less than 18.0 years at the time of randomization
3) HbA1c in the range of 7.0 to 11.0% inclusive
   The DCA2000 will be used to assess eligibility. For enrolled subjects, a blood sample will be sent to the central lab for measurement of a baseline HbA1c. Subjects will remain in the trial even if the central lab baseline HbA1c is out of range.
4) Insulin regimen stable for the last two months and 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)
5) Parent/guardian and subject understand the study protocol and agree to comply with it, including the performance of at least 4 fingerstick glucose checks a day with a home glucose monitor
6) Subjects ≥11.0 years old and primary care giver (i.e., parent or guardian) both comprehend written English
   This requirement is due to the fact that the questionnaires to be used as outcome measures do not have validated versions in Spanish or other languages.
7) For females, subject not intending to become pregnant during the next 6 months
8) No expectation that subject will be moving out of the area of the clinical center during the next 6 months
9) Informed Consent Form signed by the parent/guardian and Child Assent Form signed by the subject

2.2.2 Exclusion

Subjects who meet any of the following criteria are <u>not</u> eligible for the study:

1) The presence of skin abnormalities or a significant medical disorder that in the judgment of the investigator will affect the wearing of the sensors or the completion of any aspect of the protocol

2) Prior use of a GWB prescribed for home use (*Prior use of a GWB as part of a research study is allowable)*

3) The presence of any of the following diseases:
   - Asthma if treated with systemic or inhaled corticosteroids in the last 6 months
   - Cystic fibrosis
   - Other major illness that in the judgment of the investigator might interfere with the completion of the protocol
     - *Adequately treated thyroid disease and celiac disease do not exclude*

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

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

2.3 Assessment of Eligibility

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 as part of a usual-care examination.

2.3.1 Historical Information

A history will be elicited from the subject and parent and extracted from available medical records. Data to be collected will include: age, gender, race/ethnicity, diabetes history, history of diabetes in other family members, current insulin management, other chronic conditions, other medications being used, medication allergies, and prior sensor use.

2.3.2 Physical Exam

A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or his or her designee (a pediatric endocrinologist, pediatric endocrine fellow, or a pediatric endocrine nurse practitioner) within 2 weeks prior to enrollment. The physical exam will include inspection of the skin and Tanner staging of breast development and pubic hair in females and genital development and pubic hair in males.

2.3.3 HbA1c

HbA1c level measured using the DCA2000 will be used to assess eligibility. The measurement must be made within 2 weeks prior to enrollment.

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

2.4 Informed Consent

For eligible subjects, the study will be discussed with the subject and parent/legal guardian (referred to subsequently as 'parent'). The parent will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Subjects will either be given the Child Assent Form to read or it will be read to the child.

If the parent and child agree to participation, the Informed Consent Form and Child Assent Form will be signed.

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

2.5 Instructions for Home Procedures

Each subject will be provided with a study home glucose meter (HGM) and instructed to perform at least 4 fingerstick glucose measurements per day-prior to each meal and before bed. Additional measurements will be done at times of symptoms of hypoglycemia.

CGMS sensor use will be prescribed for at least 72 hours to establish a baseline for biochemical hypoglycemia.

The initial CGMS sensor will be inserted by a study nurse or investigator. The subject and parent will be instructed on the use and care of the CGMS, including the insertion of an additional sensor if needed.

The procedures for use of the CGMS are described in chapter 6.

The subject will be asked to measure the blood glucose with the HGM 8 times a day on 3 days out of 7. At least 2 days of testing will be done while the CGMS is being worn. The "8-point" measurements will be made prior to each meal, 1.5 – 2.5 hours after each meal, before bed, and between 12 midnight and 4 a.m.

On the days of the 8-point measurements, the subject will be asked to record blood glucose measurements on a log.

2.6 Questionnaire Completion

The following questionnaires will be completed. These will be completed prior to randomization to avoid any potential bias in questionnaire completion from knowledge of the treatment group. The questionnaires are described in chapter 9.

- Diabetes Worry Scale (Diabetes-related Anxiety Questionnaire)
- PedsQL Diabetes Module
- Diabetes Self Management Profile (Treatment Adherence Questionnaire)

CHAPTER 3
RANDOMIZATION VISIT

3.1 Timing of Visit

Enrolled subjects will return 4 to 14 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 CGMS and HGM
- Obtaining a blood sample for HbA1c determination
- Instruction on use of the home PC
- Randomization to either the GWB Group or the Usual Care Group
- For subjects in the GWB Group, initiation of GWB use

3.2 Review of HGM Data

The HGM data will be downloaded and reviewed to assess whether the subject has been compliant with home glucose monitoring.

- To be continued in the study, it will be necessary that the subject has averaged at least 3 HGM measurements a day since enrollment and to have completed at least 2 of the 3 days of 8-point testing (with at least 6 test points on each day).
- Subjects with fewer HGM measurements will be withdrawn from the study. Such subjects will not count towards the recruitment total.

3.3 Review of CGMS Use

Although a minimum of 72 hours of CGMS sensor glucose measurements is preferred, a subject may be enrolled if at least 48 hours of measurements are completed. If this is not achieved due to a mechanical failure or a correctable omission on the part of the subject/parent, at investigator discretion the CGMS use can be repeated.

Subjects who were unable to successfully use the CGMS will not be randomized and will be withdrawn from the study.

3.4 Laboratory Tests

A blood sample will be obtained and sent to the central lab for measurement of HbA1c. HbA1c also will be assessed with the DCA2000 for management decisions.

3.5 Instructions on Use of the Home PC

Each subject in both groups will be provided with a PC (to be sent from the Coordinating Center). Initial instructions on the use of the PC will be given at the clinical center. The parent and (depending on age) the subject will be given a tutorial on the use of the PC. A proficiency test must be passed in which data are downloaded from each study device. Use of the PC is described in section 4.3.

3.6 Randomization

Subjects who have been compliant with home glucose monitoring and who successfully complete the home PC proficiency test will be randomized.

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

- The Jaeb Center will construct a Master Randomization List using a permuted block design stratified by clinical center and age group (7 to <12 and 12 to <18 years), which will specify the order of randomization group assignments.

  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 and the parent/guardian will accept assignment to either group.

3.7 Use of the GWB

Each subject in the GWB Group will be provided with a GWB and Autosensors. The subject and parent/guardian will be instructed on the use of the GWB and how to download the data. A guide booklet will be provided for the subject to take home. Use of the GWB is described in chapter 5.

3.8 Diabetes Management

The initial approach to management of a subject's diabetes will be similar in the two randomization groups.

As per usual care, changes in the insulin dosing will be made based on the HbA1c, the HGM data downloaded at this visit, and the investigator's prior experience in treating the subject.

CHAPTER 4
HOME PROCEDURES AND DIABETES MANAGEMENT

4.1 Phone Calls To Subjects

Phone calls will be made from the clinical center to each subject or primary care giver 1, 2, and 4 weeks after randomization and then every 4 weeks for the duration of the study. The primary purpose of the calls will be to review the subject's diabetes management and make alterations as indicated. All subjects have the opportunity to contact their care providers as needed as per their usual standard of care.

During each phone call, the coordinator will review the subject's diabetes management. The downloaded HGM data and GWB data (for the GWB group) will be available to the coordinator for review during the call.

The Procedure Manual will contain an outline for the coordinator to follow during the call. Every effort will be made for the duration of the calls to be of similar length for the subjects in each group.

4.2 Home Glucose Monitor

The study will provide a HGM to each subject. If the subject does not receive test strips through medical insurance, the test strips will also be provided. The study HGM will be used for a fingerstick blood glucose check a minimum of four times a day (prior to each meal and bedtime). The goals for blood glucose levels will be as follows:

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

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

Additional checks will be made when hypoglycemia is suspected either because of symptoms or because of a GWB alarm. Subjects will be permitted to check a fingerstick glucose as many times a day as they choose.

4.3 Home PC Use

As indicated in section 3.5, each subject will be provided with a PC. The PC will be used for the following:

- Downloading HGM data
- Downloading GWB data (for the GWB group)
- Reporting hypoglycemia events once a week
- Viewing HGM and GWB (for the GWB group) data for self-assessment of diabetes management

CHAPTER 5
HOME USE OF GLUCOWATCH BIOGRAPHER

5.1 Frequency of Use of the GWB

Each subject in the GWB group will use a GWB sensor a minimum of two times per week. One of the uses should be during the day and one at night. Additional sensor use is at subject/parent discretion.

5.2 Instructions for Use of the GWB

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

5.3 Skin Reactions

The subject and parent will be informed about the skin reaction that can occur with the GWB. The GWB manual will include instructions on treating mild skin reactions with skin emollients.

For any skin reaction that is more than mild, the subject and parent will be instructed to contact the clinic coordinator.

For subjects who complain of irritation from GWB use, triamcinolone, which has been shown to decrease the amount of irritation from the GWB[14], will be provided to apply to the skin prior to GWB use. In addition, cortisone cream will be provided to apply to the skin after GWB use.

5.4 Self-assessment using PC Software

The Home PC will have software for reviewing the GWB glucose values.

5.5 Downloading

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

CHAPTER 6
HOME USE OF CGMS

6.1 Frequency of Use of the CGMS

The CGMS sensor will be inserted by a study nurse or investigator. The subject and parent will be instructed on the use and care of the CGMS. The subject and parent will also be instructed on the insertion of an additional sensor. Each subject will attempt to achieve a minimum of 72 hours of sensor glucose measurements.

If the sensor fails or falls out prior to 48 hours of use, the subject will have the option of returning to the clinic to have another sensor inserted or inserting the sensor at home.

6.2 Instructions for Use of the CGMS

While using the CGMS at home, the subject will be able to follow his or her usual routine including insulin use, diet, and exercise. The only restriction is that the sensor must not get wet.

6.3 CGMS Calibration Values

The subject's blood sugar will be checked with a fingerstick using the study home glucose meter at least four times a day (prior to each meal and before bedtime). The parent/subject will enter only 4 values into the CGMS as calibration values.

CHAPTER 7
THREE-MONTH AND SIX-MONTH FOLLOW-UP VISITS

7.1 Overview

Subjects will return 3 and 6 months (±1 week) after the randomization visit. The purpose of the three-month and six-month follow-up visits will include the following:

- HbA1c determination
- Skin assessment for GWB Group
- Review of data and, if indicated, alteration of diabetes management
- Insertion of CGMS and providing instructions for 3 days of home use
- Providing instructions for 8-point blood glucose testing on at least 2 days of CGMS use
- Initiation of GWB for GWB Group
- Resupplying of subjects with test strips (3-month visit only) and for the GWB Group, autosensors
- Completion of questionnaires (6-month visit only)

7.2 HbA1c Determination

At each visit, a blood sample will be sent to the central lab for HbA1c determination. HbA1c also will be measured using the DCA2000 for management decisions.

7.3 History and Physical Exam

An interval history will be elicited with regard to any new medical problems that have developed, status of any pre-existing medical problems, and medication use. The physical exam will consist of a skin assessment and a limited physical exam related to any specific complaints the subject reports.

An assessment will be made of each extremity on which a GWB has been worn. Any areas of abnormality will be noted and scored for erythema and edema on a 0 to 4 scale (as described on the case report form and in the Procedures Manual). If the sum of the erythema score and the edema score is 6 or greater, an Adverse Event Form will be completed.

7.4 Insertion of CGMS

At each visit, a CGMS will be inserted and the subject will again be provided with instruction in its use (see chapter 6). Instructions will again be provided for completion of 8-point blood glucose testing on at least 2 days while the CGMS is worn.

7.5 Questionnaires

At the six-month visit, the following questionnaires will be completed:

- Diabetes Worry Scale (Diabetes-related Anxiety Questionnaire)
- Diabetes Self Management Profile (Treatment Adherence Questionnaire)
- PedsQL Diabetes Module
- Continuous Glucose Monitor Satisfaction Scale (GWB Group Only)

The questionnaires are described in chapter 9.

7.6 Subject Data Summary

For the six-month visit, a data summary for each subject will be reviewed with the subject as part of deciding on any alterations to be made in the subject's diabetes management.

7.7 Continued use of the GWB

Interested subjects in the GWB Group who complete the six-month visit will be given the GWB to keep plus a box of 16 sensors. Subsequent sensor supplies will be provided for the following 6 months for interested subjects.

Interested subjects in the Usual Care Group will be given a GWB and instructed on its use. Each subject will be given a box of 16 sensors; subsequent sensor supplies will be provided for the following 6 months for interested subjects.

CHAPTER 8
POST-SIX MONTHS FOLLOW UP

8.1 Overview

The study subjects are expected to continue to be seen at the clinical center every 3 months for their usual care.

At usual care visits that occur approximately 9 and 12 months following randomization, the following will be obtained for the study:

- HbA1c using the DCA2000 for management purposes
- Blood sample to send to central lab for HbA1c determination
- Completion of data form, recording current insulin management and whether a GWB is being used

CHAPTER 9
QUESTIONNAIRES

9.1 Introduction

All of the questionnaires are completed at baseline and six months, with the exception of the Continuous Glucose Monitor Satisfaction Scale, which is completed by the GWB group only at six months. Each questionnaire is described briefly below. The procedures for administration are described in the DirecNet Procedures Manual.

9.2 Diabetes Worry Scale (Diabetes-related Anxiety Questionnaire)

This is a 50-item Likert-type scale. Respondents rate their level of worry about various aspects of living with diabetes from 1 = I don't worry at all to 5 = I worry a whole lot. Administration time is approximately 15 minutes.

9.3 PedsQL Diabetes Module

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

9.4 Diabetes Self Management Profile (Treatment Adherence Questionnaire)

This is administered as a structured interview (DSMP) and will be used to determine if changes in diabetes treatment adherence occur during use of the GlucoWatch and to assess whether benefit from use of the GlucoWatch varies with the patient's level of treatment adherence. Parents and younger children will be interviewed together, while parents and children $\geq$ 11 years old will be interviewed separately. Since administration of the DSMP interview yields the most reliable and valid data if administered by a person not otherwise associated with the diabetes team, all DSMP interviews will be completed via phone by experienced staff at the Nemours Children's Clinic in Jacksonville, FL. The staff completing the interviews will be masked to the assignment group for the subjects. Administration time is approximately 20 minutes.

9.5 Continuous Glucose Monitor Satisfaction Scale

This 34-item questionnaire was designed for this study to measure the impact of using the GlucoWatch on family diabetes management, general family relationships, and individual emotional, behavioral and cognitive reactions to use of the device. This questionnaire will be completed by subjects in the GWB group at the 6-month follow-up visit in addition to the other questionnaires.

CHAPTER 10
ADVERSE EVENTS

10.1 Events To Be Reported

Since the study involves an FDA-approved device and does not require an IND, adverse event reporting will be limited to (1) events that meet criteria for a serious adverse event (SAE), (2) unanticipated adverse device events, (3) skin reaction from the GWB with a score of 6 or greater (see section 9.3), (4) events that are considered to have a possible (or greater) relationship to the GWB or any study procedure, (5) hyperglycemia resulting in diabetic ketoacidosis or hyperosmolar nonketotic coma, and (6) hypoglycemia resulting in seizures or loss of consciousness.

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

10.2 Definitions

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

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

An *Unanticipated Adverse Device Event* is defined as an adverse event caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence.

The relationship of any adverse event to the device or any other aspect of study participation will be assessed and graded by a study investigator on a four-point scale: (1) not related, (2) possible, (3) probable, and (4) definite. The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

10.3 Skin Irritation

Skin irritation is a possible effect of the GWB. At the 3-month visit, 6-month visit, and at any visit conducted prior to that time because of a skin reaction, a skin assessment will be made in areas in which the GWB has been worn. Erythema and edema will be scored on a 0 to 4 scale (as described on the case report form and in the Procedures Manual). A GWB irritation score (sum of the erythema score and edema score) of 6 or greater is considered a reportable Adverse Event.

10.4 Reporting Requirements for Serious and/or Unexpected Adverse Events

Any serious or unexpected adverse event occurring during or within 7 days after completion of the study will be reported to the Coordinating Center within one working day of occurrence. A written report on such an event will be sent to the Coordinating Center within five days of occurrence, stating a description of the reaction, any required intervention, and the outcome. Each principal investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB. Contact information for the Coordinating Center is located in the front of the protocol as well as in the Study Directory.

10.5 Data and Safety Monitoring Board

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

10.6 Risks and Discomforts

10.6.1 GlucoWatch Biographer

Previous studies done at Cygnus with earlier versions of the biographer have provided evidence that the application of up to 0.3 mA/cm^2 for up to 26 hours is safe. The biographer is designed to prevent current surges and has appropriate safety features to prevent high current or voltage levels. The device can apply a maximum of 17 volts. As a safety mechanism, the biographer will shut off automatically once 16 volts have been applied. Iontophoresis can cause a mild tingling sensation. If the subject feels significant discomfort, he/she will be able to turn off the current.

The most common reaction is skin irritation. The irritation will usually manifest itself as erythema and edema at the iontophoresis site. Irritation from the iontophoretic current may cause dryness, flaking or itching at the site for several days after treatment. Slight skin discoloration may be present after treatment, which gradually fades over several days. Severe irritation (equivalent to a chemical burn at or near the application area, generally 1-3 mm in diameter) is a potential risk. The severe irritation regions with necrosis, resembling small blackheads, become evident only upon device removal. A small percentage of severe irritation events have occurred using previous versions of the biographer. The severe irritation events that occurred caused little or no discomfort to the subject. All severe irritation events caused by previous biographer versions have been addressed with the subsequent design changes. No severe irritation events have occurred using the current biographer version and are not expected to occur with the biographer version(s) being used in this study. A thermal burn is not a potential risk, as the maximum possible current the biographer can deliver is 0.4 mA.

There may be skin irritation from the two, small skin conductivity measurement probes on the underside of the biographer. The current expected to be delivered by the probes is more that 300 times lower than the iontophoretic current, and the contacted surface area is approximately 19 times smaller than the area subject to iontophoretic current. In addition, the current for the probes will only be activated for 30 seconds at a time, up to once per minute. If for some reason the conductivity probes were to malfunction, the maximum current they could deliver would be approximately 20 times less than the iontophoretic current. With the application of current at the measurement probes, severe irritation is also a potential risk. However, no severe irritation events with the current biographer version have occurred.

10.6.2 CGMS Sensor

Subjects using the CGMS will be at low risk for developing a local skin infection at the site of the sensor needle placement.

10.6.3 Fingerstick Blood Glucose Measurements

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

CHAPTER 11
MISCELLANEOUS CONSIDERATIONS

11.1 Contact Information Provided to the Coordinating Center

The Coordinating Center will be provided with contact information for each subject. Permission to obtain such information will be included in the Informed Consent Form. This is needed so that the Coordinating Center can send a PC and related materials to the subject and so that it can, communicate with the subject with regard to use of the PC, data downloads and troubleshooting.

The contact information will be maintained in a secure database and will be maintained separately from the study data.

11.2 Subject/Parent Reimbursement

Each subject will be provided with a PC to download GWB and HGM data to the Coordinating Center and to complete weekly questionnaires. At the end of the study, subjects who complete the study will be permitted to keep the PC.

The study will provide the GWB and related supplies and the HGM. If the subject does not receive test strips through medical insurance, the test strips will also be provided. At the end of the study, subjects who complete the study will be permitted to keep the GWB and the HGM.

Children will be paid $5 a week for each time the weekly questionnaire is completed on the computer, the home glucose meter results are transferred to the computer, and the GlucoWatch results are transferred to the computer (for the GWB Group). Children will be paid $2 if all of these things are done during a week but are late (maximum of $130 during the study).

The study will be paying $25 per completed visit for up to five required study visits to cover travel and other visit-related expenses. Payment will not be made for missed visits. Payment will be made after the child completes the study.

CHAPTER 12
STATISTICAL CONSIDERATIONS

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

12.1 Sample Size Estimation

The sample size for the trial has been estimated to 200 subjects (100 per group).

Data from a 40 subject randomized trial conducted by Peter Chase were used to estimate the magnitude of change expected in HbA1c and the standard deviation of change. In this study subjects were randomized to either use of the GWB or usual care. At six months the mean improvement in HbA1c was 0.5% in the GWB group and 0.0% in the usual care group (standard deviation in each group was 1.0. Using these data as population estimates, with a sample size of 200, the trial will have 90% power for an alpha level of 0.05 assuming 10% losses to follow up.

With this sample size of 200, there also will be 90% power to detect a difference between groups of the proportion of subjects whose HbA1c decreases by 0.5% if the proportion in the usual care group is 25% and the proportion in the GWB group is 50%.

12.2 Statistical Analysis

The primary analysis will be a treatment group comparison of HbA1c values obtained 6 months after randomization, adjusted for the baseline HbA1c value in an analysis of covariance (ANCOVA) model. The primary analysis will follow the “intent-to-treat” principle.

As a secondary analysis, the proportion of patients in each group whose HbA1c level improves from baseline by at least 0.5% will be determined. The difference in the proportions and the exact 2-sided 95% confidence interval will be computed using StatExact software (Cytel, Inc.).

Differences between groups in hypoglycemic events will be evaluated. The type of analysis will depend on the distribution of the data. The pilot study being conducted as a prelude to the RCT will provide data as to whether the weekly questionnaire and the 8-point glucose testing will be useful for assessing hypoglycemic events.

The treatment groups also will be compared on the scores obtained from each questionnaire.

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