A STUDY TO ASSESS CONTINUOUS GLUCOSE SENSOR PROFILES IN HEALTHY NON-DIABETIC SUBJECTS

PROTOCOL

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CHAPTER 1: INTRODUCTION

1.1 Background and Rationale

Studies aimed at improving glycemic control or preventing hypoglycemia often use continuous glucose monitoring (CGM)-measured percentages of glucose sensor values within, above or below glucose targets and glucose variability as outcome measures. Knowledge of the expected frequencies of each metric in a nondiabetic population is important for comparative purposes. The JDRF CGM RCT Study group previously assessed sensor profiles in a population of 30 non-diabetic participants in each of 4 age groups (i.e., 8 to <15, 15 to <25 and 25-45 and >45 years of age) using older generation sensors including the Dexcom STS Continuous Glucose Monitoring System™ (Dexcom, Inc., San Diego, CA), the Paradigm®/Guardian® REAL-Time Continuous Glucose Monitoring Systems (Medtronic Minimed, Northridge, CA) and the FreeStyle Navigator™ Continuous Glucose Monitoring System (Abbott Diabetes Care, Inc.)(1). Sensory accuracy has improved substantially since that time.

It would be extremely useful for comparative purposes to establish a reference range of sensor values using current generation of sensors in healthy, non-diabetic control participants. For example, determination of the frequency of sensor-derived, interstitial glucose concentrations that are <70 mg/dl in healthy subjects using current generation sensors will be particularly important in assessing the ability of closed loop systems to prevent hypoglycemia in subjects with T1D. The goal of this study is to establish a reference range of sensor values using the current generation of sensors in healthy, non-diabetic control participants.

1.2 Protocol Synopsis

1.2.1 Study Objective

The primary objective of this study is to establish reference sensor glucose ranges in healthy, non-diabetic individuals using a current generation CGM sensor.

1.2.2 Study Design

This will be a multi-center, observational study and will consist of up to 10 days of CGM sensor wear.

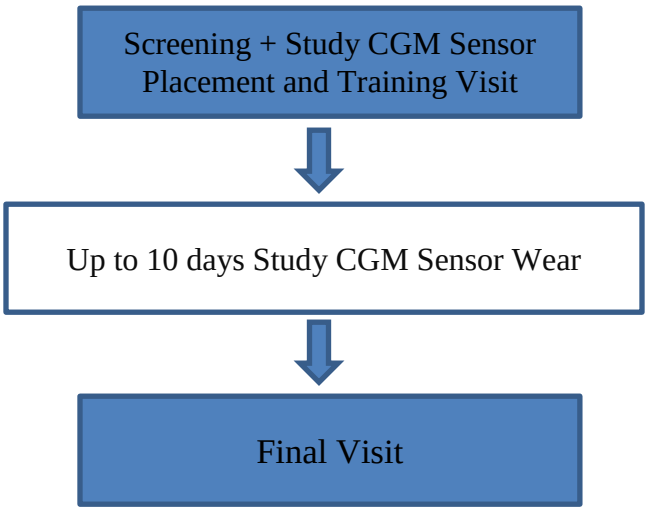
1.2.3 Sample size

65 individuals

1.2.4 Major Eligibility Criteria

- Age ≥ 6 years
- Body mass index (BMI) <30 in adult subjects and between the 5th to 85th percentile for age and sex for pediatric subjects
- No significant chronic illness or currently taking any acute or chronic medications that might affect glucose metabolism.
- No history of diabetes– participants with HbA1c ≥5.7% will be excluded
- Negative pregnancy test results for females of child-bearing age.

1.3 Study Flow Chart



** If there are less than 72 hours of sensor data available and the participant is willing to wear the sensor again, an additional sensor will be inserted and the participant will return to the clinic following the second period of sensor wear. If there are less than 72 hours of data and it is not repeated, the participant may be replaced.*

1.4 General Considerations

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

The risk level is considered to be research not involving greater than minimal risk.

A risk-based monitoring approach will be followed, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013).

The blinded CGM sensor used in this study will be provided by Dexcom, Inc. The Dexcom G6 will not be FDA approved for use during this study and therefore its use in this study will be investigational. However, since the study participants do not have diabetes and the glucose values from the blinded CGM will not be used any medical management, the investigators have determined that this protocol meets the criteria to be classified as a nonsignificant risk device study as it does not meet any of the criteria from section 812.3 (m) of the FDA investigational device exemption regulation 21 CFR 812. As such, an IDE is not required. The study will include use of the Dexcom G6 system kits by multiple participants. A validated cleaning procedure will be used in order to provide a safe and effective method of decontaminating the kits against blood borne pathogens prior to a new participant using the device.

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

CHAPTER 2: ELIGIBILITY

2.1 Study Population

Approximately 65 healthy non-diabetic individuals ≥6years old will be enrolled in the study across 2-4 T1D Exchange clinics. Across the sites, the study will aim to enroll approximately 32 children <12 years of age. Participants not completing the study may be replaced. Participants with a central lab HbA1c of ≥5.7% or positive antibodies also may be replaced.

2.2 Eligibility

To be eligible for the study, a subject must meet the following inclusion criteria and none of the exclusion criteria:

2.2.1 Inclusion Criteria

1) Age ≥6 years
2) Body mass index (BMI) <30 in subjects ≥18 years old and between the 5th to 85th percentile for age and sex for subjects <18 years old

2.2.2 Exclusion Criteria

1) History of diabetes
2) Point of care (POC) HbA1c ≥5.7%
3) The presence of a significant medical disorder that in the judgment of the investigator will affect the wearing of the sensors, glucose metabolism, or the completion of any aspect of the protocol
4) The use of any steroid or other medication that in the judgment of the investigator will affect the wearing of the sensors, glucose metabolism, or the completion of any aspect of the protocol
5) Participation in another pharmaceutical drug or device study at the time of enrollment or during the study
6) Females who are pregnant at the time of study enrollment

2.3 Informed Consent

The study will be presented to and discussed with potential adult subjects and parent/legal guardians of potential pediatric subjects. Adult subjects will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. If they agree to participate the Informed Consent Form will be signed. For pediatric subjects, the parent/guardian will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. The subject will be given the Child Assent to read or it will be read to the child. If the parent and child agree to participate, the Informed Consent Form and Child Assent Form will be signed.

As part of the informed consent process, each subject (and parent for minors) will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review what study specific information will be collected and to whom that information will be disclosed. After speaking with the subject (and parent for minors), questions will be answered about the details regarding authorization.

CHAPTER 3: STUDY PROCEDURES

3.1 Initial Visit

3.1.1 Initial Study Procedures

After informed consent (and assent where age appropriate) is signed, a history will be elicited (including family history of diabetes and menstrual cycle details), a limited physical examination performed, and a POC HbA1c measurement obtained to verify eligibility. Tanner staging will be performed to assess puberty stage for applicable age groups. The following central laboratory samples will be obtained. Participants can proceed in the study prior to the results being available; however, the results will be used to determine inclusion in the analyses.

- HbA1c
- Anti-GAD, anti-IA2,anti-insulin antibodies, and zinc-transporter-8 autoantibodies

3.1.2 Sensor Placement and Training

A CGM sensor will be inserted and the subject (and legal guardian) will be instructed on its use and care. The device will be blinded so that the participant is not able to see the sensor readings. The sensor will be inserted and initiated by the study personnel. The sensor will be worn for up to 10 days.

The participant will be provided with a study blood glucose meter (BGM) and test strips for manufacturer-required calibrations.

3.2 CGM Sensor Wear Period

3.2.1 CGM and BGM

Subjects will be instructed to use the CGM for up to 10 days, calibrating with the study BGM as needed per manufacturer specifications.

3.2.2 Completion of Home Log

The subject (and parent) will be instructed to complete a log each day indicating times and intensity of any exercise, start times of meals, snacks, and alcohol intake, as well as sleep and wake times.

3.3 Final Visit

The subject (and parent) will return approximately 10 days after the blinded CGM sensor was placed.

The sensor will be removed and the CGM data will be downloaded. The study BGM also will be downloaded and the completed home log will be collected.

The CGM data will be reviewed to assess whether the subject has used the CGM for at least 72 hours (equivalent to 3 days)

- Subjects not meeting the CGM usage requirement may be given a second opportunity to wear the blinded CGM sensor at investigator discretion
- If there are less than 72 hours of data and it is not repeated, the participant may be replaced.

Note: Subjects may also be provided with one or more activity trackers to use during the study. Data will be obtained at the final visit.

CHAPTER 4: ADVERSE EVENTS AND RISKS

4.1 Adverse Event Reporting and Monitoring

4.1.1 Definition

A reportable adverse event is any untoward medical occurrence that meets criteria for a serious adverse event or any device-related event listed below.

- Excessive pain or discomfort from system deployment (8 or greater on a 10-point Likert scale)
- Excessive bleeding
- Hematoma (slight ecchymosis is a known consequence of needle skin puncture and will not be captured as an AE)
- Excessive edema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Excessive erythema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Local infection
- Sensor or introducer needle fracture during insertion/wear/removal

Degrees of edema, erythema, or infection that may occur at the sensor insertion or adhesive tape site will be assessed by study staff. An AE will be recorded as severe in intensity if skin appearance indicates significant edema or erythema (per definition above) and/or if infection, defined as the presence of pus, at the sensor insertion or adhesive tape site occurs.

4.1.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the study participant, and appropriate medical intervention will be made.

All reportable adverse events whether volunteered by the parent of the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported on an adverse event form online. Each adverse event form is reviewed by the Medical Monitor at the Coordinating Center to verify the coding and the reporting that is required.

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device or study procedures.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events will be coded using the MedDRA dictionary.

Adverse events that continue after the study subject's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

4.1.3 Reporting Serious Adverse Events and Unexpected Adverse Device Events

A serious adverse event is any untoward occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.
- Could have resulted in death, be life-threatening, or require hospitalization without medical or surgical intervention to prevent any of these events

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 10 business days after the Coordinating Center becomes aware of the event.

4.2 Risks and Discomforts

4.2.1 Skin Reactions

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

4.2.2 Finger stick Blood Glucose Measurements

Finger sticks for calibrating the CGM may produce pain and/or ecchymosis at the site.

4.2.3 Blood Draw for Antibodies

There may be pain involved with the blood draw for testing of antibodies. There is a small risk of bleeding under the skin that will produce a bruise.

4.2.4 Anxiety

It is possible that subjects will be diagnosed with diabetes as a part of this study. It is also possible that subjects will have indicators that suggest that they are likely to develop diabetes in the future. This knowledge may cause anxiety or concern for subjects. If this happens, the clinic personnel will be available to answer any questions the subjects may have.

CHAPTER 5: MISCELLANEOUS CONSIDERATIONS

5.1 Benefits

There will be no direct benefit to the subject from participating in this study. By helping to establish a normal range of sensor glucose values in non-diabetic subjects, the subject's participation in this study is an important contribution to the development of a better understanding of the ability of CGM devices to restore glucose metabolism to normal in patients with diabetes.

5.2 Participant/Parent Reimbursement

Participants completing the study will receive a $100 payment to cover the study visits and completion of the home log. The payment may be prorated for subjects who only partially complete the study.

5.3 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. The investigator may withdraw a subject who is not complying with the protocol.

5.4 Confidentiality

For security purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. During each visit, the study devices will be downloaded to a computer that is secured and password protected and the files will be uploaded to the Coordinating Center via the secure website for the study. All files will include only the participant's identifier; no names or personal information will be included.

Laboratory specimens will be sent to a central laboratory for the study. Data from the study may be provided to Dexcom, Inc., the company that makes the CGM. Data may also be provided to the companies that manufacture the activity trackers.

5.5 Discontinuation of the Study

A study participant may be discontinued from the study if the investigator believes that it is not safe for the participant to continue.

The study may be discontinued if recommended by the study investigators for safety or other reasons or if funding for the study is lost.

CHAPTER 6: STATISTICAL CONSIDERATIONS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study.

6.1 Sample Size

The sample size is a convenience sample and is not based on statistical principles.

6.2 Data Tabulations

Only participants with: (1) central laboratory HbA1c <5.7% and no pancreatic antibodies and (2) at least 72 hours of CGM data with at least 24 hours overnight will be included in the analyses.

Results will be tabulated overall and for daytime (6am-12midnight) and overnight (12mn-6am), with daytime and nighttime periods also defined by the log in separate analyses.

- Distribution of minimum and maximum glucose level for each participant
- Frequency distribution of sensor glucose at each 10 mg/dl interval, eg 40-49, 50-59, 60-69
- Percentage of participants with one or more sensor values <70/60/50 mg/dL and percentage of values <70/60/54/50 mg/dL
- Percentage of participants with one or more sensor values >140/160/180 mg/dL and percentage of values>140/160/180 mg/dL
- Median and quartiles of glucose concentrations overall
- Standard deviation and/or coefficient of variation
- Mean and standard deviation of post-prandial peak glucose concentration and time to peak for each meal/alcohol intake
- Mean and standard deviation of minimum and maximum glucose concentration during and after exercise
- Differences in mean and nadir glucose values during the overnight period between sedentary days and days with afternoon exercise
- Relationship between sensor mean glucose concentration and A1c
- Relationship between sensor mean glucose concentration and age

REFERENCES

1. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study G, Fox LA, Beck RW, Xing D. Variation of interstitial glucose measurements assessed by continuous glucose monitors in healthy, nondiabetic individuals. Diabetes Care. 2010;33(6):1297-9.