Center for Diabetes Technology

Feasibility of a Decision Support System To Reduce Glucose Variability In Subjects with T1DM

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A. Purpose/Objectives

The purpose of this study is to demonstrate the safety and feasibility of a decision support system aimed at reducing glucose variability in T1DM patients using continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI). The system will be deployed on our portable medical application platform (DiAs) and will include the following elements:

1. An insulin pump or MDI treatment parameters optimization routine, using a month of collected CGM/insulin/meal data
2. An exercise risk warning system, capable of predicting hypoglycemia at the onset of physical activity and advising on mitigating treatments such as insulin adjustment or carbohydrate consumption
3. A smart bolus calculator based on CGM glucose measurements and insulin sensitivity estimation.

Primary Specific Aim:

To demonstrate feasibility and safety of a glucose variability-reducing decision support system, measured by non-inferiority of use of the system compared to standard SMBG-informed CSII or MDI therapy in terms of occurrence of hypoglycemia and percent time spent between 70 and 180 mg/dl as measured by blinded CGM.

Secondary Specific Aims:

To assess the effect size of using the GV advisory system compared to standard CSII or MDI therapy in terms of:

- Occurrence of hypoglycemia during and immediately after exercise
- Glycemic excursion post meals

B. Study Design Overview

Subjects**:** The study is intended to complete up to 20 subjects with Type 1 Diabetes Mellitus who use continuous subcutaneous insulin infusion (CSII) and up to 20 subjects with Type 1 Diabetes Mellitus who use multiple daily injections (MDI). The study will be a randomized cross-over design with a Control and Experimental admission. The order of the admissions will be randomized. It is estimated that there will be a higher than normal rate of screen failures, dropouts, or withdrawals, thus we intend to set a recruiting target of **70 subjects**.

Procedure**:** Data collected during an approximately 28 day data collection period will be analyzed and will be used to optimize insulin parameters. ***These new parameters are the basis for the treatment optimization, requiring a minimum of 14 valid days during the 28 days of collection to advise the system.*** The collected basal rates or basal insulin dose, insulin sensitivity factor (ISF), and carbohydrate ratio data will be used to optimize the subject's insulin parameters (basal rates or basal insulin dose, insulin sensitivity factors and carbohydrate ratios). Subjects on MDI therapy will record this data into 'MySugr', an app that helps keep track of blood sugar levels, insulin dosages, meals, activities, mood and other information. The subject may also use a novel Bluetooth connected insulin pen, called inPen, for prandial dosing (Companion Medical, San Diego CA). The optimized parameters will be approved, modified or rejected by the study MD. CGMs will be blinded during the trial.

This system will only implement a retrospective optimization of the subject's insulin therapy, with defined limits in how much it can deviate from the original (See Appendix A-3 for details). This optimization is *then reviewed by the study physician prior to the Experimental admission*. The study physician is at liberty to accept, modify, or reject the advised optimal settings. A record of these decisions will be maintained. If a change in the basal insulin dose is recommended and accepted by the physician for an MDI user, the subject will be instructed to use the new basal dose(s) for approximately 5 days prior to the Experimental admission. Upon basal dose change, subject will be instructed to maintaina minimum of 7 SMBG per day, and clinical team will check back with the subject within 72h of dose change. Considering the limit of basal dose change, and the review by the study physician, such a procedure is well within the standards of care for T1D using MDI.

The CGM is only blinded to the subject. The clinical and technical teams have access to this information via remote monitoring (password protected on DiAs) during the study admissions. The CGM is blinded to the study participant to avoid CGM-induced glucose variability reduction, as it would cloud the analysis of the impact of the system.

Subjects will use their own insulin parameters, including basal rate or basal insulin dose insulin sensitivity factor and carbohydrate ratio, and determine their own insulin usage during the Control admission.

MDI subjects will be provided with an insulin pen (NovoPen Junior, NovoPen Echo, or Companion Medical inPen Smart Pen) with short-acting insulin for treatment during the Experimental admission. These pens are capable of delivering insulin in 0.5 unit increments and are FDA approved but for the Smart Pen which is under 510(k) review (see letter of Authorization). If this option is selected, the Companion Medical pen, known as the InPen, will be used in the trial. This insulin pen contains computer chip technology built into the base and

has Bluetooth LE wireless capability. It will collect the subject's data and then transmits it to an app that contains a dose calculator and also calculates real-time insulin on board (IOB). The insulin pen has remote monitoring, permitting the subject to inform the study team of their insulin dose, BG and carbohydrates. An inPen User Guide will be available to all MDI subjects if this smart pen is used in the trial. If this pen is not available at the time of the trial, a pen that can deliver in 0.5 unit increments will be used, such as the Lilly Luxura insulin pen.

The study is also designed to test the capacity of our exercise advisory system to avoid or limit exercise-induced hypoglycemia, by challenging the subject with two 3x15min exercise bouts.

Study Diagram

Visit 1: Screening Visit. All subjects will be consented and receive a history and physical. Study eligibility will be reviewed. After a subject completes the screening criteria, the subject will be randomized to the Experimental or Control admission first.

Visit 2: CGM Placement & Training. All subjects will receive training on the use of the continuous glucose monitor (CGM) and study glucometer prior to the Experimental admission. Approximately 28 days of **blinded** CGM data will be collected with a total of 14 valid days needed to participate in the research house/hotel admission. Visit 1 and 2 can be done on the same day.

Visit 3: Data Collection Period. Blinded CGM data will be collected prior to the Experimental admission and analyzed by the study team to determine the optimal insulin therapy parameters that will be used during the Experimental admission. For CSII users, the insulin pump and CGM downloads will be reviewed approximately 72 hours before the Experimental admission by the study team to ensure proper collection procedures. For MDI users, data entered into the MySugr app and CGM downloads will be similarly reviewed. Subjects will also wear a 'Fitbit' to collect information activity, exercise, heart rate, and sleep. An anonymous Gmail account will be established for each subject. An app will be placed on the subject's smartphone or subject's personal laptop to facilitate weekly downloading of the Fitbit data. Additional Data Collection Periods may be requested to ensure proper data collection.

Visit 4 and 5: Research House/Hotel Admission. The Experimental and Control admission will be separated by approximately 4 weeks, 8 weeks or 12 weeks. The order of these two visits will be randomly selected. Subjects will be admitted to the research house/hotel at ~16:00-17:00 and will be discharged after approximately 48 hours.

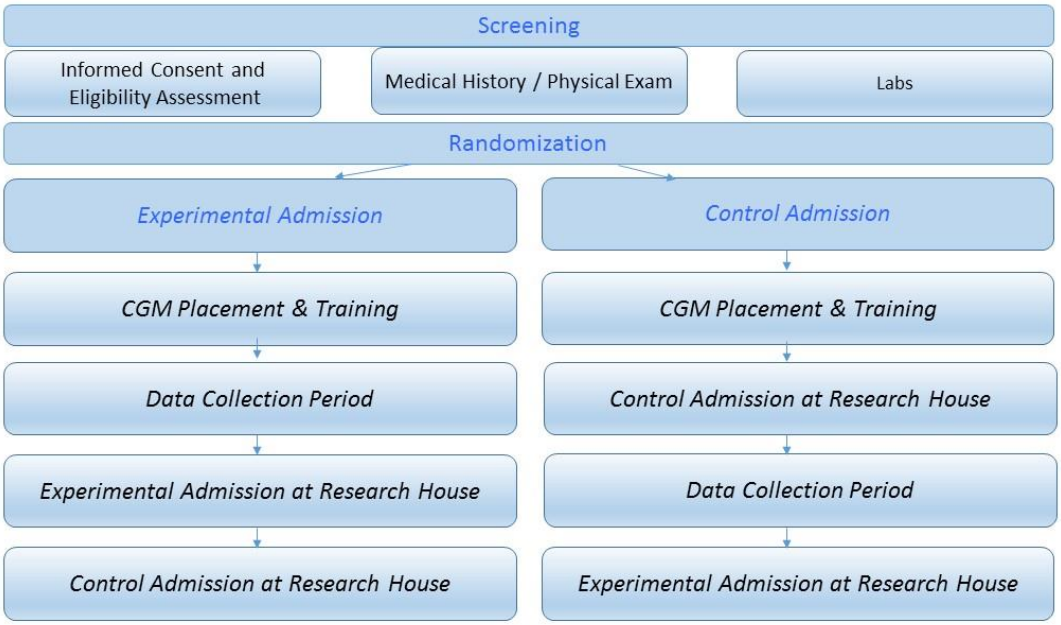

Figure 1: Study Design

C. Sample Size and Investigational Sites

This study will be conducted at the University of Virginia Center for Diabetes Technology (CDT). Twenty subjects (N=20) with Type 1 Diabetes Mellitus who use CSII and twenty subjects (N=20) with Type 1 Diabetes Mellitus who use MDI to treat their diabetes will be needed to complete the protocol. The studies will be conducted at the CDT Research House as noted below. The study may also occur at a local hotel. Vulnerable populations (i.e. pregnant women, prisoners, etc.) will be excluded from participation. Based on our experience with similar studies, we estimate an higher than normal screen failures, dropouts, or withdrawals due to the data collection requirements and admission time restrictions; thus we intend to set a recruiting target of 70 subjects.

As a safety/feasibility investigation, this study is not powered to a specific outcome. Nonetheless, based on prior work and computer simulations we estimate the likely effect size to be large (around 0.7); we therefore have chosen a sample size of 15-20 subjects for each group (CSII and MDI). Using a power analysis with a fixed sample size, significance and 0.8 power, this would allow us to detect an effect size larger than 0.67. In prior studies, 15 subjects have also been considered by regulatory bodies as an appropriate sample size to demonstrate safety in transitional settings for CGM based insulin dosing.

Investigational Site

The University of Virginia has granted the Center for Diabetes Technology the use of a facility designated Research House to perform outpatient studies related to the Artificial Pancreas Project. The facility is located 2.2 miles from the University of Virginia Emergency Department. It is a 4 bedroom/4 bath home with sleeping quarters on the first and second floors. The study team may test up to 3-5 study participants at the same time in the research house.

Minimal Staffing Requirements

At all times, a minimum of one registered nurse, trained in the execution of the protocol as well as in the management of hypo- and hyperglycemia, and a technician, trained in the use and maintenance of the DiAs system will be present during the entire trial. In addition, one of the study physicians and one senior engineer will be on call during the entire admission, with backup MDs and engineers available if the primary contact is unable to be reached. During exercise, there will be a minimum of one nurse per two subjects and one technician per two subjects on site. In the event of five study subjects tested during a single admission, two medically trained personnel will be available during the trial.

D. Study Duration

The duration of the study for each patient is intended to be up to 10 weeks. Subjects will be permitted up to a two month delay if unable to attend their second research house/hotel visit as initially scheduled. However, if more than 100 days elapse between the Control and Experimental admissions, the subject will be discontinued and replaced by another subject. Admissions to the research house may be repeated if the admission or the data collection is suspended or inadequate. Screening or re-screening labs can be done either at the UVA CRU or at a LabCorp that is convenient to the subject. Lab values collected from a prior medical appointment may be used if dated within 4 weeks of the screening appointment.

E. Inclusion and Exclusion Criteria

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

1. Clinical diagnosis based on investigator assessment, of type 1 diabetes for at least one year and either using insulin pump therapy for at least 6 months or MDI therapy for at least 6 months; 1-2 basal insulin injections per day, consistent in amount and timing (administering at approximately the same time each day). The following MDI therapy will be permitted:

- Subjects using Glargine (100 U/mL) once or twice daily.
- Subjects using Detemir (100 U/mL) twice daily.
- Subjects using Degludec (100 U/mL) once daily

A. Historical criteria for documented hyperglycemia (at least 1 must be met):

i. Fasting glucose ≥126 mg/dL.

ii. Two-hour OGTT glucose ≥200 mg/dL.

iii. Hemoglobin A1c ≥6.5% documented.

iv. Random glucose ≥200 mg/dL with symptoms.

v. No data at diagnosis is available but the participant has a convincing history of hyperglycemia consistent with diabetes.

B. Historical criteria for requiring insulin at diagnosis (1 must be met):

i. Participant required insulin at diagnosis and continually thereafter.

ii. Participant did not start insulin at diagnosis but upon investigator review likely needed insulin (significant hyperglycemia that did not respond to oral agents) and did require insulin eventually and used continually.

iii. Participant did not start insulin at diagnosis but continued to be hyperglycemic, had positive islet cell antibodies – consistent with latent autoimmune diabetes in adults (LADA) and did require insulin eventually and used continually.

2. Age 15– 65 years old.

3. Females, not currently known to be pregnant. If female and sexually active, must agree to use a form of contraception to prevent pregnancy while participating in the study. A negative urine/blood pregnancy test will be required for all premenopausal women who are not surgically sterile. Subjects who become pregnant will be discontinued from the study.

4. Demonstration of proper mental status and cognition for the study

5. CSII subjects must currently be using the bolus calculator function of the current insulin pump with pre-defined parameters for glucose goal, carbohydrate ratio, and insulin sensitivity factor.

6. MDI users must currently be using Intensive Insulin Therapy including carbohydrate counting and use of pre-defined parameters for glucose goal, carbohydrate ratio, and insulin sensitivity factor.

7. Willing to use Humalog (lispro) or Novolog (aspart) insulin during the study procedures for MDI subjects.
8. CSII subjects must be willing to use the current bolus calculator pump parameters and enter all carbohydrate intake into the pump during the 28 day data collection period.
9. MDI users must be willing to use their carbohydrate counting parameters for all meal dosing and enter the information into the MySugr app.
10. Ability to access the Internet to provide data to the clinical team or to travel to the research center so that the study equipment and personal pump can be downloaded.
11. An understanding of and willingness to follow the protocol and sign the informed consent.

Exclusion Criteria: The presence of any of the following is an exclusion for the study:

1. Diabetic ketoacidosis (DKA) in the 6 months prior to enrollment.
2. Severe hypoglycemia resulting in seizure or loss of consciousness in the 6 months prior to enrollment.
3. Current treatment of a seizure disorder.
4. Coronary artery disease or heart failure, unless written clearance is received from a cardiologist.
5. Atrial or ventricular arrhythmias (benign premature atrial contractions [PACs] and premature ventricular contractions [PVCs] allowed)
6. Cystic fibrosis.
7. Pregnancy, breast-feeding, or intention of becoming pregnant over time of study procedures.
8. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
    i. Inpatient psychiatric treatment in the past 6 months
    ii. Presence of a known adrenal disorder
    iii. Abnormal liver function test results (Transaminase >2 times the upper limit of normal); testing required for subjects taking medications known to affect liver function or with diseases known to affect liver function

iv. Abnormal renal function test results (calculated GFR <60 mL/min/1.73m2); testing required for subjects with diabetes duration of greater than 5 years post onset of puberty

v. Active gastroparesis

vi. If on antihypertensive, thyroid, anti-depressant or lipid lowering medication, lack of stability on the medication for the past 2 months prior to enrollment in the study

vii. Uncontrolled thyroid disease (TSH undetectable or >10 mlU/L); testing required within three months prior to admission for subjects with a goiter, positive antibodies, or who are on thyroid hormone replacement, and within one year otherwise

viii. Abuse of alcohol or recreational drugs

ix. Infectious process not anticipated to be resolved prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis, deep tissue infection).

x. Uncontrolled arterial hypertension (Resting diastolic blood pressure >100 mmHg and/or systolic blood pressure >180 mmHg).

xi. Oral steroids

xii. Uncontrolled microvascular complications such as current active proliferative diabetic retinopathy defined as proliferative retinopathy requiring treatment (e.g. laser therapy) in the past 12 months.

9. A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication or disease in the judgment of the investigator will affect the completion of the protocol.

10. Basal Rates <0.01 units/hour for CSII subjects.

11. Allergy for or intolerance of both Novolog (aspart) and Humalog (lispro) insulin for MDI subjects.

12. Diagnosed food allergies.

13. Current use of the following drugs and supplements:

i. Regular acetaminophen user, or not willing to suspend acetaminophen 24 hours before and during the entire length of the trial

ii. Any other medication that the investigator believes is a contraindication to the subject's participation

14. Any reason for which the study MD considers the subject not properly fitted for the trial (i.e. insulin pump that does not record what is needed for the trial).

15. Current enrollment in another clinical trial.

F. STUDY TIMELINE

a. Visit 1: Screening / Enrollment Visit

At the Screening Visit, the following procedures will be performed / criteria will be checked and documented:

1. Signed and dated informed consent
2. Inclusion and exclusion criteria
3. Demographics (date of birth, gender, race and ethnicity)
4. Medical history
5. Details of the diabetic history: duration of disease (number of years), diagnosis details, current treatment (including basal rates or basal insulin dose(s), carbohydrate ratios, insulin sensitivity factors, target glucose, average total daily insulin, history of DKA, history of severe hypoglycemia, and self-monitoring blood glucose values)
6. Surgical history
7. Menstrual history (females) and Sexual Activity/Contraception (females)
8. Allergies
9. Medications and supplements
10. Social history including drinking, smoking, and drug habits
11. Physical examination
12. Weight and height
13. Vital signs
14. EKG
15. Blood and Urine testing for screening labs:

- Hemoglobin A1c
- Comprehensive chemistry panel
- Pregnancy test: either urine or qualitative serum HCG in women with childbearing potential. If not performed, document reason (surgically sterile, postmenopausal)
- Thyroid stimulating hormone (TSH)

If a study subject has had a recent physical exam (less than 6 months) and blood work done (less than one month), the study physician will have the discretion to repeat any test as needed. Once all results of the screening evaluations are available, a decision will be made to determine the subject's eligibility for the study or if one or more parts of the screening will have to be repeated. If at the first screening or repeat screening an exclusionary condition is identified, the study subject will be excluded from participation and referred to their primary care physician as needed. If the study subject is pregnant, the study physician will discuss the results of the blood test with the subject and the subject will be asked to seek confirmation of the test and the appropriate medical care. If the study subject has an abnormal initial blood pressure, the subject will be allowed to relax for >10 minutes and have the blood pressure reassessed. Subjects may be re-screened at a later date if their clinical situation changes as determined by the study physician.

The total amount of blood to be withdrawn during the screening visit is ~22 cc. The screening visit will last approximately 2 hours. If the subject cannot schedule Visit 2 within 16 weeks of screening, screening labs, vital signs, and recent medical illness/medications will be re-evaluated. The study physician will have the discretion to repeat any test as needed.

If a subject meets all the study criteria, he/she will be enrolled in the trial and randomized to begin the Experimental or Control admit first. Visit 2 may be completed at the conclusion of Visit 1 if all eligibility requirements are met and the subject is randomized first to the Experimental admission.

All subjects will also be given instructions to avoid acetaminophen prior to their study intervention or to reschedule their study intervention if they require acetaminophen, as there is potential for interference with glucose oxidase systems for measuring glucose such as the CGM. These instructions will also advise the subject to contact the study team in the event of a febrile illness within 24 hours of the study intervention, so that the study outpatient admission can be rescheduled. All subjects will be given instructions to bring all of their current medications and CSII or MDI supplies with them for use during or after the admissions.

Ideally, the admissions will be 4 weeks apart. If the subject cannot schedule the second admission in 4 weeks, he/she may complete the admission 4, 8, or 12 weeks after the initial

admission (Visit 4). If the second admission has not been completed within 12 weeks after Visit 4, the subject will be discontinued from the trial.

Visit 2: CGM Placement & Training Visit

Continuous Glucose Monitor Training

1. An outpatient visit will be scheduled for training on the blinded CGM. Subjects that are currently using a CGM at home may use the study CGM in the unblinded mode during data collection.
2. Female subjects of childbearing potential will perform a urine pregnancy test, unless Visit 2 follows immediately after Visit 1. If the test is positive, the subject will discontinue study participation. The subject will be asked to seek confirmation of the test and the appropriate medical care.
3. The subject's insulin pump, CGM receiver, and the study glucometer will be set using atomic clocks as a reference.
4. The subject will be supervised during the initial CGM sensor placement. A CGM sensor will be inserted into fatty tissue under the skin and will stay attached 7 days and replaced per manufacturer directions.
5. If the CGM device experiences a sensor failure while at home, the subject will replace the sensor. The study team will be available for questions or will provide any necessary guidance.
6. The subject will be taught how to calibrate the CGM per manufacturer's guidelines. The subject will be asked to perform all required calibrations with fingerstick glucose measurements via the study glucometer.
7. The subject will be taught to look for skin irritation after sensor removal.
8. The subject will be reminded to avoid products containing acetaminophen 24 hours prior to wearing the CGM and while the CGM is in use.
9. If the subject requires an MRI, the sensor will be removed from the patient and the reason for removal will be noted. This will not be an adverse event. The visit may be rescheduled.
10. The outpatient visit will last approximately 2 hours depending on prior knowledge of the equipment.

11. The subject will be given an instruction sheet with 24-hour contact information of the research team to address any problems or questions.

12. Unlimited additional appointments and telephone calls to the study team and study physician will be available.

Study Glucometer Training

1. The study glucometer will be the same through all phases of the study (Visit 2-5) and will be used for glucose measurements, safety/data and calibration of the CGM.

2. Quality control testing will be performed on the study glucometer as recommended in the manufacturer guidelines. A tested glucometer will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling.

3. The subject will be trained on the use of the study glucometer and will demonstrate proficiency with a fingerstick test. The subject will be instructed that all fingersticks should be preceded by hand washing with warm water and a dry towel. The subject will be instructed to obtain fingerstick, avoiding alternative sites, when obtaining blood glucose (BG) values. The first drop will be discarded. The second hanging drop will be used to measure the glucose level.

4. The subject will be informed that all treatment decisions should be based on fingerstick values and not on CGM values.

5. The subject will be asked to obtain at least four BG fingerstick readings per day to comply with the study requirements. Two of these measurements must be upon the subject's waking up and at bedtime. Any additional BG tests normally done by the participant should continue without interruption.

Visit 3: Data Collection Period Prior to Experimental Admission

Special emphasis will be noted to the study subject that all meal information (i.e. carbohydrate quantity, insulin and SMBG) must be recorded in their insulin pump or in the MySugr app during the Data Collection Phase.

1. Data will be collected for approximately 28 days.

2. The subject will be instructed on how to download the equipment (i.e. personal insulin

pump, glucometer, CGM). The subject will be asked to provide downloaded data periodically during the month (approximately 3-5 times) using a web-based diabetes management system (e.g. Diasend, Carelink Pro, etc.) and local diabetes device management software (e.g. Dexcom Studio). The study team will review subject data to ensure proper data collection. Study team will review quantity and quality of the data. Additional download request may occur depending upon the quality of the data collected.

3. Subject will be advised to consistently use the bolus calculator (or "wizard") of their insulin pump if on CSII or their carb counting parameters to calculate meal insulin if on MDI.
4. Optional: Subjects will be asked to wear a Fitbit during the data collection phase, removing prior to bathing and participating in water activities.
5. The subject may be asked to repeat up to 4 weeks of the Data Collection Period.
6. If the subject is unable to provide the downloaded data from home, the subject will be asked to return to the office so the study team can assist them.
7. The subject may return to the office at any time for additional support.
8. If a change in the basal insulin dose is recommended and accepted by the physician for an MDI user, the subject will be instructed to use the new basal dose(s) for approximately 5 days prior to the Experimental admission. The subject will be instructed to maintain a minimum of 7 SMBG per day, and the study clinical team will contact the subject within 72h of the dose change to monitor safety.
9. Visit 5 admission may be delayed no greater than 100 days.

Visit 4: Research House/Hotel Admission (Randomized)

Pre-Admission Procedures

1. The subject will insert new CGM sensor ~24-36 hours prior to the start of the research house/hotel admission.
2. Subjects will be asked to maintain their regular exercise pattern on the day prior to each research house/hotel admission.
3. The subject will meet the study team and check in to the research house/hotel at approximately 16:00-17:00.
4. The subject will be asked to perform a fingerstick using the study glucometer and ketone

meter shortly after arrival. If glucose is <80 mg/dL or >300 mg/dL or β-Ketone test is >0.6 mmol/L, the study physician will suggest appropriate treatment per the Glycemic Treatment Guidelines. The study subject may continue participation in the trial when blood glucose levels are between 80-300 mg/dL and ketone values are below 0.3 mmol/L.

5. The study team will confirm that the subject brought his/her insulin, insulin pump or MDI supplies, and regular medications. The study team will also confirm the absence of a febrile illness and absence of acetaminophen use while wearing the CGM sensor. The subject may be rescheduled if these criteria are not met.

6. Female subjects of childbearing potential will perform a urine pregnancy test. If positive, the subject will discontinue study participation. The subject will be asked to seek confirmation of the test and the appropriate medical care.

Admission Procedures

Day 1

1. **General Information:** During both admissions, the subject will wear a blinded Dexcom CGM connected to DiAs for remote monitoring capabilities. The staff will remotely monitor the subject using the remote monitoring website. DiAs will be programmed with the home insulin dosing parameters during the Control admission and with the optimized insulin dosing parameters during the Experimental condition. DiAs will be used for meal insulin dosing advice for both admissions and for pre-exercise advice during the Experimental admission. DiAs will be informed of any BG values, meals, carb treatments, correction doses, or snacks during the admission. The DiAs system will be initiated prior to dinner.
    a. **Experimental Admission** – The DiAs will be programmed with the new optimized basal rates or basal insulin dose (entered as a basal rate U/hr = Lantus, Tresiba, Levemir dose/24hr), insulin sensitivity factor(s), and carbohydrate ratio(s). These new parameters will be used for insulin dosing advice during the entire admission. MDI users will use the study insulin pen for meal insulin dosing and the home insulin pen or syringe for Lantus (glargine), Tresiba [degludec], or Levemir [Detemir] dosing. Pump users will use the home pump for both meal insulin dosing and basal insulin administration during the admission.
    b. **Control Admission** –The study subject will use the home basal/bolus MDI or CSII insulin regimen via the home insulin pens or pump and determine the amount of insulin to give for the entire admission per the subject's home carb counting parameters and as calculated by the DiAs meal screen.

2. **Dinner:** A dinner meal will be provided between 18:00-19:00. The subject will define the amount of carbohydrates at the dinner meal. The amount of carbs designated by the subject will be consistent between the Control and Experimental admission.
    a. **Experimental Admission** – The subject will inform DiAs of the dinner meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the new therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison.
    b. **Control Admission** – The subject will inform DiAs of the dinner meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the subject's regular therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison.

3. **Optional Snack:** The subject may eat a snack in the evening with optional insulin coverage per their usual care. If chosen, this snack must be replicated at both admissions. The subject will inform DiAs of the carbohydrates in the snack and current blood glucose level by activating the meal screen of the system if insulin will be given with the snack. Otherwise the snack carbohydrates will be entered in DiAs using the hypoglycemia treatment screen. DiAs will advise an insulin dose using the usual patient carb ratio during the Control admission and using the optimized ratio during Experimental admission. The DiAs-advised insulin dose will be self-administered by the subject and supervised by the study staff.

4. At approximately 23:00, lights will be turned out, and the subject will be encouraged to sleep.

Day 2

1. The subject will be awakened approximately between 7:00-8:00 AM and allowed time for routine hygiene.

2. A BG fingerstick value will be obtained upon waking while the subject is still fasting.

3. **Breakfast:** A breakfast meal will be served at approximately 8:00-9:00 AM. The subject will define the amount of carbohydrates in the breakfast meal. The subject will be informed of the planned exercise and may choose to underestimate the carbs in the breakfast meal. The amount of carbs designated by the subject will be consistent between the Control and

Experimental admission.

a. **Experimental** Admission – The subject will inform DiAs of the breakfast meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the new therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison.
b. **Control Admission –** The subject will inform DiAs of the breakfast meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the subject's regular therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison. The subject may use a temporary basal rate in preparation for exercise per the subject's usual routine.

4. **Exercise Session:** The subject will perform a controlled exercise activity designed to maintain (HR) at ~140 bpm and starting at approximately 11:00 AM. The exercise will consist of 45 minutes of cardiovascular activities that are divided into consecutive 15 minute periods. Fingerstick BG will be performed before and after each 15 minute exercise bout and entered into DiAs via the BG entry screen. Blood glucose value must be ≥80 mg/dL to initiate each 15 minute exercise bout. Immediately prior and during exercise, fingerstick BG <100 mg/dL will be treated according to the Hypoglycemia Treatment Guidelines. Subjects will wear a heart rate monitor during this exercise session.

   a. **Experimental Admission** – The subject or study staff will inform DiAs of the impending exercise session by pressing the exercise advice button. The exercise advice given by DiAs will be followed and may consist of the following:

      i. If no risk of hypoglycemia is detected, no intervention will be recommended.

      ii. If a mild-moderate risk of hypoglycemia is detected, DiAs will recommend a 0% temp basal rate x 1 hour for CSII users and a 12-16 gram snack for MDI users.

      iii. If a high risk of hypoglycemia is detected, DiAs will recommend a 0% temp basal rate x 1 hour plus a 12-16 gram snack for CSII users and a 24-32 gram snack for MDI users.

   After this initial advice, **any carbs consumed during exercise will be per the**

Hypoglycemia Treatment Guidelines. Carbs advised by the system may replace additional hypoglycemia treatment if the amount is appropriate (no double treatments)

b. **Control Admission** – Any carbs consumed during exercise will be per the Hypoglycemia Treatment Guidelines.

Lunch: A lunch meal will be served at approximately 12:00-1:00 PM. The subject will estimate the amount of carbohydrates in the lunch meal. The amount of carbs designated by the subject will be consistent between the Control and Experimental admission.

a. **Experimental Admission** – The subject will inform DiAs of the lunch meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the new therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison.
b. **Control Admission** – The subject will inform DiAs of the dinner meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the subject's regular therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison.

Quiet activities will be conducted during the afternoon and evening hours.

5. **Dinner:** A dinner meal will be provided between 18:00-19:00. The subject will define the amount of carbohydrates at the dinner meal. The amount of carbs designated by the subject will be consistent between the Control and Experimental admission.

   a. **Experimental Admission** – The subject will inform DiAs of the dinner meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the new therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison.

b. **Control Admission** – The subject will inform DiAs of the dinner meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the subject's regular therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison.

6. **Optional Snack:** The subject may eat a snack in the evening with optional insulin coverage per their usual care. If chosen, this snack must be replicated at both admissions. The subject will inform DiAs of the carbohydrates in the snack and current blood glucose level by activating the meal screen of the system if insulin will be given with the snack. Otherwise the snack carbohydrates will be entered in DiAs using the hypoglycemia treatment screen. DiAs will advise an insulin dose using the usual patient carb ratio during the Control admission and using the optimized ratio during Experimental admission. The DiAs-advised insulin dose will be self-administered by the subject and supervised by the study staff.

7. At approximately 23:00, lights will be turned out, and the subject will be encouraged to sleep.

Day 3

1. The subject will be awakened approximately between 7:00-8:00 AM and allowed time for routine hygiene.

2. A fingerstick value will be obtained upon waking while the subject is still fasting.

3. **Breakfast:** A breakfast meal will be served at approximately 8:00-9:00 AM. The subject will define the amount of carbohydrates in the breakfast meal. The subject will be informed of the planned exercise and may choose to underestimate the carbs in the breakfast meal. The amount of carbs designated by the subject will be consistent between the Control and Experimental admission.

   a. **Experimental Admission** – The subject will inform DiAs of the breakfast meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the new therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison.

b. **Control Admission** – The subject will inform DiAs of the breakfast meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the subject's regular therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison. The subject may use a temporary basal rate in preparation for exercise per the subject's usual routine.

4. **Exercise Session:** The subject will perform a controlled exercise activity designed to maintain (HR) at ~140 bpm and starting at approximately 10:00 AM. The exercise will consist of 45 minutes of cardiovascular activities that are divided into consecutive 15 minute periods. Fingerstick BG will be performed before and after each 15 minute exercise bout and entered into DiAs via the BG entry screen. Blood glucose value must be ≥80 mg/dL to initiate each 15 minute exercise bout. Once exercise is started, fingerstick BG <100 mg/dL will be treated according to the Hypoglycemia Treatment Guidelines. Subjects will wear a heart rate monitor during this exercise session.

   a. **Experimental Admission** – The subject or study staff will inform DiAs of the impending exercise session by pressing the exercise advice button. The exercise advice given by DiAs will be followed and may consist of the following:

      i. If no risk of hypoglycemia is detected, no intervention will be recommended.

      ii. If a mild-moderate risk of hypoglycemia is detected, DiAs will recommend a 0% temp basal rate x 1 hour for CSII users and a 12-16 gram snack for MDI users.

      iii. If a high risk of hypoglycemia is detected, DiAs will recommend a 0% temp basal rate x 1 hour plus a 12-16 gram snack for CSII users and a 24-32 gram snack for MDI users.

   After this initial advice, **any carbs consumed during exercise will be per the Hypoglycemia Treatment Guidelines.** Carbs advised by the system may replace additional hypoglycemia treatment if the amount is appropriate (no double treatments)

   b. **Control Admission –** Any carbs consumed during exercise will be per the Hypoglycemia Treatment Guidelines.

5. **Lunch:** A lunch meal will be served at approximately 12:00-1:00 PM. The subject will estimate the amount of carbohydrates in lunch meal. The amount of carbs designated by

the subject will be consistent between the Control and Experimental admission.

a. Experimental Admission – The subject will inform DiAs of the lunch meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the new therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison.
b. Control Admission – The subject will inform DiAs of the dinner meal carbohydrates and current blood glucose level by activating the meal screen of the system. Insulin will be administered based on the subject's regular therapy regimen (basal profile, correction factor and carbohydrate ratio profiles) and according to the subject's estimate of the carbohydrate content of the meal. The subject will self-administer the DiAs-calculated meal bolus under study staff supervison.

6. Quiet activities will be conducted during the afternoon and evening hours.

G. Procedures Related to Discharge

1. At approximately 16:00, DiAs will be stopped and study equipment will be removed.
2. The subject will resume his/her normal home CSII or MDI insulin therapy.
3. The subject will be discharged if the fingerstick value is 80-300 mg/dL and ketone <0.6 mmol/L. Staff will also review to ensure that the glucose trend is stable.
4. If the subject's glucose is out of the specified parameters, the Glycemic Treatment Guidelines (Appendix A-6) will be followed until the subject is in the specified range.
5. The subject will be offered a meal prior to discharge.
6. Subjects will be asked to check BG before dinner, at bedtime, and upon awakening the following day and to monitor for possible symptoms of hypoglycemia since discharge.
7. Study staff will contact the subject within 24-48 hours after discharge to enquire about AEs or BG <50 or >400 mg/dL.
8. If the first admission was the Control admission, the subject will participate in Visit 3 approximately 30 days prior to the Experimental admission. Appropriate study supplies will be provided.

Meals

1. Distribution of meals will be determined by the parameters defined by the subject's weight (Rounded to the nearest 10 kgs.) and multiplied by the carbohydrate/fat/protein ratio as described in Figure 2. Meals will be a wide variety of carbohydrate/fat/protein to fully test the optimization capabilities of the bolus calculator.

2. Meals will be replicated during each admission.

3. The subject or study staff will enter the amount of carbohydrates into the DiAs meal screen for each meal. Carbohydrate amounts may be underestimated prior to exercise if that is the usual home routine.

4. Snacks will only be permitted if advised by DiAs prior to exercise and per the usual routine prior to bedtime. Snacking between meals will not be permitted.

Meal	***Carb***	***Fat***	***Protein***	***Carb (g/kg)***	***Fat (g/kg)***	***Protein (g/kg)***
			Day 1			
Dinner	High	Low	Moderate	1	0.2	0.27
			Day 2			
Breakfast	Low	Low	Moderate	0.5	0.14	0.27
Lunch	Moderate	High	Moderate	0.75	0.46	0.27
Dinner	High	High	Moderate	1	0.53	0.27
			Day 3			
Breakfast	Low	Low	Moderate	0.5	0.14	0.27
Lunch	Moderate	Low	Moderate	0.75	0.17	0.27

Figure 2: Meal Composition

Equipment Specifications

1. All study equipment including the DiAs cell phone, computers, insulin pump (for CSII subjects), and CGM receivers will be set to the same time using an atomic clock as a reference.

2. The study team will train the subject on the DiAs interface until all questions are answered. However, study staff will supervise all interactions with the DiAs, including entering information for meal dosing, FSBG results, hypoglycemia treatments and temporary basal

rates.

3. The CGM tracing will be blinded on the DiAs and on the CGM receiver.
4. Subjects will wear a heart rate monitor during each exercise session.

Blood Glucose Measurements

- The subject will be instructed that all fingersticks should be preceded by hand washing with warm water and a dry towel. The subject will be instructed to obtain fingerstick, avoiding alternative sites, when obtaining blood values. The first drop of blood will be discarded. The second hanging drop will be used to measure the glucose level.
- The subject will be reminded that all treatment decisions should be based on fingerstick values and not on CGM values.
- Once a fingerstick is obtained for any reason during the admissions, the Glycemic Treatment Guidelines (Appendix A-6) will be followed to determine timing of subsequent fingersticks.
- Scheduled times: prior to meals and snacks, before and after each 15 minute exercise bout, and at bedtime (23:00).
- Prior to calibration of CGM and/or if calibration is requested by CGM.
- The subject may request any additional fingersticks as desired.
- Study personnel may also request additional fingersticks at their discretion.
- BG treatments will be based on Glycemic Treatment Guidelines (Appendix A-6) although hypoglycemic treatments can occur at any time per the subject's request.
- If CGM <80 mg/dL, SMBG will be performed every 15 minutes. If SMBG <100 mg/dL, the Glycemic Treatment Guidelines (Appendix A-6) will be applied.
- If CGM >300 mg/dL, SMBG will be performed every 60 minutes. If SMBG >300 mg/dL, the Glycemic Treatment Guidelines (Appendix A-6) will be applied.
- In case of remote monitoring unavailability or in case of CGM failure (an alert will sound on the DiAs and on the remote monitoring), SMBG will be collected at bedtime, 3am and 7am until the issue is resolved.
- Calibrations of the CGM will be per manufacturer guidelines. Hypoglycemia treatment (e.g. glucose tablets, glucose gel/liquid, and a glucagon emergency kit) will be available for

treatment at all times.

- The subject will have access to ad lib glucose-free beverages.
- A study MD will be available for any clinical concerns.
- The Senior DiAs Engineer with remote monitoring capability will be available if needed to view the study from another location. A DiAs trained technician will be on site for any system issues.
- The subject will be accompanied by a medically qualified staff member and a technician during the admissions.

SAFETY MONITORING / RISK ANALYSIS

- **Monitoring Procedures by Staff**

1. CGM values are updated onto DiAs every 5 minutes.
2. Study staff will be constantly monitoring the CGM and subject-entered SMBG values from the remote monitoring website and alert nursing and physician staff when the CGM is <80 or >300 mg/dL.
3. If CGM < 80 mg/dL, SMBG will be performed every 15 minutes. If SMBG >80 mg/dL, the Glycemic Treatment Guidelines (Appendix A-6) will be applied during both the Experimental and Control admissions.
4. If CGM >300 mg/dL, SMBG will be performed every 60 minutes. If SMBG >300 mg/dL, the Glycemic Treatment Guidelines (Appendix A-6) will be applied Experimental and Control Admissions.
5. The DiAs trained technician will monitor the system for the first floor of the research house/hotel during the entire admission.
6. Medical personnel and emergency supplies are on the first floor of the research house/hotel but the study staff periodically round subjects' rooms on both floors during the overnight hours.

- **Glucose Monitoring Risk:**

Bayer CONTOUR NEXT glucometer is a FDA approved 510K Class II Medical Device (510K number K121087).

- **Hypoglycemic/Hyperglycemic Risk:**

The Glycemic Treatment Guidelines will be followed during Visit 4 and Visit 5. The treatment guidelines are attached in Appendix A-6.

- **Calibration of CGM Risk:**

The CGM will be calibrated using fingerstick values before meals, bedtime, and as requested by the device during both the Experimental and Control Admissions. The study team may recommend calibrations as needed.

- **Sterilization Risk:**

Study equipment cannot be sterilized in an autoclave. Cleaning instructions for study equipment provided to study the subject are provided below.

- **Device Reuse Risk:**

The Dexcom Continuous Glucose Monitors are labeled for single use only. The sensor, the component of the system that enters the skin, will be single use only. The transmitter and receiver will be reused after cleaning as described below. The transmitter is attached to the sensor but does not enter the skin and the receiver is a hand held device. The transmitter and receiver will be cleaned adhering to hospital protocol as described below. The subject will be informed that the FDA has approved these devices for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

Cleaning Procedure: Equipment that touches intact skin will be cleaned with ethyl or isopropyl alcohol (70-90%), quaternary ammonium germicidal detergent (i.e. CaviCide) or household bleach. The contact time on the surface depends on the method used to clean the equipment. CaviCide requires three minutes on the surface. Clorox Germicidal Bleach Wipes require two minutes on the equipment. The surface should remain wet (i.e. slightly damp) with the disinfectant to be considered effective though not wet enough to leave drops of liquid. Equipment will be stored in a clean zipped bag.

The study glucometers are single use devices.

The insulin pens are single use devices.

Hb1Ac Risk: The University of Virginia central labs have College of American Pathologist (CAP) and the Clinical Laboratory Improvement Amendments (CLIA) certifications. While the central lab is not NGSP certified, the calibrators for the HbA1c assay are traceable to NGSP. The equipment (Tosoh G7) is NGSP certified.

- **Misuse Risk:**

CGM Training:

The subject will be introduced to the blinded CGM by a qualified member of the study team. The subject will be instructed how the device is inserted, calibrated and removed. The subject will be trained how to upload the CGM data. The subject will verbalize understanding of how the device is used, how to insert the device, how to calibrate the device and how to remove the device. The subject, with the guidance of the study team, will then insert the sensor and begin wearing the CGM. The study team will teach the subject how to calibrate the device as needed. The study team will confirm that all questions have been answered and that the subject has understood the training. The subject will be given a contact sheet containing phone numbers for the study team to call with any questions 24 hours per day.

Study Glucometer Training:

The Bayer CONTOUR NEXT Blood Glucose Monitoring System will be used during visit 2-5 as the study glucometer. The subject will be trained on proper use of the meter as described in the user manual. The subject will then be required to demonstrate proficiency on the use of the device. The subject will be instructed to wash their skin with warm water and a clean towel prior to obtaining fingerstick values. The subject will be instructed to obtain a fingerstick, avoiding alternative sites, when obtaining blood values. The first drop will be discarded. The second hanging drop will be used to measure the glucose level. QC will be completed prior to the subject receiving the study glucometer. The study team will confirm that all questions have been answered and that the subject has understood the training.

DiAs Training:

During the Control and Experimental admissions, a brief introduction to the DiAs UI will occur with a qualified clinical member of the study team. DiAs will be used as an insulin-dosing calculator for both admissions and the advice recommended by DiAs will be instituted using the home insulin pump for CSII users or the study insulin pen (Experimental admission) or home insulin pen (Control admission) for MDI users. For the Control admission, DiAs will be pre-programmed by the study team with the subject's home insulin parameters. For the Experimental admission, DiAs will be pre-programmed with the optimized insulin parameters per the decision support system and that have been approved by the study physician. To minimize risk associated with the use of DiAs:

1. The study team will confirm the home pump parameters entered in DiAs during the Control admission and the physician-approved optimized parameters during the Experimental admission.

2. DiAs CGM tracing will be remotely monitored at all times and monitored by a qualified study technician. Nursing and physician staff will be informed when the CGM is <80 or >300 mg/dL.

3. Qualified study staff will supervise the subject during all interactions with the DiAs UI and during all administration of insulin.

Risks of blood sampling collection, contamination from sampling techniques

Hand washing with either soap & water or waterless hand sanitizer will be used prior to caring for the study subject. Gloves will be worn during blood sample collection and processing. Medical personnel will continue to practice hygiene for the patient's protection (i.e. hand washing, changing gloves frequently, disposing needles properly). Gloves will be removed and hands washed prior to leaving and upon return to the subject's room. Soiled linen will be changed to minimize the transfer of pathogenic organisms.

Study personnel with direct subject contact are required to complete Bloodborne Pathogens and Infection Control training annually.

MEDICAL PERSONNEL TRAINING

All study nurses will be currently licensed RNs or Nurse Practitioners. Emergency Medical Technicians or nursing students currently enrolled in accredited nursing program will be supervised by licensed nursing personnel. All medical personnel who will have direct contact with the study subject have current certification in CITI Training, Basic Life Support including CPR and AED. Medical personnel are oriented to the study protocol.

In addition, liquid fast-acting rescue carbohydrates, glucagon injection, automated external defibrillator (AED) and Ambu-bag for ventilation will be available during the study procedures.

STOPPING RULES

Entire study

The study will be stopped if two similar AE's occur that result in stopping the study for individual study subjects or if there are system communication failures, which may trigger revision of the system software. The Principal Investigator and Senior DiAs Engineer will evaluate this data and make recommendations concerning continuation, modification, or termination of the trial. Additionally, the Principal Investigator or the IRB-HSR may decide to stop the trial or part of the trial at any time. In this case, the Principal Investigator will promptly inform the subjects and assure appropriate therapy and follow-up. Additionally the Principal Investigator will notify the IRB if the study is temporarily stopped. The pertinent regulatory

authorities will be informed according to national regulations.

Early study stop will be documented and following information will be collected:

1. Date and cause of the ending
2. Description of any serious adverse event leading to the study ending
3. In the case of an unanticipated adverse device effects (UADE), the overall study may be suspended while the problem is diagnosed and the Principal Investigator investigates the UADE. If the Principal Investigator determines that the UADE poses an unreasonable risk to subjects, the study should be suspended until this UADE can be resolved. If it cannot be resolved, the study should be terminated. Termination should occur no later than 5 working days after Principal Investigator makes the decision to end the trial. The result of the investigation and the Principal Investigator's decision to terminate the study shall be reported the site IRB, and the FDA per 21CFR 812.46(b) (2). The Principal Investigator must determine if the UADE presents an unreasonable risk to subjects. If so, all investigations, or parts of investigations presenting that risk, are terminated or halted as soon as possible but no later than 5 working days after making this determination and no later than 15 working days after first receipt notice of the UADE.
4. The study may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension. The IRB will be notified if the study is stopped, and permission to resume will be obtained from the FDA and IRB prior to restarting.

Criteria for stopping study an individual subject

1. The subject may request to be withdrawn (withdrawal of informed consent) from the study at any time for any/no reason. The Principal Investigator, IRB-HSR, or Senior DiAs Engineer may decide to stop the trial or part of the trial at any time. In this case, the Principal Investigator will promptly inform the subject and assure appropriate therapy and follow-up, if needed. The pertinent regulatory authorities will be informed according to national regulations.
2. The subject will be stopped if time between Visit 4 and Visit 5 exceeds 100 days.
3. A subject who does not complete the protocol may be replaced or rescheduled.

4. If the subject has a positive pregnancy test, she will be stopped.

5. If the subject has a serious adverse event, he/she will be stopped.

Study procedures other than those required for subject safety would be stopped during the admissions if:

a. The subject has a positive pregnancy test.
b. The subject had a serious adverse event deemed related to study.
c. Glucagon is required to treat hypoglycemia.
d. The subject experiences a seizure.
e. The subject experiences loss of consciousness.
f. The subject becomes unable to eat or drink.
g. The subject develops ketones >3.0 mmol/L.
h. The subject develops abdominal pain, vomiting illness, fever ≥101.5ºF, clinical need for acetaminophen, significant illness, or need to use epinephrine or glucocorticoids.
i. Subjects who were not able to complete the study for reasons other than a serious adverse event (i.e. hypoglycemic seizure, etc.) will be permitted to repeat the session.

The subject may resume the study after the following problems are resolved:

1. Correction of a malfunction of the system or controller once the problem is clearly identified and the system has been repaired

2. Correction of ketones ≥0.6 mmol/L or BG ≥300 for 2 hours or more: Study may be resumed when ketones are <0.6 mmol/L and the meter glucose is between 80-250 mg/dL.

3. Loss of sensor data acquisition for more than three hours

4. If remote monitoring cannot be restored within 180 minutes, the CGM receiver will be unblinded and study staff will monitor it at least hourly. Values will remain blinded to the subject by covering the display.

Reason Study Stopped	Repeat Session?
Equipment Failure or similarly related issues that invalidate study data	Can repeat session
Hyperglycemic Events that did not result in Serious Adverse Event	Can repeat session
Hypoglycemic Events that did not result in Serious Adverse Event	Can repeat session
PI initiated discontinuation of study due to patient or equipment concerns	Can repeat session
Serious or Unanticipated Adverse Event deemed related to the study	Unable to repeat session

Table 1: Repeat Session Table

SAFETY MONITORING

Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches

Reporting of events are noted below:

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation (Note: An internal event is one that occurs in a subject enrolled in a UVa protocol.)	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. Timeline includes submission of signed hardcopy of AE form.	IRB Online www.irb.virginia.edu/
For Device Studies: Unanticipated adverse device effects (internal)	IRB-HSR	Within 10 day calendar days of the study team receiving knowledge of the event	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 10 day calendar days of the study team receiving knowledge of the event	IRB Online www.irb.virginia.edu/

Protocol Violations/Noncompliance The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by the sponsor OR Enrollment Exceptions	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Data Breach	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation, Noncompliance and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* Go to 3rd bullet from the bottom
Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- Police if breach includes items that are stolen: Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 ITC: Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html UVa Police- Phone- (434) 924-7166
UVa PI HELD IDE			
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative

Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
Unanticipated adverse device effects (internal or external)	FDA	Within 10 working days of the study team receiving knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IDE annual report

Table 2: Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches

Definition of Adverse Event: A reportable adverse event is any untoward medical occurrence or any unexpected medical occurrence in a study subject.

Hypoglycemic events are recorded as Adverse Events if the event required assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat him or herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Hyperglycemic events are recorded as Adverse Events if evaluation or treatment was obtained from a health care provider or if the event involved diabetic ketoacidosis (DKA), as defined by the Diabetes Control and Complications Trial (DCCT), and had all of the following:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

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 subject, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the subject at each visit and

complete all adverse event forms.

The 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 that continue after the participant'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.

Adverse events will be coded using the MedDRA dictionary.

Definitions of relationship and intensity are listed on the data entry form.

Reporting Serious or Unexpected Adverse 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 significant disability/incapacity, or
- is a congenital anomaly/birth defect

An *Unanticipated Adverse Device Event* (UADE) 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.

All anticipated Adverse Events will be reported in details to both the IRB and FDA with the results of the study within 3 months of the completion of the trial.

UADE will be thoroughly investigated and as required by 21 CFR 812.46, they will be reported to FDA and IRB no later than 10 working days after the sponsor first receives notice of the effect.

The CGM (Dexcom Share AP) malfunctions which are not related to the modifications of the interface to include them as components of the AP device will be reported to its respective manufacturers as a complaint per MDR requirements (Dexcom for the Share AP CGM).

Malfunctions related to the interfaces of the CGM with the DiAs platform will also be reported to their respective manufacturers within 10 days.

The principal investigator/s is responsible for informing the UVA IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB

Definition of an unanticipated problem

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- not anticipated or foreseen (e.g., not described in the consent form);
- involves risk or harm to a research participant or others; and
- probably, definitely related to, or caused by, the research.

Definition of a protocol violation

A protocol violation is defined as an accidental or unintentional change to the IRB approved protocol that harmed participants or others or that indicates participants or others may be at increased risk of harm.

Definition of a Protocol Enrollment Exception

No enrollment exceptions will be permitted in this trial.

Definition of a Data Breach

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Data Collection

Endpoint data be collected/recorded in the form of source documents and will be stored on a database on a Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA.

At UVa, safety data oversight will be completed by a member the UVa Clinical Trials Office. An example of the Monitoring Form is presented in Appendix A-10.

The PI will conduct an aggregate review of the following data:

- All adverse events
- Unanticipated Problems
- Protocol violations
- Audit results

- Early withdrawals
- Data processing review

IRB-HSR will be updated annually on the IRB-HSR continuation status form. This annual report will address:

- Brief summary of research progress
- Whether adverse event rates are consistent with pre-study assumptions
- Enrollment status
- Reason for dropouts from the study
- Whether continuation of the study is justified
- Conditions whereby the study might be terminated prematurely

The relevant device regulation for reporting adverse events to the FDA will also be followed.

Data from each subject will be reviewed by the PI after completion of participation to determine whether the DiAs system was working properly and whether there were safety concerns.

Adverse Events / Unanticipated Problems

Recording, Reporting, and Grading

Only adverse events that are deemed related AND serious will be recorded, reported, and graded. The principal investigator will be responsible for the overall safety monitoring of the study. The principal investigator, along with the sub-investigators, will review the individual adverse events as they occur. Any event that merits adverse event reporting will be collected and recorded in the IRB database by completing the IRB Adverse Event Reporting form online. The principal investigator can then use this database to produce a report of all adverse events reported on the study to do an aggregate review. If the AE is unexpected and serious, a signed hard copy of the IRB Adverse Event Reporting form will be submitted to the IRB within 7 calendar days.

Grading of Adverse Events

- Mild/Moderate/Severe
- Serious/Not serious

The PI will determine the relationship of adverse events to the study using the following scale:

- Related: AE is clearly related to the intervention
- Possibly related: AE may be related to the intervention
- Unrelated: AE is clearly not related to intervention

Reporting/recording of adverse events/unanticipated problems will begin after the subject begins study drug/device placement/intervention/study-related procedure/specimen collection.

Reporting/recording of adverse events/unanticipated problems will end at the end of study drug/device/ intervention/participation.

CATASTROPHIC EVENT PLAN

The Outpatient Emergency Plan will go into effect should a catastrophic event occur during the study admissions. A catastrophic event is defined as any event that requires emergency treatment by medical professionals that exceed the expected parameters of the protocol. A copy of this plan will be located at the monitoring desk. Staff will be aware of its location at all times.

In the unlikely event of a disruption in 911 phone service, the sites will contact their local non-emergency number (e.g. Charlottesville-UVA-Albemarle Emergency Communications Center can be reached via their non-emergency number 434-977-9041). This number feeds into their main call area where 911 dispatchers are available 24/7.

Event	RN Response	Tech Response
Respiratory Arrest	1) Tell Tech to call 911 2) Begin Basic Life Support	Refer to Study Physician
Cardiac Arrest	1) Tell Tech to call 911 2) Begin Basic Life Support	Refer to Study Physician
Severe Hypoglycemic Event as defined by hypoglycemia accompanied by unconsciousness or seizure	1) Tell Tech to call 911 2) Administer glucagon IM (described in Glycemic Treatment Guidelines Appendix A-6) 3) Remove study pump	Refer to Study Physician
Severe Hyperglycemic Event as defined by β-ketone level ≥3.0 mmol/L	1) Discuss correction dose of insulin to administer s.c. via syringe with study M.D. 2) Encourage P.O. water intake 3) Remove study pump and start home insulin pump 4) Go to nearest medical facility for evaluation and treatment.	Refer to Study Physician

Table 3: Outpatient Emergency Plan

ENDPOINTS

We assess the risk to the subject by computing the two classical hypo and hyperglycemia risk indices LBGI and HBGI, based of the blinded CGM data, retrofitted to the SMBG point (see DelFavero et al. JDST 2015). Gaps of less than 3h will be filled using spline based interpolation. LBGI is the primary endpoint.

LBGI and HBGI are measures of glycemic risk that were developed by our groups in the late 1990s and have been shown to be predictive of increased frequency of severe hypoglycemia and increased HbA1c. Detailed formula can be found in Kovatchev et al. Diabetes Care 1998.

In addition we will capture:

- Quality of glycemic control using the percent time spent between 70mg/dl and 180mg/dl.
- Meal insulin coverage will be assessed using Area Under the glucose Curve in the postprandial state.

- Glucose variability will be assessed using the Risk Index (sum of LBGI and HBGI).

SUCCESS CRITERIA / GOAL

As a general rule, a session will be considered useful for data analysis if the subject completes more than 80% of the active study protocol. Subjects completing less than 80% of the protocol may be rescheduled.

Safety and feasibility will mean that using our system, subjects will not increase either their risk of hypoglycemia as measured by LBGI (non-inferiority claim)

STATISTICAL ANALYSIS PLAN

All variables are continuous and though bounded by 0 unlikely to be close to their lower bound, therefore we will compare the control and experimental admissions using a paired Student t-test for equality of mean. Nonetheless, LBGI may be very low in some subjects during the control admission. If such effect is observed in more than 5 subjects, LBGI will studied using the Wilcoxon signed rank test.