The Accuracy of Continuous Glucose Monitors in Children with Type 1 Diabetes

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CHAPTER 1
STUDY SYNOPSIS AND BACKGROUND INFORMATION

1.1 Overview and Objective

This is a study to assess the accuracy of two FDA-approved continuous glucose monitors, the GlucoWatch® biographer (GW biographer) and the Continuous Glucose Monitoring System® (CGMS), in children with type 1 diabetes.

The primary objective of the study is to assess the accuracy of each sensor in comparison with gold standard blood glucose measurements in an inpatient setting. As part of this, accuracy will be assessed during periods of rising and falling blood glucose.

Prior accuracy studies using the CGMS and GW biographer have largely been performed with adult subjects. There is a need to obtain additional accuracy data for sensor use in children. Additionally, many of the prior studies used capillary blood glucose measurements from meters as reference values for assessing accuracy. Thus, there is a need for additional accuracy data using methods considered to be the gold standard for measuring the blood glucose level.

1.2 Synopsis of Study Design

At five clinical centers, 90 subjects (1 to <18 years old) with type 1 diabetes will be hospitalized for approximately 26 hours to assess the accuracy of the continuous glucose monitors compared with 'gold standard' blood glucose measurements.

In order to assess the accuracy of the CGMS sensor throughout the 72 hours of sensor function, subjects will initiate use of the CGMS sensor 2 days prior to admission, 1 day prior to admission, or at the time of admission.

During the hospitalization, each subject will simultaneously use both the GW biographer and CGMS sensors and have blood drawn for gold-standard blood glucose measurements.

- The gold standard measurements will be made every 60 minutes during the day and every 30-60 minutes overnight.
- More frequent measurements will be made during a period of meal-induced hyperglycemia and during a period of an insulin-induced decrease in the blood glucose level (subjects 7 years and older only).

To complete all these studies up to 81 blood draws could be required for subjects $\geq$7 years old. The number of studies that can be performed may be limited by the weight of the subject and the manner in which a blood specimen is collected. Among the participating centers, some centers will employ reinfusion of blood drawn to clear the dead space in intravenous catheters and other centers will discard the blood drawn to clear the dead space.

- Centers that reinfuse blood will be able to perform all studies in this protocol.
- Centers that discard blood will limit the number of studies performed on a given subject so that no more than 5% of the subject's blood volume is withdrawn.

1.3 Background Information on the GlucoWatch Biographer

The GlucoWatch biographer was developed and is distributed by Cygnus, Inc. It looks like a watch and is worn on the forearm, three or more inches from the wrist or elbow joint.[1] An adhesive pad incorporating two hydrogel discs attaches the device to the skin. Each disc is the size of a dime. A triple 'A' battery from the biographer sends a small current through the discs to pull glucose from

the interstitial fluid underneath the skin. The glucose in the interstitial fluid is then measured. The maximal current used is very small (that of the triple 'A' battery). Each cycle lasts for 20 minutes.

The biographer model to be used in the study (GlucoWatch 2 biographer) gives up to 6 readings per hour, for 13 hours. The subjects can read glucose values displayed on the biographer. 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 70 mg/dl and/or more than 300 mg/dl). A two-hour warm-up time followed by a single glucose meter value is needed to calibrate the device. The GlucoWatch 2 biographer is the identical mechanical device as the GlucoWatch biographer, 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. This device will not require an IDE.

The biographer can be affected by the following:

- Sweat. There are two small metal bars on the bottom side of the GlucoWatch biographer that measure how much sweat is on the skin. If excessive sweating is detected, the cycle will be skipped (i.e. no value given for that 10-minute period).
- Temperature. If the temperature or rate of change in temperature is beyond a pre-programmed level, the cycle will be skipped.
- Glucose values outside the range of 40-400 mg/dl are just read as either LOW or HIGH.

Subjects wearing the GlucoWatch biographer may develop erythema and a localized skin reaction to the adhesive used to secure the GlucoWatch biographer to the skin, or to the hydrogel iontophoresis pads. Very rarely a severe skin reaction could result in scarring.

The Food and Drug Administration (FDA) has approved the GlucoWatch biographer for adults, and data have been submitted to the FDA requesting its approval for children. Although the accuracy of the device has been demonstrated,[1-6] the FDA approval does not allow for immediate changes in therapy (such as insulin dosing) to be based solely on the biographer values. All treatments and changes to insulin dosages during this study will be made using only the meter values and not the biographer values.

1.4 Background Information on the Continuous Glucose Monitoring System

The CGMS was developed and is distributed by Medtronics Minimed, Inc.[7] 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.[8] In human studies the interstitial glucose levels generally lag behind the blood glucose by 3 to13 minutes.[9,10] 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 for 24 to 72 hours; many sensors will not function for a full 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 range (from 2 weeks to 74 years old), and sex, race and duration of diabetes do not appear to influence sensor function.[11,12] The sensor is well tolerated with the only side effect being mild to moderate site irritation in 2% of patients.[11]

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 hypoglycemia 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. There are several reasons for sensor "failure": 1) A faulty connection between the sensor and the connecting cable will cause frequent "disconnect" warnings. This problem can be avoided by careful insertion of the cable into the sensor, with the sensor and the cable connection maintained in a flat, horizontal plane at the time of connection. 2) The sensor becomes "fouled."

CHAPTER 2
SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Study Population

Approximately 90 subjects will be enrolled in this study at five clinical centers with approximately 18 enrolled at each center.

Enrollment will include approximately 30 subjects in each of the age groups of 1.0 to <7.0 years old, 7.0 to <12.0 years old, and 12.0 to <18.0 years old.

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

A goal of recruitment will be to enroll a minimum of 10 African-Americans and recruitment of other minorities is encouraged.

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 injections) 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. There is no minimum or maximum HbA1c for eligibility.
2) Age 1.0 year to less than 18.0 years
3) Weight $\geq$12.0 kg for subjects less than 7.0 years old and weight $\geq$16.0 kg for subjects 7.0 years or older
4) For subjects over 2 years of age, body mass index (BMI) between the 5^{th} and 95^{th} percentile for age and sex
5) Normal hematocrit
6) Parent/guardian and subject understand the study protocol and agree to comply with it
7) Informed Consent Form signed by the parent/guardian and Child Assent Form signed by subjects 7 years of age and older

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 of the protocol testing specified for the subject's age and weight
2) History of seizures not attributable to either hypoglycemia or high fever
3) Current use of oral glucocorticoids

2.3 Patient Enrollment and Baseline Data Collection

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

2.3.1 Informed Consent

For eligible subjects, the study will be discussed with the subject and parent/legal guardian. The parent will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Subjects who are 7 years of age or older 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 (where applicable) will be signed and the inpatient hospital stay will be scheduled.

2.3.2 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, 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.

2.3.3 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). 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.

2.3.4 Laboratory Tests

HbA1c (with the DCA2000) and hematocrit (by whatever method is in standard use at the center) will be measured either in an office visit within two weeks prior to admission or at the time of admission to the CRC.

- There are no HbA1c limits for eligibility.
- If the hematocrit is measured at the time of hospital admission, no gold standard blood draws will be done until the results are available and verified to be in the normal range.

2.4 Initiation of CGMS Use

Each subject will be assigned by the clinical center staff to initiate CGMS use 2 days prior to CRC admission, 1 day prior to admission, or at the time of admission. This assignment will be made such that by the end of the study, each clinical center will have assigned equal numbers of subjects in each of the three age groups (1 to <7, 7 to <12, 12 to <18) to each of the three start days.

2.5 Home Use of the CGMS

For initiation of CGMS use, one-third of the subjects will have an outpatient visit 2 days prior to hospital admission and one-third a visit on the day prior to admission. At this visit, the CGMS will be inserted and training will be provided in its use. The subject/parent will be asked to record the ISIG and VCTR after one hour if they leave the office prior to that time.

During the time period of CGMS use 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. The subject's blood sugar will be checked with a fingerstick using the study home glucose meter (referred to subsequently as study HGM) at least four times a day. The parent/subject will be given a log to record these blood sugars.

CHAPTER 3
INPATIENT STUDY PROCEDURES AND MANAGEMENT

3.1 Overview

On admission to the CRC, an intravenous catheter will be inserted for the gold standard glucose measurements and a GW biographer will be placed. Subjects assigned to initiate CGMS use at the time of admission (see section 3.5) will have the CGMS sensor inserted. Subjects will be in the CRC for approximately 26 hours.

The inpatient procedures are summarized below and detailed in subsequent sections. The procedures to be done are dependent on the type of blood draw being utilized at the clinical center (reinfusion versus discard-see section 3.3.1) and the age and weight of the subject.

The study will consist of the following:

1) The accuracy of the CGMS sensor will be assessed for approximately 24 hours, with 1/3 of the subjects assessed over the first 24 hours of sensor function, 1/3 over the second 24 hours of sensor function, and 1/3 assessed in the last 24 hours of sensor function. Simultaneous use of a second CGMS sensor during the inpatient stay will be optional.
2) The accuracy of the GW biographers will be assessed over approximately 24 hours of use, with a minimum of a 2-hour period of time in which the use of two biographers will overlap.
3) Subjects will be assessed for nocturnal hypoglycemia with either hourly or ½ hour blood glucose readings based on blood volume limitations.
4) In subjects ≥7 years old who meet weight requirements for the number of blood samples, the function of the sensors will be assessed during an insulin-induced decrease in the blood glucose, which will be terminated if the blood glucose decreases to ≤55 mg/dl. This testing will evaluate the accuracy of the sensors during a rapidly decreasing blood glucose level. It will allow for: a) an evaluation of the accuracy of the sensors during hypoglycemia and b) an assessment of the lag time in detection of hypoglycemia.
5) In subjects who meet weight requirements for the number of blood samples, the function of the sensors during a rapidly rising blood glucose will be tested in order to: a) evaluate the accuracy of the sensors during a rapidly rising blood glucose and b) assess the lag time in detection of hyperglycemia. This will be accomplished by frequent sampling of blood glucose levels following a meal.

The procedures to be done are summarized in Table 3.1 according to the type of blood draw being employed at the clinical center (reinfusion or discard-see section 3.3.1) and the age and weight of the subject. The table assumes that the blood volume per blood draw will be 1.3 ml at “discard” clinical centers and 0.3 ml at “reinfusion” clinical centers. If at a clinical center the blood volume in a blood draw exceeds this amount, the number of allowable blood draws per subject will be adjusted such that the maximum blood draw volume for a subject will not exceed 5% of blood volume for body weight.

Table 3.1: Study Procedures According to Subject Age and Weight

	Type of Blood Draw Employed at the Clinical Center	
Procedure	**"Reinfusion"**	**"Discard"**
A. Hourly GS measurements for 24 hrs	All subjects	All subjects
B. Blood draws for hypoglycemia	All subjects	All subjects
C. ½ hour overnight GS measurements	All subjects	Subjects ≥15.6 kg
D. Insulin-induced hypoglycemia test	Subjects ≥7 yrs old	Subjects ≥7 yrs old and ≥23.1 kg
E. Meal-induced hyperglycemia test	All subjects	Subjects <7 yrs old/ ≥20.1 kg and ≥7 yrs old/ ≥27.6 kg

GS = gold standard

The study staff will customize a schedule of inpatient procedures for each subject.

3.2 Sensor Management and Procedures

3.2.1 GlucoWatch Biographer

The second generation device will be used for these studies. Subjects will wear the biographer on the arm or leg. The time of placement and the placement site of each biographer will be recorded (right or left, inner or outer, upper or lower). An assessment will be made of the skin in the area of sensor placement.

The biographer alarm settings will be at the discretion of the investigator. The alarm settings will be recorded on the data form. At centers participating in the ancillary study to assess alarm function, the alarm settings will be standardized. Section 3.5 details the procedures to be followed if a hypoglycemic alarm occurs.

Calibration of the biographer will be performed by study/CRC personnel. The first biographer (GWB#1) will be placed at the time of admission and calibrated two hours later. The second biographer (GWB#2) will be placed after GWB#1 is calibrated and no later than 9 hours after GWB#1 is calibrated, with its calibration completed two hours later. Assuming that GWB#1 does not prematurely shut off without being replaced, there will be at least two hours of overlap between the two biographers. If the timing of placement of GWB#2 is such that it will be removed prior to the end of the 24 hours of gold standard measurements, then GWB#1 will be used a second time with a second sensor (placed coincidentally with removal of the first GWB#1 sensor and calibrated two hours later). If GWB#2 sensor is removed 4 or more hours prior to the last 24-hour gold standard measurement, then a second GWB#2 sensor can be placed at investigator discretion. A sensor may be removed and replaced with a new sensor prior to the end of 15 hours if necessary to avoid having to place a new sensor overnight while the subject will be asleep.

A gold standard measurement will be made to coincide with the study HGM reading used for calibration. Additional calibrations will be performed when the required CGMS calibrations are performed.

Prior to hospital discharge, a skin assessment will be made by two observers for all areas where a biographer was worn. Both erythema and edema will be scored on a 0 to 4 scale (as described on the case report form and in the Procedures Manual). If the sum of the erythema score and the edema score is 6 or greater, an Adverse Event Form will be completed.

3.2.2 Continuous Glucose Monitoring System

The CGMS sensor will be inserted in the abdomen or upper buttocks in an area of normal appearing skin. The site and time of insertion will be recorded. The area where the sensor will be inserted may be numbed with Elamax or EMLA cream for at least 15 minutes prior to insertion.

For subjects who begin using the CGMS prior to CRC admission, the CGMS data will be downloaded at admission to verify that the sensor is functioning. If the sensor is not functioning, it will be replaced.

During CGMS use at home, the subject/parent will enter the calibration values. During the inpatient study, this will be done by the study/CRC personnel. After the initial calibration, four glucose measurements will be obtained by fingerstick and entered into the CGMS system each day before each meal and before bed.

Simultaneous use of a second CGMS sensor will be optional. If the investigator believes that the child can successfully use two CGMS sensors and the subject and parent agree, a second sensor will be inserted in an area of normal appearing skin, similar to the procedure described above for the first sensor. There is no increased risk to the subject of having two sensors.

Prior to hospital discharge, the CGMS will be removed and the insertion site will be assessed for induration (measured in millimeters), and erythema (measured in millimeters). Continued use of the CGMS as an outpatient after insertion of a new sensor will be an option for the investigator and subject/parent. If this is done, it will be considered part of usual care and the CGMS data will not be collected for the study.

3.2.3 Sensor Failure and Related Issues

If a GlucoWatch biographer sensor fails with fewer than 4 hours of gold standard measurements remaining, it will not be replaced, unless it is the only functioning biographer and the insulin-induced hypoglycemia test or the meal-induced hyperglycemia test is scheduled in the following 4 hours. The schedule for subsequent sensor placement will not be altered.

If a CGMS should fail (ISIG < 10 with glucose >120) or there are frequent interrupt alarms, or the sensor fails to accept a calibration glucose value, then a new CGMS sensor will be inserted and the failing sensor will be removed. If the sensor is removed because of frequent interrupt alarms, a new cable will be used. If a sensor fails within 3 hours of the completion of the inpatient study, it will not be replaced, unless it is the only functioning CGMS sensor and the subject is still scheduled to have either the meal-induced hyperglycemia or insulin-induced hypoglycemia test.

A subject who is unable to use the sensors will be withdrawn from the study and will not be counted towards the recruitment goal when he or she is unable to successfully use the CGMS for 12 hours and one biographer for 12 hours as an inpatient. If the subject has used at least one sensor successfully as an inpatient for 12 hours, the inpatient phase will be completed as long as one sensor is still being used.

3.3 Gold Standard Glucose Measurements

An intravenous catheter will be inserted in an arm vein. The area where the catheter will be inserted may be numbed with Elamax or EMLA cream for at least 15 minutes prior to catheter insertion.

The gold standard measurements will be timed to be on the hour and, when specified in the protocol to be performed overnight, on the half-hour. The first hourly measurement will be made at the first

hour point that is at least one hour following insertion of the CGMS. Half-hourly measurements will be made from 9:00 p.m. to 7:00 a.m. If the catheter stops functioning, it will be replaced if there are any protocol-specified gold standard measurements still to be made.

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

3.3.1 Volume of Blood Draws

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

Table 3.2: Blood Volume Requirement for Each Study Procedure According to Type of Blood Draw (Reinfusion or Discard)

		Type of Blood Draw Employed at the Clinical Center	
	Maximum # of blood draws	**"Reinfusion" (0.3 ml per blood draw)**	**"Discard" (1.3 ml per blood draw)**
Procedure		*blood volume (ml)*	
A. Hourly GS measurements for 24 hrs	24	7.2	31.2
B. Blood draws for Hypoglycemia*	5	1.5	6.5
C. ½ hour overnight GS measurements	10	3.0	13.0
D. Insulin-induced hypoglycemia test	18	5.4	23.4
E. Meal-induced hyperglycemia test	12	3.6	15.6
F. Quality control samples*	3	0.9	3.9
		"Reinfusion" and "Discard" Centers (0.3 ml per blood draw)	
G. 'Safety' glucose measurements during IV insulin test*	9	2.7	

*this is a maximum number; see section 3.5 for details on additional blood draws at times of hypoglycemia, section 3.3.2 for details on quality control specimens, and section 3.7 for details on the 'safety' blood draws during the IV insulin test.

Additional blood draws may be needed for the GlucoWatch biographer calibrations. One to three duplicate blood samples will be drawn for quality control purposes from each subject. At the time of admission, the maximum number of blood draws that can be performed based on a subject's weight will be determined so that the maximum blood volume in the blood draws will not exceed 5% of the subject's blood volume (calculated by multiplying the subject's weight in kilograms by 70 [70cc / kg blood volume] and then multiplying by .05). The maximum number of blood draws is then determined by dividing this maximum blood volume by the amount of blood in each blood draw at the center. At the time of admission, a log form will be started on which the maximum number of blood draws for the subject will be indicated, and each blood draw will be logged to assure that this maximum number is not exceeded.

Table 3.3: Procedures to Be Done and Blood Volume Required According to Age of Subject

A. "Reinfusion" Centers

	Procedure (*see description in Table 3.2 for each 'letter'*)							
Subject Age	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**Total Blood Volume***
< 7	7.2	1.5	3.0	-	3.6	0.9	-	16.2
≥ 7	7.2	1.5	3.0	5.4	3.6	0.9	2.7	24.3

* assumes 0.3 ml per blood draw

B. "Discard" Centers

	Procedure (*see description in Table 3.2 for each 'letter'*)							
Subject Age and Weight	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**Total Blood Volume***
<7, 12.0-15.5 kg	31.2	6.5	-	-	-	3.9		41.6
<7, 15.6-20.0 kg	31.2	6.5	13.0	-	-	3.9		54.6
<7, ≥20.1 kg	31.2	6.5	13.0	-	15.6	3.9		70.2
≥7, 16.0-23.0 kg	31.2	6.5	13.0	-	-	3.9		54.6
≥7, 23.1-27.5 kg	31.2	6.5	13.0	23.4	-	3.9	2.7	80.7
≥7, ≥ 27.6 kg	31.2	6.5	13.0	23.4	15.6	3.9	2.7	96.3

*assumes 1.3 ml per blood draw for A-F and 0.3 ml per blood draw for G

3.3.2 Quality Control Specimens

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

3.4 Glucose Measurements with the Study Home Glucose Meter

Bedside blood glucose monitoring will be performed using the study HGM. Four glucose measurements must be obtained entered into the CGMS system each day for calibration. If the need for a HGM glucose measurement coincides with a gold standard blood draw, venous blood can be used. If not, a fingerstick will be done to obtain capillary blood for the glucose measurement.

The study HGM testing can be done by the subject, a parent, or a nurse.

3.5 Blood Glucose Testing for Hypoglycemia

If either a subject reports symptoms of hypoglycemia or a GW biographer hypoglycemia alarm occurs (for low or falling blood glucose), the blood glucose will be checked on the study HGM.

A gold standard blood draw will only be done if (1) the HGM value is <65 mg/dl, (2) a gold standard measurement has not been done in the prior 15 minutes, and (3) an extra blood draw for hypoglycemia has not been done in the prior 15 minutes.

If an extra gold standard blood draw falls within 5 minutes of the next scheduled blood draw, then the next scheduled blood draw will be skipped.

3.6 Meal-induced Hyperglycemia Test

In subjects of appropriate weight to accommodate the volume of blood required for testing, the sensors will be assessed following a physiologic rise in blood glucose after a high carbohydrate meal/drink (1.75 gm CHO/kg such as a "fruit smoothie", up to a maximum of 75 grams).

Two hours prior to the meal-induced hyperglycemia test, a HGM blood glucose level will be obtained. If the glucose value is greater than 250 mg/dl, the subject will be given a subcutaneous insulin dose (Humalog or Novolog) estimated to decrease the blood glucose to 150 mg/dl

Before starting the meal-induced hyperglycemia test, a HGM blood glucose level should again be obtained. If the blood glucose level is greater than 250 mg/dl, then an insulin dose should be given as described above to lower it to be less than 250 mg/dl. The start of the meal test should be deferred until the blood glucose level is less than 250 mg/dl.

If an insulin injection or pump bolus would ordinarily be given at this time, it will be withheld until 30 minutes after the carbohydrate meal/drink.

Gold-standard glucose levels will be obtained every 5 minutes for 60 minutes after the subject finishes the meal/drink.

3.7 Insulin-induced Hypoglycemia Test

In subjects 7 years of age and older only, the sensors will be assessed following an insulin-induced decrease in the blood glucose.

Two and a half hours before the scheduled start of the test, the subject must have at least one functioning biographer and one functioning CGMS. If this is not the case, a new sensor (CGMS or biographer) will be initiated at that time. If sensor failure occurs prior to the start of the test, the start of the test will be delayed until sensor calibration has been completed.

Approximately one hour prior to the test, a blood glucose will be obtained with the study HGM.

- If the glucose level is between 70 - 80 mg/dl, 10 grams of carbohydrate will be given orally, and if the glucose is less than 70 mg/dl, then 15 grams of carbohydrate will be given as per usual treatment of hypoglycemia. For subjects with a glucose of less than 80 mg/dl, blood glucose monitoring and treatment will continue every 15 minutes until the blood glucose is greater than 80 mg/dl.

If the testing time overlaps with a meal, the meal will be withheld until after the test.

A physician will be present during this test.

If the usual timing of an injection of intermediate acting insulin would occur within 2 hours prior to the scheduled start of the test, it will be withheld until after the test is completed. For subjects using an insulin infusion pump, the basal rate will be continued during the test.

Prior to starting the test, the blood glucose level will be checked with the study HGM.

- If the glucose level is less than 80 mg/dl, then 10 grams of carbohydrate will be given orally and the glucose will be rechecked in 10 minutes.
- If the glucose was less than 70 mg/dl, then 15 grams of carbohydrate will be given as per usual treatment of hypoglycemia.

- The blood glucose will be checked every 10 minutes, and when the blood glucose is > 80 mg/dl, the IV insulin test can begin.

For the test, regular insulin will be given by IV bolus.
- If the starting blood glucose is 80-100 mg/dl, then 0.05 units/kg of IV insulin will be given.
- If the starting blood glucose is >100 mg/dl, then 0.1 units/kg of IV insulin will be given.
- At any time between 30 to 60 minutes after the initial dose of IV insulin, a second dose of insulin (between 0.05 to 0.1 units/kg) may be given at the discretion of the attending physician if the target glucose has not been achieved.

During the test, blood glucose levels will be monitored every 5 minutes.
- Monitoring will be done with the study HGM until the blood glucose is <80 mg/dl (on the study HGM). Thereafter, a YSI, Beckman, or similar instrument will be used.
- Venous blood from the gold standard blood draw can be used instead of a fingerstick.
- At the end of the test, a meal may be needed to prevent a recurrence of hypoglycemia.
- Monitoring will continue every 5 minutes until the blood glucose is > 80 mg/dl and thereafter will be performed at least once an hour for two hours using the study HGM.
- If the subject should have hypoglycemic symptoms that concern the attending physician, then IV dextrose will be given at a dose of 0.5 grams/kg intravenous over 3 minutes as D25 or D50.
- Symptoms of hypoglycemia during and/or after the test will be recorded.

3.8 Diabetes Management

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

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

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

3.9 Daily Activities

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

3.10 Diet

The prescribed diet will be at the discretion of the investigator. For subjects meeting the weight requirement, one meal will consist of a measured amount of carbohydrate for the meal-induced hyperglycemia test (see section 3.6).

3.11 Hospital Discharge

Prior to discharge, all sensors will be removed and a CRC nurse and a study nurse or investigator will independently assess the skin in the area of each GW biographer wear and each CGMS insertion (see sections 3.2.1 and 3.2.2).

CHAPTER 4
POST- DISCHARGE FOLLOW UP

4.1 Follow-up Visit

All subjects will return 3 to 5 days after discharge from the CRC for an inspection of the CGMS insertion site and the biographer wear sites for any redness, swelling or blistering.

4.2 Additional Follow-up for Sensor Skin Effects

If at the day 3-5 visit, there is any redness, swelling, or blistering, the subject will be contacted by phone by the study investigator or his/her designee 10 to 14 days after discharge. If there are persistent skin changes, the subject will be asked to return for a physical assessment.

A subject with persistent active skin changes will be called weekly until the changes resolve.

CHAPTER 5
ADVERSE EVENTS

All adverse events occurring during the course of the study will be recorded on the appropriate case report form. Skin irritation from sensor wear will be recorded in a specific section of the case report form. Other reportable adverse events will be reported on an adverse event case report form. Special reporting requirements for hyperglycemia and hypoglycemia are described in section 7.3.

5.1 Definitions

An *Adverse Event* (AE) is defined as any untoward medical occurrence in a research subject treated with a medical device during a clinical trial or post-study follow-up period, regardless of causality assessment. This includes adverse clinical or laboratory findings, intercurrent illness, or an exacerbation or progression of a disease/condition present at baseline. The event(s) will be reported with reference to: time and date of event, relationship to the device, severity, and final outcome. For this study all adverse events, regardless of causality and relationship to sensor use or study procedures, will be reported during the period of time of sensor use. 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.

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.

5.2 Skin Irritation

Skin irritation is a possible effect of the biographer. For all subjects, skin irritation will be formally assessed at the time of CRC discharge (see section 3.2.1 and 3.2.2). A biographer irritation score of 6 is considered an Adverse Event and will be recorded on an Adverse Event Form in addition to being recorded on the skin assessment case report form. Skin changes in the area of the insertion of the CGMS catheter (induration and erythema) also will be assessed.

5.3 Reporting of Hyperglycemia and Hypoglycemia as Adverse Events

For the diabetic subjects, high and low blood glucose levels are expected and will not per se constitute adverse events.

Hyperglycemia is only recorded as an adverse event if diabetic ketoacidosis or hyperosmolar nonketotic coma develops.

Hypoglycemia is only recorded as an adverse event if seizures or loss of consciousness occurs and/or the episode requires treatment other than oral ingestion of carbohydrate.

5.4 Reporting Requirements for Serious and/or Unexpected Adverse Events

Any serious or unexpected adverse event occurring during or after completion of the study, irrespective of the treatment received by the patient, 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.

5.5 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.

5.6 Risks And Discomforts

5.6.1 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 2 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 ionophoresis 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.

5.6.2 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. Toddlers wearing the CGMS will have the cable wrapped around the monitor worn on their belt so there will not be a possibility of the cable wrapping around their neck while they are sleeping.

5.6.3 Fingerstick Blood Glucose Measurements

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

5.6.4 Hypoglycemia and Hyperglycemia

Subjects may develop hyperglycemia or hypoglycemia. Hypoglycemia may be associated with profuse diaphoresis, shock, tachycardia, and seizures. Hyperglycemia is usually acutely benign, but may be associated with thirst, glycosuria, ketoacidosis, and hyperosmolar coma. The risk of these complications is an inherent risk of having diabetes.

The protocol-specified insulin-induced decrease in blood glucose may produce symptoms of hypoglycemia similar to those that the subject might experience at home. The risk of severe hypoglycemia resulting in loss of consciousness or seizures should be no greater than the risk that occurs with spontaneous hypoglycemia at home and is probably less because of the close monitoring.

Hypoglycemia occurs frequently in children with diabetes. In a typical child with a hemoglobin A1c between 7-8%, it is usual for at least 15% of home glucose readings to be less than 70 mg/dl, when the child is doing 4-6 blood tests a day. With near continuous glucose monitoring, the frequency of hypoglycemic events has been much greater, due to more frequent monitoring of glucose levels (every 5 minutes with the CGMS and every 20 minutes with the biographer). This is most evident when assessing glucose values overnight. In a recent study of continuous subcutaneous glucose monitoring (CGMS), over 60% of children had overnight glucose levels < 55 mg/dl with a mean duration of 220 minutes, nearly 4 hours.[13] One of the major uses of near continuous glucose monitoring will be for the detection of hypoglycemia. It is therefore critical that we assess the accuracy of these devices in detecting hypoglycemia. We need to determine the false positive as well as the false negative rate, the lag time of interstitial readings compared to blood glucose readings, and the function of device alarms in warning of hypoglycemia. We propose to do this in a controlled environment with blood glucose levels monitored every 5 minutes and a physician in attendance. Once a glucose value reaches a nadir of 55 mg/dl, hypoglycemia will be treated. If subjects experience severe symptoms of hypoglycemia, intravenous glucose will be available for immediate correction of hypoglycemia. The insulin doses we are using are conservative and consistent with the doses used to test for growth hormone deficiency. Children tested for growth hormone deficiency are typically given 0.1 u/kg of insulin with a fasting glucose of 70 to 110 mg/dl (and these children are thought to have deficiencies in hormones which normally correct hypoglycemia such as growth hormone and cortisol). Testing is being done in these children because they are at risk for short stature. In contrast, children with diabetes are at risk for frequent hypoglycemic episodes, and may have seizures and learning disabilities as a result of these episodes. If these devices are found to be accurate in detecting hypoglycemia, children with diabetes would receive significant benefit.

CHAPTER 6
MISCELLANEOUS ISSUES

6.1 Benefits

It is expected that continuous glucose monitors will have an important role in the management of diabetes in children. The development of a non-painful, non-invasive, automatic glucose meter would benefit approximately 5% of the population who have diabetes and should be monitoring their glucose levels. The subject's participation in this study is an important contribution to the development of such a device. Therefore, the results of this study are likely to be beneficial for children with diabetes.

It is possible that the blood sugar information from the monitors will be useful for the subject's diabetes management by identifying hyperglycemia and hypoglycemia that might indicate a need to alter the subject's insulin dosage and/or diet. In addition, the subject may benefit from participation in the ancillary studies to assess carbohydrate counting and to assess the accuracy of the glucose meter that is being used at home.

6.2 Subject/Parent Reimbursement

The subjects and their families will be paid $100 for the CRC admission as compensation for their travel expenses and potential time lost from work for the hospitalization phase of the study. They will also receive $25 for each outpatient visit. If the optional second CGMS sensor is inserted, an additional $25 will be paid.

The study will provide the sensors and related supplies, home meters and test strips.

6.3 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.

Subjects who withdraw or are withdrawn from the study without completing at least 12 hours of sensor use will be replaced if the full cohort has not yet been recruited at the time the subject is withdrawn from the study.

An enrolled subject who is found to have an abnormal hematocrit or who is unable to use the sensors will be withdrawn and will not be counted towards the recruitment goal when he or she did not successfully use at least one CGMS and one biographer for 12 hours as an inpatient.

Subjects who are admitted to the CRC and have at least one gold standard blood measurement will receive payment for the inpatient stay even if withdrawn prior to completion of the study.

6.4 Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection upon request by the Coordinating Center, the NIH, and auditors of regulatory agencies as required by law.

Data will be transmitted to the study's Coordinating Center for storage and analysis. The names and any other identifying information of the subjects and parents will not be part of the information that is sent to the Jaeb Center. The Coordinating Center maintains secure patient data files (both physical files and the computerized database). Data are stored such that no direct links exist between the patient's data and information that would identify the patient.

CHAPTER 7
STATISTICAL CONSIDERATIONS

7.1 Sample Size

Sample size estimates were made for the number of subjects and number of gold standard (GS) measurements (matched to a sensor measurement) per subject for several different measures of accuracy using a dataset from a prior study. The underlying principle in the sample size estimations was to determine the sample size required for a prespecified width of a two-sided 95% confidence interval for each measure of accuracy.

A sample size of 90 subjects was selected for the study. With this sample size, it can be seen below in Table 7.1 that the 95% confidence interval for each accuracy measure will be narrow. With 30 subjects in each of three age groups, it can be seen in Table 7.1 that with 20 paired data points per subject, a subgroup analysis of 30 subjects will have a 95% confidence interval half-width of approximately .02 for the proportion of paired points in Clarke error grid zones A+B and .03 for the mean relative absolute deviation.

Table 7.1: Half-width of a 95% Confidence Interval for Each Accuracy Measure According to the Number of Subjects in the Analysis (assuming 20 paired data points per subject)

			Sample Size			
			90	**60**	**30**	**15**
	Mean*	Standard Deviation*	***Half-width of 95% CI***			
Accuracy Measure Computed for Each Subject						
Proportion in Clarke grid A	.61	.18	.04	.05	.06	.09
Proportion in Clarke grid A+B	.95	.06	.01	.02	.02	.03
Proportion with deviation $\leq$30%	.77	.15	.03	.04	.05	.08
Mean Relative Absolute Deviation	.21	.09	.02	.02	.03	.05
Mean Relative Deviation	.08	.14	.03	.04	.05	.07
Mean Absolute Deviation	30.6	11.1	2.3	2.8	4.0	5.6
Mean Deviation	5.0	21.5	4.5	5.5	7.7	10.9

*estimate

7.2 Statistical Analysis

For analysis, the gold standard blood glucose values will be paired with the appropriate corresponding sensor values, and the difference between values will be computed. The difference scores will be assessed by several methods.

- The difference scores will be plotted using the Clarke grid[14] and the modified Clark grid. The values will be also evaluated across the range of blood glucose values in Bland-Altman plots
- As a binary variable, accuracy will be evaluated as (1) proportion of difference scores in Clarke grid area A, (2) proportion in Clarke grid area A+B, (3) proportion in modified Clarke grid area A, (4) proportion in modified Clarke grid area A+B.[15]
- As a continuous variable, accuracy will be evaluated by computing the mean and standard deviation for the following parameters and then constructing 95% confidence intervals around the mean: difference, absolute difference, relative difference and absolute relative difference. In addition, standard linear and Deming regression models will be fit.

Each accuracy measure will be computed on a subject level and then the mean, standard deviation, and 95% confidence interval around the mean will be computed across subjects.

Separate analyses will be conducted in subgroups based on age, gender, and race. Accuracy will be assessed for both high and low blood glucose values and during periods of increasing blood glucose, decreasing blood glucose, and sleep. The accuracy of the sensors early in their lifespan will be compared with the accuracy late in their lifespan.

The sensor failure rate will be determined. The frequency of missed sensor readings and the reasons will be tabulated. Adverse events will be tabulated and their incidence estimated.

The sample size estimation and analytic methods will be detailed in a separate Statistical Analysis Plan document.

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