A Pilot Study to Assess the Accuracy of Continuous Glucose Monitors in Normal Children

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CHAPTER 1
STUDY SYNOPSIS AND BACKGROUND INFORMATION

1.1 Overview and Objective

The glucose profile of normal healthy children has not been well described over a 24h period. The ccharacterization of the glucose values in normal children during day and nighttime is critical to the interpretation of glucose values in pathological states, such as diabetes. This is particularly important in analyzing the levels of low glucose values overnight observed in diabetic children. As a first step, we will conduct a pilot study to determine whether continuous glucose monitors measuring subcutaneous fluid glucose levels are sufficiently accurate to use for this purpose. There are two continuous glucose monitors, the GlucoWatch® biographer (GW biographer) and the Continuous Glucose Monitoring System® (CGMS), that are FDA-approved for use in patients with diabetes. A study is presently being conducted by our group looking at the accuracy of these monitors in children with diabetes comparing the results obtained with these monitors against the gold standard blood glucose measurements. If these monitors are found to be sufficiently accurate, then their use provides the opportunity to assess glucose values in normal children as they go about usual daily activities in the home environment. However, the assessment of the variation of blood glucose concentrations in normal children as well as how well these numbers correlate with those obtained using the continuous glucose sensors will necessitate first an inpatient study to measure blood glucose at frequent regular intervals over a 24-hour period using both the continuous glucose sensors (CGMS and GW biographer) as well as the gold standard blood sugar.

At one of the DirecNet centers (Yale University), the CGMS was used by 31 normal children in the home environment (unpublished). Twenty-seven of the 31 children had at least one glucose value <60 mg/dl during up to 72 hours of sensor use. Eighteen children had at least 30 minutes of sensor values <60 mg/dl, primarily overnight, during the first 24 hours of sensor use. For some of the children, the duration of the nocturnal low glucose levels was two or more hours. Additional anecdotal information of normal subjects wearing the continuous glucose sensor having frank hypoglycemic values also abound. Whether these decrements in glucose concentrations are real or whether they represent an inherent analytical issue with this instrumentation remains to be elucidated.

1.2 Synopsis of Study Design

At five clinical centers, a pilot study will be conducted on 20 healthy subjects (7 to <18 years old) who do not have type 1 or type 2 diabetes nor history of the disease in the immediate family. Each subject will be hospitalized for approximately 26 hours to assess the accuracy of the continuous glucose monitors compared with 'gold standard' blood glucose measurements. The data will be evaluated after the first 10 subjects to determine whether any modifications in the protocol should be considered for the second 10 subjects.

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 every 60 minutes during the day and every 30 minutes overnight.

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 and 9 minutes in animal studies.[8] In human studies the interstitial glucose levels generally lag behind the blood glucose by 3 to 13 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

Up to 20 healthy subjects will be enrolled in this study at five clinical centers with approximately equal numbers enrolled at each center.

Enrollment will include approximately 10 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 equal sex distribution in each age group.

A goal of recruitment will be to enroll a minimum of 3 African-Americans.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

To be eligible for the study, a subject must meet the following criteria:

1) Age 7.0 to less than 18.0 years
2) Weigh at least 16.0 kg
3) Body mass index (BMI) between the 10^{th} to 90^{th} percentile for age and sex (based on CDC, 2000 nomogram)
4) Normal HbA1c (<6.0 with the DCA2000)
5) Normal hematocrit (according to normal range at the clinical center's lab)
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 the subject

2.2.2 Exclusion

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

1) Family history of type 1 or type 2 diabetes in a sibling or parent
2) History of diabetes or positive islet cell antibody testing
3) The presence of skin abnormalities or 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.
4) Use of any medications (prescription or nonprescription) in the 7 days prior to CRC admission

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. The subject will either be given the Child Assent 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 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, history of diabetes in family members, chronic medical conditions, medications being used, and medication allergies.

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 (with particular attention to rashes, eczema, sun burn, and lipohypertrophy), and Tanner staging of breast and pubic hair in females and genital development and pubic hair in males.

2.3.4 Laboratory Tests

1. Hemoglobin A1c (using the DCA2000)
2. Hematocrit (using whatever method is in standard use at the center)

These can be measured either during an office visit within two weeks prior to admission or at the time of admission to the CRC.

If either the HbA1c or 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.

CHAPTER 3
INPATIENT STUDY PROCEDURES AND MANAGEMENT

3.1 Overview

On admission to the CRC, (1) a GW biographer will be placed, (2) a CGMS inserted, and (3) an intravenous catheter inserted for the gold standard glucose measurements. Subjects will be in the CRC for approximately 26 hours.

The inpatient procedures are summarized below and detailed in subsequent sections.

The study will consist of the following:

1) Gold standard blood glucose measurements will be hourly during the day and every half hour overnight.
2) The accuracy of the CGMS sensor will be assessed for approximately 24 hours. Simultaneous use of a second CGMS sensor during the inpatient stay will be optional.
3) The accuracy of the GW biographer will be assessed over approximately 24 hours of use, with a minimum of a 2-hour period of time where the use of two biographers will overlap.

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 forearm or upper arm. The time of placement and the placement site of each biographer will be recorded (right or left arm, inner or outer arm, forearm or upper arm). An assessment will be made of the skin in the area of sensor placement. The biographer alarm settings will be set to be 40 mg/dl (low) and 400 mg/dl (high).

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.

Calibration glucose values will be obtained with the study HGM using venous blood obtained at the time of a gold standard blood draw. After the initial 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.

Calibration values will be obtained with the study HGM using venous blood obtained at the time of a gold standard blood draw. After the initial calibration, glucose measurements will be entered 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).

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. 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.

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 total blood volume withdrawn during the study for the hourly blood draws for 24 hours and the half-hour blood draws overnight for 10 hours will be 10.2 ml with reinfusion (assuming a blood volume of 0.3 ml per blood draw) and 44.2 ml with discard (assuming a blood volume of 1.3 per blood draw).

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. For four calibration blood draws and three quality control blood draws, the blood volume will be 2.1 ml at reinfusion centers and 9.1 ml at discard centers.

The minimum weight requirement of 16 kg for subject eligibility assures that the maximum blood volume in the blood draws (53.3 ml at discard centers) will not exceed 5% of a subject's blood volume (calculated by multiplying the subject's weight in kilograms by 70 [70cc / kg blood volume] and then multiplying by .05).

3.4 Daily Activities

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

3.5 Diet

A regular diet for age will be prescribed.

3.6 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(s). Skin irritation from sensor wear will be recorded in a specific section of the case report forms. Other adverse events will be reported on an adverse event case report form.

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 (8) 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 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.

5.4 Data and Safety Monitoring Board

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

5.5 Risks And Discomforts

5.5.1 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 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 surface area contacted by 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.

5.5.2 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.

CHAPTER 6
MISCELLANEOUS ISSUES

6.1 Benefits

There will be no a direct benefit to the subject from participating in this study. The subject's participation in this study is an important contribution to the development of a better understanding of normal glucose metabolism in children.

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.

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.

A subject who is enrolled but at the time of CRC admission is found to have an abnormal HbA1c or hematocrit will be withdrawn. An enrolled subject who at the time of CRC admission reports having used a systemic medication (prescription or nonprescription) in the prior 7 days will either be rescheduled or withdrawn.

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

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.

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

The sample size of 20 normal subjects was selected to provide preliminary data on the accuracy of the sensors in normal children. Based on outpatient use of the CGMS, it is expected that at least several of the 20 children will demonstrate prolonged periods of low blood glucose values using the CGMS. Thus, a sample size of 20 should provide the opportunity of determining whether or not these low values are false positives. If they are false positives, this sample size will provide the opportunity of determining whether this phenomenon is unique to the CGMS or whether it also occurs with the GW biographer.

These results will then be used to determine the objectives for subsequent studies and will provide variance estimates to be used in sample size determinations.

An estimate of the precision possible with 10 and 20 subjects can be obtained from data available for sensor use in diabetic subjects. The table below shows the 95% confidence interval half-width for a sample size of 10 subject based on standard deviations estimated from a prior accuracy study of diabetic subjects.

			Sample Size	
			20	**10**
	Mean*	Standard Deviation*	***Half-width of 95% CI***	
Outcome Measure Computed for Each Subject				
Proportion with deviation ≤20%	.61	.18	.08	.11
Proportion with deviation ≤30%	.77	.15	.07	.09
Mean Relative Absolute Deviation	.21	.09	.04	.06
Mean Absolute Deviation	30.6	11.1	4.9	6.9
Mean Relative Deviation	.08	.14	.06	.09
Mean Deviation	5.0	21.5	9.4	13.4

*estimate from dataset of diabetic subjects

7.2 Statistical Analysis

Analyses will primarily be exploratory.

To assess the accuracy of low blood glucose values obtained with the sensor, time periods of sensor values below 60 mg/dl will be identified and sensor values will be compared with gold standard values obtained during the same time period.

- To assess overall accuracy, analyses will be conducted similar to those planned for the diabetic subject protocol. 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. 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.

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.

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.

After the first 10 subjects, the data will be assessed to determine whether any subjects have experienced periods of nocturnal hypoglycemia with the sensors and, if yes, whether the low values were corroborated on the gold standard measurements. If false low glucose values with the sensor occur, then consideration will be given to modifications in the protocol or data collection to try to determine why this is occurring.

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