Use of continuous glucose monitoring system with intensive feedback in adolescents with poorly controlled type 1 diabetes
Version Date: 04/26/2018

Study Summary

Title	Use of continuous glucose monitoring system with intensive feedback in adolescents with poorly controlled type 1 diabetes
Short Title	Use of continuous glucose monitoring system with intensive feedback in adolescents with poorly controlled type 1 diabetes
Protocol Number	16-01011
NCT Number	NCT03020069
Principal Investigator	Dr. Bonita Franklin
Methodology	Randomized open label
Study Duration	Estimated duration for the main protocol (e.g. from start of screening to last subject processed and finishing the study)
Study Center(s)	Single-center or multi-center. If multi-center, note number of projected centers to be involved.
Objectives	to determine if using a glucose sensor helps adolescents with t1D understand their range of options in controlling their diabetes
Number of Subjects	60
Diagnosis and Main Inclusion Criteria	Adolescents with type 1 diabetes and an HbA1c > = 8 %

Type 1 diabetes (T1D) is one of the most common chronic diseases presenting in childhood. The prevalence ranges from 1 case per 1430 children at 5 years of age to 1 case in 360 at 16 years of age worldwide in the last few years. The incidence of TIDM has increased by about 2-3 % each year. Management of T1D requires frequent blood glucose monitoring, insulin injections and careful attention to diet. Hemoglobin A1c is a measure of average blood glucose over the prior 60-90 days. The 2014 ADA goal for target HbA1c in adolescents is below 7.5 % but this is seldom achieved. There are multiple challenges to managing T1D in adolescents. The insulin requirements are constantly changing as adolescents go through puberty, lead more independent lives and make their own food choices. In addition, adolescents may not feel the need to work hard to control their diabetes as they feel healthy and have a sense of invulnerability and immortality. Tight blood glucose control requires frequent changes in the insulin regimen and pattern recognition. Even when patients check blood glucose levels regularly, it is measured only 4-8 times per day while fluctuations in blood glucose occur continuously. Introduction of continuous glucose monitoring (CGM) provides a measure of blood glucose level every 5 minutes. CGM is FDA approved for use in children as an adjunct to but not a replacement for capillary blood glucose testing. In the Type 1D exchange clinic registry {Wong, 2014 #75}, 9 % of over 17,000 participants used CGM (6% of children <13 years old, 4% of adolescents 13 to <18 years, 6% of young adults 18 to <26 years, and 21% of adults ≥26 years). On July 21, an FDA advisory panel voted 8-2 to allow patients to use Dexcom's G5 CGM data for making treatment decisions without a finger stick verification. Society representative Dr. Nicholas Argento testified in support of the label change citing the device's safety and the need for additional guidance on how to use unverified CGM data effectively. The panel's recommendation will now be considered by the FDA which, if accepted, will carve a path forward for Medicare coverage of the device. Currently CGM is not universally covered by private insurance. This wealth of information could theoretically allow adolescents to understand their diabetes better as well as help the physician in making changes in insulin regimen while avoiding hypoglycemia. Studies in adults have shown CGM significantly lowers HbA1c levels without increasing risk for hypoglycemia. However research has shown that HbA1c did not improve in adolescents with T1D placed on CGM (presumably due to the lack of consistent use) but HbA1c was lowered in young children and adults on CGM. While development of a closed loop system for diabetes management will require CGM, adolescents are often resistant to wearing the CGM device.

AIM:

To determine if short-term use of continuous glucose monitoring systems (CGMS) with intensive real time feedback about diabetes management from medical staff to the patient will affect motivation and/or behavior, in adolescents with poorly controlled type 1

diabetes. Previous CGMS studies have tended to focus on participants who are in better glycemic control at baseline and who report better adherence and diabetes-related quality of life than expected of a randomly selected sample of subjects with type 1 diabetes.

Studying a more broadly representative group that includes subjects with poor glycemic control will provide helpful information about glycemic and psychological effects of CGMS in an at risk group(1). Research indicates that various psychological skills and psychosocial factors, including coping and social support play a large role in the efficacy of CGMS use(2).

We hypothesize that short-term CGMS use with feedback (and/or lack thereof) and patients' sense of self-efficacy will influence their stage of change and potentially glucose levels.

SUBJECTS:

Sixty adolescents, ages 13-22 years, with type 1 diabetes and an HbA1c > = 8 % who are also naive to CGMS or who have not used a CGMS in at least six months use will be recruited from the diabetes outpatient population followed at Bellevue Hospital, Lutheran Hospital, Woodhull Hospital, and the NYU Fink Pediatric Ambulatory Care Center. Forty subjects will be randomly assigned to the CGMS group and 20 subjects will be assigned to the control group.

Screening procedures to determine eligibility:
At the medical appointment for each patient to determine eligibility for the study the research personnel will verify age, diagnosis of t1D, and HbA1c from data in the electronic medical record, investigator will also determine if the potential subject has any exclusion criteria listed below.

Exclusion Criteria:
Patients with developmental delay, and patients who do not use a glucose meter to test capillary blood glucose level, and patients without access to a telephone will be excluded.

METHODS:

Throughout the study, all communication with the subject and his/her parent will be conducted in the preferred language of the patient and in that of his/her parent. If required, an interpreter will be utilized by telephone.
An introduction to the relationship between HbA1c, average blood glucose, and the complications of chronically elevated blood sugar levels will be provided during recruitment. Potential subjects will be identified at their regularly scheduled clinic

appointments and staff will determine if they are interested in participation in the study using a recruitment script uploaded under recruitment materials section.

The study is minimal risk (MR). The device is approved by the FDA and is being used according to its cleared/approved labeling. The probability and magnitude of harm or discomfort anticipated in this research is similar to those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

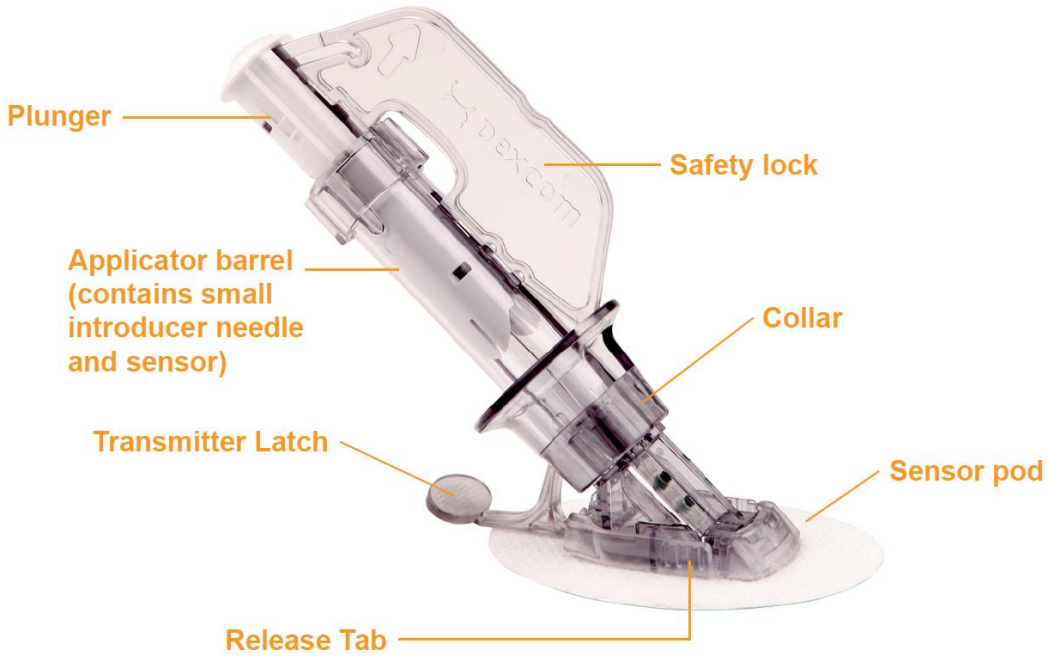
The use of the CGMS will be described.

The study will consist of 4 phases.
1: For all participants at entry into the study the participant's HbA1c will be measured in the lab at the location of the patient's visit and his/her glucose meter will be downloaded as part of routine care. The average capillary glucose level, (with range and standard deviation) and the average number of tests per day over the prior 14 days will be recorded. The current individual care plans for self-management of type 1 diabetes will be reviewed by the study personnel with the participant.

Questionnaires will be administered to all the participants except Appendix F:
1) Appendix A - Stages of Change measure (original). We created a 5 item questionnaire to assess the patient's current stage.
2) Appendix B - Psychosocial self-efficacy (University of Michigan Diabetes Research and Training Diabetes Empowerment Scale short-form) - DES. 8 items. Also available for use.(3-6)
3) Appendix C - Knowledge and risk perception (University of Michigan Diabetes Research Training Center Diabetes Knowledge Scale). 23 items - DKT. We are substituting rapid acting insulin for NPH insulin in item 17 since NPH is not used in our study population. Available for use without permission as long as the source is quoted.(7, 8)
4) Appendix D - Quality of life (Peds QL 3.2, Diabetes module,)[1] – Peds QL. 33 items on a Likert scale.(9)
5) Appendix E - Depression (PHQ-2.). 2 items. If the patient receives a score of 3 or above, a referral to psychiatric services will be made. No permission required to reproduce, translate, display or distribute.(10, 11)
6) Appendix F – CGM Satisfaction Scale. To be administered at second visit. See below number 2 on protocol. Will only be administered to study group.
7) Appendix G - Demographic variables will be collected.
8) Appendix H - Telephone administered questionnaire.
9. Appendix I – data to be tabulated in research database in RedCap

Standard scoring will be used for the DKT, DES, PHQ-2 and Peds QL.
Standard scoring instructions will be followed for published tests.
The CGMS will be used only in the study group. The CGMS that will be used will be Dex-COM® which consists of the sensor, transmitter and the receiver. The Dec-COM CGM device is FDA approved for use in patients 2 years and older.

Sensor - The sensor is packaged in a sterile sealed pouch, containing an applicator, sensor pod and sensor wire. The applicator barrel helps to insert the sensor wire inside the sensor pod under the skin. After inserting the sensor wire, the applicator barrel is removed. The sensor wire stays in the sensor pod with the pod attached to the skin by adhesive. The sensor wire is made of silver and platinum with polymer membranes. Once inserted, the thin and flexible wire measures the glucose levels in the fluid between the cells (interstitial fluid) for up to seven days. Dexcom sensor is inserted in the belly/abdomen (ages 2 years and older) or the upper buttocks (ages 2 to 17 years). The sensor is water resistant



Transmitter - Snapping into the sensor pod, the gray plastic transmitter wirelessly sends your glucose information to your display devices—receiver. The transmitter is re-usable and water-resistant.

Receiver - The receiver is a small hand-held device. The receiver shows the sensor glucose readings, trend graphs, trend arrows and alerts you when your glucose is too high or too low or if there is something you should be aware of or need to do. The receiver is neither water resistant nor waterproof and can get damaged if moisture gets inside, so keep it away from any liquids and very high humidity.

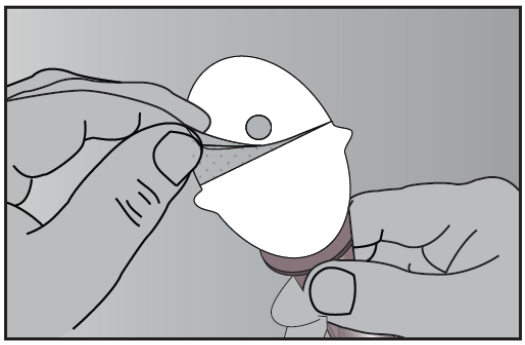
Adverse Effects / Risks.
Inserting the sensor and wearing the adhesive patch might cause infection, bleeding, pain or skin irritations (redness, swelling, bruising, itching, scarring or skin discoloration). There is a low chance of this happening. In the clinical study for the Dexcom G4 PLATINUM System, only slight redness and swelling occurred in a few patients. If any of these events happen, the patient might feel discomfort in the area the sensor is inserted. There is a remote chance that a sensor fragment could remain under your skin if the sensor breaks while patient is wearing it. This did not happen in the clinical study for the Dexcom G4 PLATINUM System. If you think thinks a sensor has broken under your skin, he shall contact contact the study personnel and call Dexcom's Technical Support. Sensor breakage may cause some anxiety, but it is not a significant medical risk.

Contraindications.
The Dexcom sensor, transmitter, and receiver must be removed before Magnetic

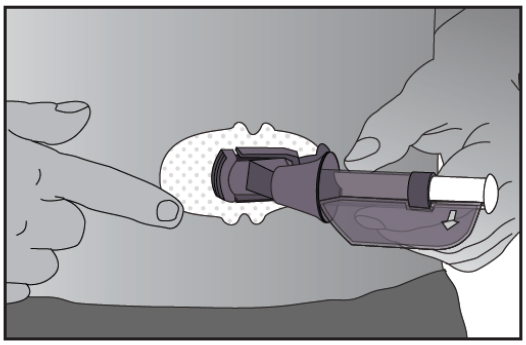
Resonance Imaging (MRI), Computed Tomography (CT) scan, or diathermy treatment. The device is MR Unsafe. The magnetic fields and heat could damage the device so that it might not display sensor glucose readings or provide alerts, and patients might miss a low or high blood glucose value.
Taking medications with acetaminophen (such as Tylenol) while wearing the sensor may falsely raise the sensor glucose readings. The level of inaccuracy depends on the amount of acetaminophen active in the body and may be different for each person.

Benefits.
Real-time CGM provides benefits beyond the information one gets from a blood glucose meter. It provides glucose readings every five minutes for up to seven days to help detect trends and patterns in glucose levels. This trend information can help you see where the glucose is now as well as where the glucose may be heading and how fast the patient may be getting there. Understanding the glucose trends may help take action to help avoid high or low glucose values. Alerts and the low alarm tell when your glucose is outside of the target glucose range and may help avoid low and high blood sugar. Rise and fall glucose alerts can also provide benefit by alerting when your glucose is rapidly going down or up. This way the patient can be alerted to this information before the glucose is too high or too low and take action to avoid it. Real-time CGM can help increase time in the target glucose range without increasing time in the low or high glucose range. Real-time CGM can help improve diabetes control (lower A1c values, reducing glycemic variability and time spent in low and high blood glucose ranges) which can help reduce diabetes related complications. In some cases, patients perceived an increase in their quality of life and peace of mind when using real-time CGM as well as reporting a high satisfaction with CGM.

Inserting the Device.
It is necessary to choose an area that is at least 7.62 cm from where the insulin can be injected or from where the pump infusion site is located.
1. Clean the area first with an alcohol wipe. Make sure the area is clean and completely dry before the sensor is inserted.
2. Using the white tabs on the adhesive backing, remove the adhesive backing from the sensor pod one half at a time. Hold the sensor by the applicator barrel and try not to touch the sticky adhesive patch.
3. Place the sensor flat on the selected area, to the left or right of the belly button. Make sure the sensor is placed in the same direction shown in the picture below. One not place the sensor pointing in the up or down direction.

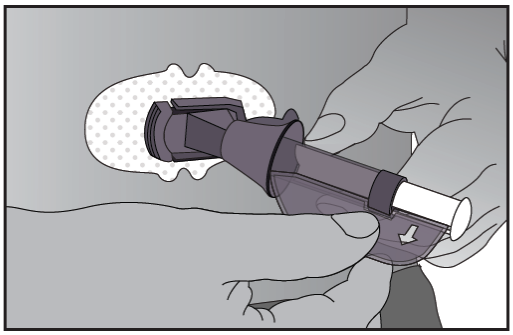


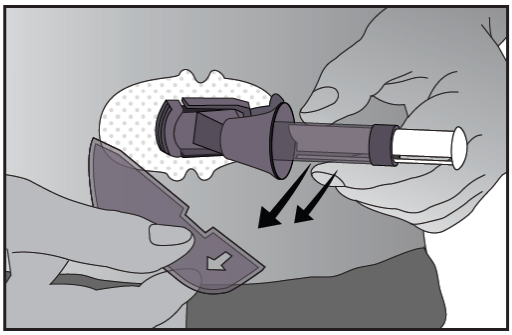
Remove the adhesive backing



Adhere the sensor on the skin

4. Press the finger firmly around the adhesive patch to make sure it is smooth.
5. Hold on to the applicator. Then pull the safety lock straight out away from the applicator, in the direction the arrows show in the following picture.





Remove the safety lock

Once the sensor is inserted, we need to snap the transmitter into the sensor pod. Follow the steps below to attach the transmitter.
1. Clean and dry the bottom of the transmitter with a damp cloth or an alcohol wipe before every use.
2. Place the transmitter in the sensor pod with the flat side facing down.

3. With one hand, pinch up on your skin at the front edge of the white adhesive.
a. Place one finger on the transmitter to keep it in place while securing the transmitter into the sensor pod.
b. Pull the transmitter latch over the transmitter to snap the transmitter into place. The transmitter should lie flat in the sensor pod. We should hear 2 “clicks.” If we do not hear 2 “clicks,” the transmitter might not be fully snapped in. We can release your pinch on the adhesive edge at this time.
c. Make sure the transmitter is secure by sliding your first and second fingers under the sensor pod wings and press down on the transmitter with your thumb.

4. Hold the transmitter in place with one hand. Using your other hand, remove the transmitter latch by holding the end of the latch and quickly twisting off the latch away from your body.

The use of the CGMS (Dex-COM ®) device will be explained and the device placed on the subject's abdomen by a trained study personnel. The participant will be instructed to continue to perform capillary glucose testing as usual at home, and to calibrate the Dex-COM ® at least twice daily. The participant will be encouraged to review the CGMS readings as often as possible, particularly before meals, bedtime, and 1-2 hours after eating. If the glucose result on the CGMS is >= 300 mg/dl, or <= 80 mg/dl, he/she will be instructed to verify the results by using the glucose meter, follow the usual care instructions and then call the Pediatric Diabetes team for advice. An alarm upper limit will be set on the CGMS device at 300 mg/dl, and a lower limit at 80 mg/dl. He/she and the investigator will agree on a time of day for daily phone contact. The phone advice will be based on standard medical management of type 1 diabetes mellitus, focusing on details of insulin dosing, carbohydrate counting, and exercise. A tally will be kept of the number of daily phone calls completed with the medical staff and the participant. The parent will be able to speak to the medical staff during phone calls, but the primary contact will be with the adolescent participant.

2: Study visit # 2 will be in 1 week from the initial visit for both the study and control groups. The patients in the study group will return the CGMS device at the time of the 1 week appointment. The glucose meters of all participants will be downloaded, and the data will be extracted as above. The Empowerment Scale short form and the measure of Stages of Change will be administered to both groups. A brief questionnaire about the participant's response to use of CGMS will be given to the study group (CGM Satisfaction scale – Appendix F). Study and control groups will both be given a $50

reimbursement for time and travel.
3. Study visit #3 will be scheduled at 1 month for both the study and control groups. The patient's glucose meter will be downloaded and the data will be extracted as above. The Empowerment Scale short-form, Quality of Life, Family Management Measure and the Stages of Change questionnaires will be administered. There will be an open-ended interview with the participant. The patient will be given $20 on completion at this visit.

4: Study visit #4 will be scheduled at 3 months for both the study and control groups. The patient's HbA1c will be measured in the lab at the location of the patient's visit, his/her glucose meter will be downloaded and the data will be extracted as above. The Empowerment Scale short-form, PHQ-2, Quality of Life and the Stages of Change questionnaires will be administered. The patient will be given $20 on completion at this visit.

CONSENT:

The study personnel will describe the procedures: filling out the questionnaires, wearing the CGMS device for 1 week, participating in daily phone calls with study personnel for the 1 week when the device is used, and the requirements of returning the CGMS device, and of bringing the glucose meter to all appointments. The participant and his/her parent must sign the consent for these items. The study personnel will change the sensor in 1 week to put a new sensor for the second week.
The use of the CGMS device involves the insertion of a subcutaneous sensor that will transmit data to the CGMS receiver which is carried by the subject. Minor skin irritation or bruising may occur, and there is a low risk of skin infection. Restrictions in terms of submersion in water will be described and consented. The Dex-Com ® CGMS device is FDA approved for use in children and adolescents with type 1 diabetes.

ANALYSIS:

Measures of the level of glycemic control will be assessed primarily by HbA1c and secondarily by the average glucose tests results on the patient's glucose meter. Comparison of the glucose results (average, range, standard deviation, number of daily tests) between the study entry, 1 week, 1 month and 3 month follow up visits will be done. Comparison of HbA1c at entry and at 3-month follow-up will be performed. Questionnaire scores will be compared between study entry, 1 week follow up, 1 month follow up and 3-month follow-up visits for DES and Stages of Change scales. We will determine if there is a correlation between the scores on the questionnaires and measures of glucose control. We will classify study and control participants into adherent and non-adherent groups.

Dichotomizing participants into adherent and non-adherent:
Study subjects will receive points for calibrating the CGM device and for successfully completing phone contact with the pediatric diabetes team. The patient will receive 2 points for calibrating the device 2 times/day for at least 5 days, 1 point for calibrating the device 2 times on at least 3 days and 0 points for calibrating any less. Similarly the patient will receive 2 points for completing successful phone contact with study personnel for at least 5 days, 1 point for completing phone contact on at least 3 days and 0 point for contact any less than mentioned before. The two scores will be added to get a total score. Patients with scores 3-4 will be classified as adherent and scores 0-2 will be classified as non-adherent. Control subjects who complete 4 or more phone calls on different days will be classified as adherent and those who complete fewer phone calls will be classified as non-adherent.

Statistical methods:
Demographic data will be tabulated. Statistical analysis of questionnaires will be done according to published standards. The paired t-test will be used for comparisons involving stages of change score.
Independent variables will include the empowerment score, average glucoses, HbA1c and whether the subjects fall into the adherent vs. non-adherent groups. Dependent variables include glucose level(s) and stage of change. We will analyze the 7 day average glucose by meter download and categorize the results in terms of change: No change (-15 to + 15), Higher (>= + 15) or Lower (<= -15). We will analyze the HbA1c and categorize the results in terms of change: No change (> -0.5 to + 0.5), Higher (>= + 0.5) or Lower (<= -0.5). Stages of change (Appendix A) will be categorized as unchanged, improved or worsened. In addition, descriptive statistics including quality of life, diabetes knowledge scale, and demographic variables will be tabulated.

Statistical Analysis for sensor study:
Questionnaires:
Demographics (Appendix G): data will be put in table form, with range, mean, s.d. scores for age; % Male/Female; and descriptive data for the remainder of the items. In Questions #11, 13 and 14, with 1-5 scales, the range, mean, and s.d. scores will be given.
Stages of Change (Appendix A): scores can be given categorically, with each question assigned a score of 1 for a “yes” answer, and zero for a “no” answer; then range, mean, s.d. will be calculated before and after the intervention. In addition, a “yes” or “no” answer to these questions will determine which “stage of change” category the subject belongs in, according to the definition of “stages of change”. This is categorical data. We will analyze movement in the “stages of change” by comparing the score before and after the study intervention. This will be categorical: improvement, no change, deterioration.

Diabetes Empowerment Scale-Short Form (Appendix B): the average of the scores of the completed items will be tabulated. Each question is answered as 1-5, and there are 8 questions. Thus, the scores can range from 1-5. The scores will be compared before and after study intervention.
Diabetes Knowledge Test (Appendix C): There are 23 multiple choice questions, scored as correct or incorrect. This will be administered only at baseline.
Peds Quality of Life 3.2 Diabetes Module: (Appendix D): There are 33 questions with Likert scale answers (0-4). Scores are transformed on a scale of 0-100. This test will be administered before and after the study intervention.
PHQ-2: (Appendix E): The score ranges from 0-6. The scores will be compared before and after the study intervention.
CGM Satisfaction Scale: (Appendix F): We are using an abbreviated version of a previously published CGM-SAT scale. Each question is scored 1-5 and the mean is calculated. This will be given after the intervention and only in the intervention group.
Daily Phone Log: (Appendix H): Scoring will be done for each day of the initial week of the study, in both CGM intervention group, and control group based on the following: Study subjects will receive points for calibrating the CGM device and for successfully completing phone contact with the pediatric diabetes team. The patient will receive 2 points for calibrating the device 2 times/day for at least 5 days, 1 point for calibrating the device 2 times on at least 3 days and 0 points for calibrating any less. Similarly the patient will receive 2 points for completing successful phone contact with study personnel for at least 5 days, 1 point for completing phone contact on at least 3 days and 0 point for contact any less than mentioned before. The two scores will be added to get a total score. Patients with scores 3-4 will be classified as adherent and scores 0-2 will be classified as non-adherent. Control subjects who complete 4 or more phone calls on different days will be classified as adherent and those who complete fewer phone calls will be classified as non-adherent.

The distribution of the data will be assessed using the Kolmogorov-Smirnov test. All categorical variables will be presented as mean +standard deviation. For categorical variables the differences between the compliant and non-compliant groups will be assessed using the Mann Whitney or rank order Wilcoxon test based on normality. For categorical variables independent sample t test will be used. Univariate analysis will be used to establish correlation between variables of interest.

Protocol Section 8: Data Safety Monitoring Plan:
Safety and Adverse Effects:
In case of unanticipated problems involving risk to subjects or others, such as intercurrent illness or experience that develops or worsens in severity during the course of the study, or worsening of a pre-existing condition, the P.I. will be notified and determine if this event is related to the study, if further medical investigation must be done, if the event is

of clinical significance, and if the subject should be withdrawn from the study. Since this study does not involve changing the subject's current medical care for t1D it is not anticipated that the study will result in serious or important adverse events, such as hospitalization or surgery. If there are any adverse events, even if considered non-serious, these will be addressed by the P.I. as appropriate, and reported from the initiation of the study to the end of the study (the study period of 3 months plus 30 days). All unresolved adverse events will be followed by the P.I. until the events are resolved, the subject is lost to follow-up, or the adverse event is explained.
At the last scheduled visit, the P.I. or research personnel will instruct each subject to report any subsequent adverse events so that these may also be recorded and documented.

General Physical Examination Findings
At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will be recorded and documented as an adverse event.

Abnormal Laboratory Values
A clinical laboratory abnormality will be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. discontinuing use of the CGM device.

Recording of Adverse Events
At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though should be grouped under one diagnosis.

Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

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Reporting of Serious Adverse Events and Unanticipated Problems

Investigator reporting: notifying the IRB

P.I. will submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**

Other Reportable events:
P.I. will make a prompt report to the IRB, though ***no later than 5 working days for***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Process
Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form), or in a narrative format.

Stopping Rules

Since this study is low-risk to subjects there is no need to develop a safety endpoint

Medical Monitoring

The Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Protocol Section 9: Data Handling and Record Keeping;

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Research personnel will obtain a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If

a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Records Retention

The study data will be entered into RedCap.
REDCap is a secure web application for building and managing online surveys and databases. The study will use REDCap's process for both surveys and data collected during this study.

The principal investigator will retain study essential documents for at least 2 years after the last IRB approval .

Protocol #10: Study Monitoring, auditing and inspecting Plan:

Study Monitoring Plan

This study will be monitored according to the monitoring plan. The investigator will allocate adequate time for such monitoring activities. The P.I. will verify that the subjects in the study have signed consent/assent to participate, and that the documentation at each study visit is complete. The P.I. will also review the database, including survey material, lab results, clinical assessment, and subjective responses of the subjects in the study. If any adverse events occur the P.I. will adhere to the required reporting protocol.

The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

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