NCT03709108

PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

Exogenous insulin therapy in individuals with Type 1 Diabetes is needed to compensate for the practically absent internal insulin secretion which follows from the autoimmune destruction of pancreatic β-cells. As a consequence, the quality of glucose control in Type 1 diabetes is heavily dependent on multiple daily treatment decisions by the patient, whose effect on blood glucose variability is mediated by individual glucose metabolism parameters, such as insulin sensitivity (SI) [1-4].

SI is a key parameter in the treatment of diabetes describing how sensitive the body is to the effects of insulin. In general, if someone has higher SI, the amount of insulin required to lower his blood glucose levels is smaller than that needed by someone who has low sensitivity. However, SI levels within the same person are not constant, and fluctuations of SI happen very frequently in the life of subjects with diabetes, e.g., in response to physical activity, making insulin dosing and therapy parameters very difficult to tune [5-12].

In such context, the purpose of the study is to demonstrate safety and feasibility of an SI-informed bolus calculator, aimed at improving insulin dosing by adjusting insulin boluses to the patient's sensitivity to insulin action at the time the bolus is administered. To modulate the insulin bolus, we first track the subject's SI fluctuations from continuous glucose monitor data, insulin, and meal records collected over several days of monitoring (e.g., 2 to 4 weeks). This allows us to build a 24-hour profile of SI for the subject, which represents the usual pattern of sensitivity to insulin action the subject shows across the day. At the time a bolus is administered, we then estimate the real-time subject's SI, and correct the bolus based on the ratio between usual SI at this time of day (from the profile) and real-time SI level. The SI-informed insulin bolus can be calculated as follows:

$$B_t^{SI} = \frac{SI_t^{PRF}}{SI_t}\left(\frac{carbohydrate\ intake}{insulin\text{-}to\text{-}carbohydrate\ ratio} + \frac{BG_t - target\ BG}{correction\ factor} + IOB_t^{BASAL}\right) - IOB_t^{TOTAL}$$

where the regular insulin bolus computed from insulin-to-carbohydrate ratio, correction factor and insulin on board (IOB), is modulated by the ratio of usual SI at time t (SI_t^{PRF}) and real-time SI assessed at time t (SI_t). The idea behind the bolus modulation is that insulin therapy parameters are tuned to account for the usual SI pattern, and do not account for acute changes of SI introduced, e.g., by physical activity. As seen from the formula, if $SI_t = SI_t^{PRF}$, the administered bolus will remain unchanged, while it will be increased/decreased if the subject is less/more sensitive than usual at the time the bolus is administered. The ratio used to modulate the bolus will be saturated in order not to allow modifications larger than 30% of the original bolus amount (this means that during the experimental admission the dose suggested by the computed bolus modulator will be between 70% and 130% of the standard dose indicated by the DiAs system using the participant's insulin therapy parameters). If this change of insulin dose is deemed not

to be safe by the licensed endocrinologist conducting this study, this insulin dose will not be administered and the standard dose calculated using the participant's insulin therapy parameters will be indicated for administration.

The proposed SI-informed bolus calculator has been tested *in silico* using the UVa/Padova Type 1 Diabetes Simulator - a simulation platform approved by the FDA as a substitute to preclinical trials in testing insulin treatments [13,14]. The platform consists of a mathematical model of differential equations describing glucose metabolism in Type 1 Diabetes and is equipped with a population of 100 *in silico* adult subjects with metabolic behaviors similar to those observed in individuals with Type 1 Diabetes. Resorting to the simulator, the scenario proposed for the Research Admissions of this study has been reproduced. A model of mild-to-moderate physical activity impact on glucose metabolism has been used to simulate the exercise session at the local gym. A dinner meal has been administered at 7PM following the exercise session, and the postprandial control obtained with the use of the SI-informed bolus calculator has been compared to the one obtained when the standard bolus calculator (or functional insulin therapy) was utilized. Postprandial (i.e., 6 hours following dinner) Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI) – glucose variability indicators used to quantify the exposure to hypo- and hyperglycemia, respectively [15,16] – have been computed from glucose sensor data. The number of hypoglycemia treatments administered in the same postprandial time interval has also been tracked. Figure 1 shows these metrics in bar graphs for the SI-informed bolus calculator (Experimental Admission [EX]) and standard bolus calculator (Control Admission [CON]). The use of the SI-informed bolus calculator decreased the total number of hypoglycemia treatments from 34 to 6 and allowed to considerably reduce LBGI (from 2.4 to 1.3) at the price of a minor increase in HBGI (from 0.17 to 0.18).

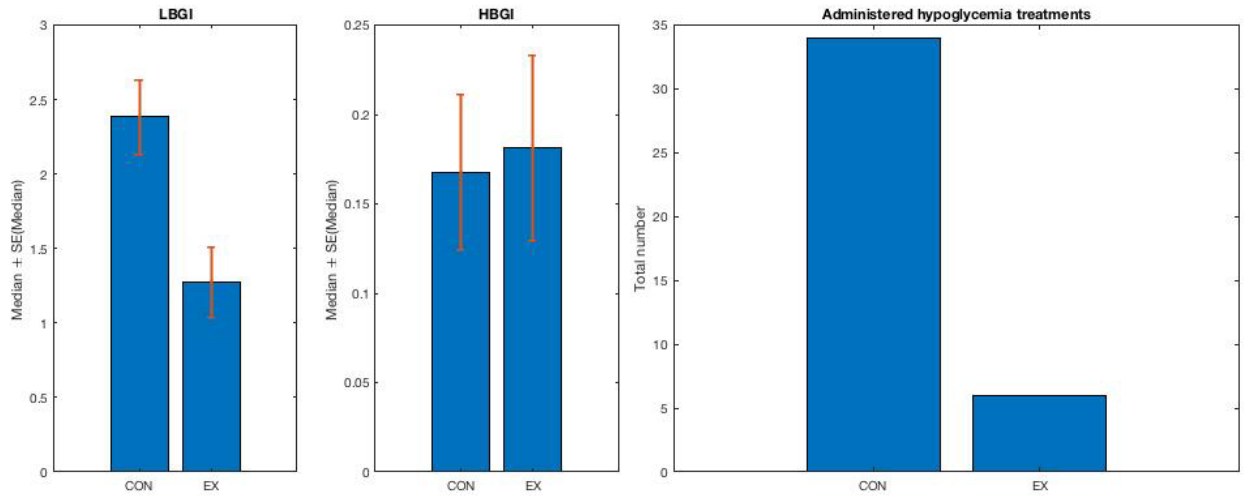

Figure 1: LBGI, HBGI and number of hypoglycemia treatments in the 6 hours following the simulated controlled dinner meal using the SI-informed bolus calculator (EX) and the standard bolus calculator (CON).

Also, an initial version of the SI-informed bolus calculator has been deployed as part of a CGM-informed decision support system, which showed reduction of glucose variability in individuals with Type 1 Diabetes using an insulin pump or multiple insulin injection [17].
Because of the known impact of physical activity on post-exercise SI fluctuation [18], the purpose of this study is to test the feasibility of using the SI-informed bolus calculator in a clinical trial, where it would be deployed for the control of one supervised meal following an afternoon exercise period.

The proposed intervention is an insulin bolus calculator based on continuous glucose monitoring and insulin/meal history. The glucose sensor used in the study (Dexcom G6) is FDA-approved for the non-adjunctive measurement of blood glucose and is the first to follow the interoperable continuous glucose monitoring (iCGM) guidelines and is "*to be used as part of an integrated system with other compatible medical devices and electronic interfaces, which may include automated insulin dosing system, insulin pumps, blood glucose meters, or other electronic devices used for diabetes management"* [19]. Under these guidelines, *"FDA recognized this as an opportunity to reduce the regulatory burden for this type of device by establishing criteria that would classify these as "moderate risk" class II medical devices"*. Furthermore, the proposed intervention results in a meal bolus that is presented to the user (the participant) and not automatically transferred to the injection device (the pump); the SI-informed bolus is also provided to the study MD for approval prior to use at the time of the one supervised meal. The study physician may overwrite the insulin dose computed with the use of the SI-informed bolus calculator at any time.

Objectives/Hypothesis

The primary aim of the research project is to demonstrate safety and feasibility of a new SI-informed bolus calculator, based on a continuous glucose monitor (CGM)-informed algorithm for the real-time tracking of SI. The SI-informed bolus calculator will be compared to standard therapy in terms of overall and postprandial occurrence of hypoglycemia as measured from CGM data using the Low Blood Glucose Index (a glucose variability measure and predictor of severe hypoglycemia, designed to aggregate the frequency and extent of low blood glucose events into a single number), which will be expected to be better when the optimized bolus calculator is used.

Study Design: Biomedical

1. **Will controls be used?** Yes.

   ►IF YES, explain the kind of controls to be used.
   Each participant will be his/her own control, participating in an experimental admission as well as a control admission.

2. What is the study design?

This is a single-center randomized crossover trial. We will target completion of 15 adults (age 18-65 years) with Type 1 Diabetes who use an insulin pump. Subjects will undergo an initial Screening Visit and randomization will occur if the visit is successfully completed. After completion of the Screening Visit, each subject will participate in an at home Data Collection Period that will last approximately 14 to 28 days while using their personal insulin pump, a personal glucometer, a study CGM, and a study activity tracker (i.e., Fitbit). This data collection period may be extended to gather more days of quality data, if needed per principal investigator judgement. Once the data has been collected and processed, subjects will participate in two 24-hour admissions (Experimental and Control Admission) in a semi-controlled environment (i.e., hotel), performed in the assigned random order. During both admissions, subjects will use their personal insulin pump and glucometer, and a study CGM. Subjects will be admitted around 9AM. Subjects will be advised to have their home breakfast per their normal routine; around 12PM, they will be provided lunch, followed by an exercise session around 2:30PM. The exercise session will consist of three 15-minute bouts of moderate-intensity exercise (i.e., stationary bicycle). Around 7PM, subjects will be provided a controlled dinner; the SI-informed bolus calculator will be used in the Experimental Admission while standard therapy will be used in the Control Admission. Subjects will then be observed overnight and discharged in the following morning.

3. Does the study involve a placebo? No

►IF YES, provide a justification for the use of a placebo

Human Participants

Ages: 18-65
Sex: Male and Female
Race: All

Subjects- see below

1. **Provide target # of subjects (at all sites) needed to complete protocol.**
   Fifteen (15) subjects are needed to complete the study.

2. **Describe expected rate of screen failure/dropouts/withdrawals from all sites.**
   Because of the length of the study, we expect an approximately 40% rate of dropouts/withdrawals from the study.

3. **How many subjects will be enrolled at all sites?**
   This is a single site clinical trial to be completed at UVa. Given the potential of a 40% dropouts/withdrawals rate, up to 25 people will be enrolled.

4. **How many subjects will sign a consent form under this UVa protocol?**
   This study will have up to 25 subjects sign the consent form with the goal of completing 15 study subjects.

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

1. Type 1 diabetes for at least 12 months
2. Current use of an insulin pump for at least 12 months
3. Current or historical use of a CGM system for at least 6 months
4. Age ≥18 to ≤65 years old
5. HbA1c <8.5% at screening; if HbA1c <6.0% then total daily insulin must be ≥0.5 U/kg
6. For females, not currently known to be pregnant. If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative urine pregnancy test will be required for all premenopausal women who are not surgically sterile. Subjects who become pregnant will be discontinued from the study
7. Willingness to use the same set of insulin therapy parameters (i.e., basal rate, insulin-to-carbohydrate ratio, correction factor) during both admissions
8. Willingness to upload data during the study
9. An understanding of and willingness to follow the protocol and sign the informed consent

2. List the criteria for exclusion

1. Diabetes ketoacidosis (DKA) in the 6 months prior to enrollment
2. Clinically significant electrocardiogram (ECG) found at Screening as determined by the study medical physician
3. Severe hypoglycemia resulting in seizure or loss of consciousness in the 6 months prior to enrollment
4. Currently being treated for a seizure disorder
5. Coronary artery disease or heart failure, unless written clearance is received from a cardiologist or primary care provider and documentation of a negative stress test within the year
6. History of cardiac arrhythmia (except for benign premature atrial contractions and benign premature ventricular contractions which are permitted)
7. Cystic fibrosis
8. Pregnancy, breast-feeding, or intention of becoming pregnant over time of study procedures
9. Abnormal liver function test results (Transaminase >2 times the upper limit of normal)
10. Abnormal renal function test results (calculated GFR <60 mL/min/1.73m2)
11. Uncontrolled thyroid disease (TSH undetectable or >10 mIU/L)
12. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
    - Inpatient psychiatric treatment in the past 6 months for either the subject or the subject's care companion
    - Presence of a known adrenal disorder
    - Active gastroparesis

- 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

13. Abuse of alcohol or recreational drugs
14. Infectious process not anticipated to resolve prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis)
15. Uncontrolled arterial hypertension (Resting diastolic blood pressure >90 mmHg and/or systolic blood pressure >160 mmHg)
16. 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
17. Basal Rate <0.01 units/hour
18. Inability to be physically active for more than 30 minutes per day
19. Conditions that would make use of a CGM difficult (e.g., blindness, severe arthritis, immobility)
20. Current enrollment in another intervention clinical trial

3. List any restrictions on use of other drugs or treatments.

1. Medications being taken to lower blood glucose, such as Pramlintide, Metformin, GLP-1 Analogs such as Liraglutide, and nutraceuticals intended to lower blood glucose
2. Any other medication that the investigator believes is a contraindication to the subject's participation

Statistical Considerations

1. Is stratification/randomization involved? Yes

►IF YES, describe the stratification/ randomization scheme.

1. Randomization will be done at the Screening Visit and will be performed by simple randomization schedule (like flipping a coin)
2. Randomization will not be blinded; it will determine the order of the Experimental and Control Admissions after the initial 14-28 days of Data Collection

►IF YES, who will generate the randomization scheme?

_____ Sponsor
_____ UVa Statistician. Insert name Answer/Response:
_____ UVa Investigational Drug Service (IDS)
___X___ Other*:* Specify : Center for Diabetes Technology (CDT) personnel

2. What are the statistical considerations for the protocol?

Study Design:

The study is designed as a 14-to-28-day at home Data Collection Period followed by two 24-hour admissions (Experimental and Control Admission) in a semi-controlled environment (i.e., hotel), performed in random order. During the entire duration of the study, subjects will be using their personal insulin pump, personal glucometer, a study CGM, study ketone meter, and a study activity tracker. The Data Collection Period is used to collect up to 28 days of CGM data, insulin and meal records, with the aim of building a 24-hour SI profile for the subject that will be used to modulate the insulin bolus during the Experimental Admission. On admission days, subjects will arrive at the hotel at approximately 9AM after a home breakfast per their normal routine; at approximately 12PM, they will be provided lunch, which will be followed by an exercise session at approximately 2:30PM. The exercise session will consist of three 15-minute bouts of moderate-intensity exercise (i.e., stationary bicycle). At approximately 7PM, subjects will be provided a controlled dinner; the SI-informed bolus calculator will be used in the Experimental Admission while standard therapy will be used in the Control Admission. Subjects will then be observed overnight and discharged the following morning.

Study Objectives and Endpoint Definitions:
The objective of the study is to test the safety and feasibility of the SI-informed bolus calculator. Overall and postprandial occurrence of hypoglycemia as measured by the Low Blood Glucose Index (LBGI) computed on CGM data, will be compared between the optimized bolus calculator (Experimental Admission) and standard therapy (Control Admission), with the purpose of assessing whether the optimized paradigm for insulin dosing allows to improve postprandial control after an afternoon exercise session.

Power/Precision of the study to address major study endpoints:
As a safety and feasibility study, this trial is not powered to a specific outcome. A sample size of 15 subjects has been chosen with the purpose of being able to compute the Cohen's *d* once the trial is completed. Cohen's *d* is defined as the difference between two means divided by a standard deviation for the data (standardized difference between two means), and will serve as effect size to appropriately power the subsequent main trial.

3. Provide a justification for the sample size used in this protocol.
The sample size is determined based on the fact that this study is a pilot trial. 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, and existent literature suggests that a sample size of 10-30 participants is appropriate for pilot studies.

4. What is your plan for primary variable analysis?
We will compute CGM metrics with the primary outcome analysis of LBGI by CGM following dinner, comparing the Experimental Admission to Control Admission.

5. What is your plan for secondary variable analysis?

In addition, descriptive glycemic analyses for secondary efficacy measures will be tabulated for each subject based on CGM data, including:

- mean glucose
- percentage of readings in the target range of 70-180 mg/dL
- percentage of readings <70, 60, and 54 mg/dL
- percentage of readings >180, 250, and 300 mg/dL

6. Have you been working with a statistician in designing this protocol? No

IF YES, what is their name?

7. Will data from multiple sites be combined during analysis? No. This is a UVa only study.

INSTRUCTIONS: IF YES, answer the following questions

7(a). Does the study involve randomization?

IF YES, will randomization be done at each site or among sites?

7(b). Has the sample size calculation considered the variation among sites?

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?

7(d). Is there a common protocol used in all sites?

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?

Study Procedures-Biomedical Research

1. What will be done in this protocol?

Visit 1: Screening Visit.

All subjects will be consented and receive a history and physical. Study eligibility will be reviewed. If a subject satisfies all the study inclusion criteria and does not meet any exclusion criteria, he/she will be enrolled in the study and randomized to the Experimental or Control Admission occurring first.

At the Screening Visit, the following procedures will be performed, and 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 and smoking
11. Physical examination
12. Electrocardiogram (ECG)
13. Weight and height
14. Vital signs
15. Blood and urine testing for screening labs:
    - Hemoglobin A1c
    - Comprehensive chemistry panel
    - TSH
    - Pregnancy test: either urine or qualitative serum HCG in women with childbearing potential. If not performed, document reason (surgically sterile, postmenopausal)

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 repeated 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 urine/blood test with the subject, and the subject will be asked to seek confirmation of the test and the appropriate medical care. 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.

All subjects will be advised to contact the study team in the event of a febrile illness within 48 hours of the study visits, so that the study visits can be rescheduled. All subjects will be given

instructions to bring all of their current medications and insulin pump supplies with them for use during or after the study visits.

Visit 2: Study Equipment Placement & Training and Data Collection Period.

Visit 1 and 2 can be completed on the same day. All subjects will receive training on the use of the 1) CGM and 2) study-supplied commercially available activity monitor (e.g., Fitbit or similar device). New sensors will be issued to each subject; the CGM may be reused after it has been cleaned as required using a dilute mixture of bleach or another appropriate cleaning agent.

Continuous Glucose Monitor Training

1. An outpatient visit will be scheduled for training on the study CGM.
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 will be supervised during the initial CGM sensor placement. A CGM sensor will be inserted as per manufacturer directions.
4. 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.
5. The subject will be taught how to calibrate the CGM per manufacturer's guidelines and if prompted by the DiAs system during the admissions. The subject will be asked to perform all required calibrations with fingerstick glucose measurements.
6. If the subject owns a personal laptop device, he/she will be asked to bring it to the visit for the study team to download specific software to be used during data collection. If the subject does not own a laptop device but owns a desktop computer, he/she will be provided with a memory drive storing the appropriate resources to be used at home.
7. The subject will be taught to look for skin irritation after sensor removal.
8. If the subject requires an MRI/CT or diathermy, 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.
9. The outpatient visit will last approximately 1-2 hours depending on prior knowledge of the equipment.
10. The subject will be given an instruction sheet with 24-hour contact information of the research team to address any problems or questions.
11. Unlimited additional appointments and telephone calls to the study team and study physician will be available.

Data Collection Period

1. Subjects will collect data for approximately 14 to 28 days prior to Visit 3 and Visit 4.

2. The CGM and insulin pump data will be analyzed by the study team at the end of the Data Collection Period, to determine the SI profile that will be used during the Experimental Admission (Visit 3 or 4). Special emphasis will be noted to the study subject that all meal information (i.e., carbohydrate quantity and insulin) must be recorded in their insulin pump.
3. Subjects will be instructed on how to download the equipment (i.e., personal insulin pump, personal glucometer, study CGM, study activity monitor). Subjects will be asked to provide downloaded data periodically during the data collection period (approximately one time per week) using a web-based diabetes management system (e.g., Diasend, CareLink Pro, etc. – Figure 2) 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 requests may occur depending upon the quality of the data collected.
4. Subjects will be asked to wear the study activity monitor during the data collection phase, removing prior to bathing and participating in water activities. Subjects will also wear the activity monitor to collect information on activity, exercise, heart rate, and sleep. A study Gmail account will be established for each subject. The commercially available app associated with the activity monitor will be placed on the subject's smartphone or subject's personal laptop to facilitate weekly downloading of data. If the subject has an existing personal account with the commercially available activity monitor and the subject would prefer to use their existing personal account rather than creating an anonymous account, the subject will be allowed to do so and the study team would request access to that account.
5. Subjects will be advised to consistently use the bolus calculator (or "wizard") of their insulin pump, and not to use temporary basal rates to compensate for meals.
6. Subject may be asked to repeat up to 4 weeks of the Data Collection Period.
7. 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.
8. The subject may return to the office at any time for additional support.
9. Subjects will be asked to consistently use insulin parameters such as insulin-to-carbohydrate ratio and correction factor to dose insulin for meals and corrections and avoid modifying their insulin therapy parameters (i.e., basal insulin, insulin-to-carbohydrate ratio and correction factor profiles) for the entire duration of the study. If a change in insulin therapy parameters is recommended or required, it will have to be approved by the study physician; in such scenario, the subject may be asked to extend the Data Collection Period per principal investigator judgement.
10. Visit 3 will take place no more than 100 days after the end of the Data Collection Period.

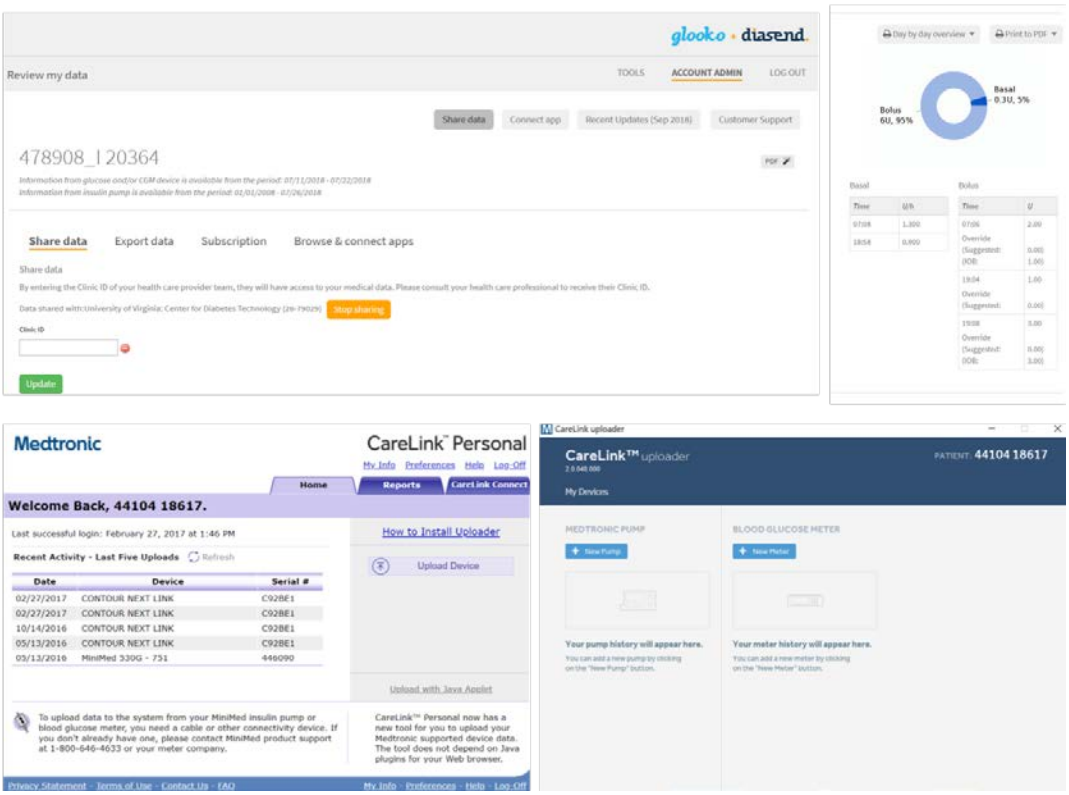

Figure 2: Example of web-based diabetes management systems used for data upload (Diasend top, CareLink bottom)

Visit 3 and 4: Research Admission (i.e., Hotel).

The Experimental and Control Admission will be separated by at least 48 hours with a maximum of 100 days. The order of these two visits will be randomly selected. Subjects will be admitted to the research location at approximately 9:00AM and will be discharged after approximately 24 hours.

All procedures will be the same for Visit 3 and Visit 4 with the following exception:

- Insulin Boluses during the Control Admission: All meal and correction boluses during the control admission will be per the subject's usual insulin parameters. The two admissions will use consistent insulin-to-carbohydrate ratio, correction factor, and basal profiles.
- Insulin Boluses during Experimental Admission: The dinner meal bolus will be determined with the use of the SI-informed bolus calculator during the Experimental Admission. The calculations will be performed on a study smartphone (Diabetes Assistant, DiAs), approved by the study MD, and subsequently communicated to the subject. The suggested insulin bolus will be administered through the subject's personal insulin pump. The study physician will override the insulin dose computed with the use of the SI-informed bolus calculator at any time if he/she considers it is not safe for the participant subject in the following way:

1 The dinner insulin dose suggested by the SI bolus calculator will be ±30% of the dose that the subject should receive while using his/her own insulin pump bolus calculator (usual care). This is by design of the SI bolus calculator.
2 If the licensed endocrinologist conducting the study considers the dinner dose suggested by the SI bolus calculator to be unsafe he/she will override this dose.
3 In order to avoid bias between the physicians involved, every effort will be made to have the primary MD supervising all the experimental admission.
4 Since the visits will be randomized, regardless of when the experimental visit occurs, the MD supervising the trial will look at the standard dose suggested by the DiAs system using the participant's insulin therapy parameters and will indicate that dose (control) if the assigned insulin dose suggested by the SI bolus calculator is deemed to be unsafe. This will be equal regardless of who is the physician supervising the visit. In this way any bias will be avoided since the criteria used by all MDs listed on this protocol will be the same.
5 During both visits, control and experimental, the same procedures will be followed. Therefore, the dose suggested by the DiAs system using the participant's insulin therapy parameters during the experimental admission to override the dose suggested by the SI bolus calculator, should be consider safe and usual care for that particular participant.

Visits 3 and 4 will be fully supervised by a research team located at the hotel and gym at all times and will be monitored and supervised by the primary physician. In the event that the primary physician could not be available for a particular visit, the backup MDs will cover. The team will consist of 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). In addition, one of the study medical physicians, primary MD, and one senior engineer will be on call during the entire admission, with backup physicians and engineer available if the primary contact is unable to be reached.

The CGM used in the study is FDA-approved for the non-adjunctive measurement of blood glucose and will be remotely monitored in real-time during the entire admission (including exercise) by the study team via the DiAs Web Monitoring platform. The CGM readings will be the primary source of blood glucose levels. There are no protocol fingerstick blood glucose measurements other than at times of CGM calibration and if directed by the study team.

Study Procedures that will occur during both Visit 3 and Visit 4 (Hotel):

Prior to Research Visit

1. Subjects may be asked to insert a new CGM sensor up to 48 hours prior to the start of Visit 3 and Visit 4, per study staff judgement.

2. Subjects will be asked to avoid physical activity and alcohol consumption in the 48 hours prior to Visit 3 and Visit 4.
3. The study physician will review the data collected during the at home Data Collection Period and will determine the set of parameters to be used by the subject during the Experimental and Control Admission in order to optimize postprandial glycemic control.

Procedures at beginning of Research Visit

1. Subjects will meet the study team and check in to the research location at approximately 09:00AM, after a morning breakfast consumed at home per regular subject's habit.
2. The study team will confirm that the subject brought his/her insulin, insulin pump supplies, and regular medications. The study team will also confirm the absence of a febrile illness and may reschedule the admission if this criterion is not met.
3. 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.
4. The study team will take the subject's vital signs, measure ketone concentration using the study ketone meter, and connect the DiAs system to the subject's CGM transmitter via Bluetooth connection (the DiAs is not connected to the subject's insulin pump, only to the CGM).

Procedures during Research Visit (Figure 3**)**

1. After checking in, subjects will be asked to conduct quiet activities (i.e., reading) until lunch is served.
2. **Lunch:** A lunch meal will be served at approximately 12:00PM. 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.
3. **Exercise Session:** The subject will be transported to a local gym at approximately 2:00PM to perform a controlled exercise activity in the early afternoon, designed to alter insulin sensitivity in the late afternoon and evening. Exercise will start at approximately 2:30PM and will consist of 45 minutes of moderate intensity exercise (~70% maximum heart rate) divided in 3 periods of 15 minutes each.
4. Quiet activities will be conducted during the afternoon until dinner is served.
5. **Dinner**: A dinner meal will be served at around 7:00PM. The subject will estimate the amount of carbohydrates in the dinner meal. The amount of carbs designated by the subject will be consistent between the Control and Experimental admission. The dinner bolus will be computed with the insulin sensitivity-informed bolus calculator during the Experimental Admission. Should this dose be considered to be safe, the procedures detailed previously (pages 12 and 13) will be applied. The override dose indicated will be the one suggested by the DiAs system using the participant's insulin therapy parameters to avoid variability and/or discrepancies between the MDs listed in this protocol. Every effort will be made to have the primary physician supervising all admissions.

6. At approximately 10:00PM participants will be instructed to go to sleep and the following morning at approximately 9:00AM the subjects will be discharged after being offered breakfast with no dietary restrictions.
7. Subjects will be allowed to consume caffeine at breakfast before the admission and at the end of the admission before discharge; no caffeinated beverage consumption is allowed during the study admissions otherwise.
8. The subject will have access to ad lib glucose-free beverages.
9. All meal and correction boluses during the admissions will be based on CGM.
10. Fingerstick will occur prior to calibration of CGM if calibration is needed per manufacturer's guidelines or if it is prompted by the DiAs system. The subject may request any additional fingersticks as desired. Study personnel may also request fingersticks at their discretion.
11. Hypoglycemia treatment (e.g., glucose tablets, glucose gel/liquid, and a glucagon emergency kit) will be available for treatment at all times.
12. A study MD will be available for any clinical concerns and will approve the SI-informed meal bolus for dinner during the Experimental Admission.
13. The subject will be accompanied by a medically qualified staff member during the admissions.
14. Blood glucose will be monitored remotely during the entire duration of the admission.

Procedures Related to Discharge

1. At approximately 9AM, subjects will be discharged.
2. Subjects' vital signs will be checked.
3. The subject will resume his/her normal home insulin therapy.
4. The subject will be offered breakfast prior to discharge.
5. Subjects will be asked to check their blood glucose the following day and to monitor for possible symptoms of hypoglycemia since discharge.
6. Study staff will contact the subject by phone within 24-48 hours after discharge to enquire about AEs or BG <50 or >400 mg/dL.
7. Subjects may be asked to repeat up to two admissions (i.e., either 2x Visit 3 or 2x Visit 4) in the event that there is inadequacy of data collection during the admission, inaccurate CGM readings or the need to refine the optimization strategy based on the data collection period.

Glycemic Guidelines during Research Visit

1. Upon arrival, the subject will be asked to check the CGM reading and ketone concentration using the study ketone meter. If CGM <70 mg/dL or >300 mg/dL or ketone test is >0.6 mmol/L, study physician will suggest appropriate treatment. The study subject may continue participation in the trial once CGM is between 70-300 mg/dL and ketone concentration ≤0.6 mmol/L.
2. If CGM >300 mg/dL for more than 1 hour or >400 mg/dL at any time, study physician will be notified to suggest appropriate treatment and ketones will be checked. If ketone

concentration is >0.6 mmol/L, the study team will check the insulin pump infusion site and correction insulin will be administered per study physician judgement via the subject's insulin pump or study-supplied insulin pens. The study team will monitor CGM decay and ketones will be checked every 60 minutes until ≤0.6 mmol/L.

3. If ketone concentration is ≥3.0 mmol/L, the study subject will be discontinued, DiAs will be changed to Stopped mode, and appropriate medical treatment will be sought. If the subject is discontinued, he/she may repeat the admission at discretion of the PI.
4. If CGM <60 mg/dL at any time, subjects will be given approximately 16 grams of fast-acting rescue carbohydrates. Study team will monitor CGM rise and will consider treating again if CGM <80 mg/dL after 20 minutes. Hypoglycemic treatments can occur at any time per study physician request.
5. If CGM <80 mg/dL at any time during the exercise session, subjects will suspend the exercise activity and take approximately 8-16 grams of fast-acting rescue carbohydrates. Study team will monitor CGM rise and will consider treating again if CGM <80 mg/dL after 20 minutes. Exercise activity will resume once CGM ≥80 mg/dL.
6. Prior to the subject being discharged from the admission after either completing the study procedures or discontinuation, the CGM and ketones will be checked. The subject will be discharged once the CGM reading is between 80-250 mg/dL and ketone concentration ≤0.6 mmol/L.

STOPPING RULES

Entire Study

1. 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. Early study stop will be documented and the 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. 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 IRB prior to restarting.

Criteria for stopping the study for 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.
2. A subject who does not complete the protocol may be replaced or rescheduled.
3. If the subject has a positive pregnancy test, she will be stopped.
4. 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, significant illness, or need to use epinephrine or glucocorticoids.

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. Loss of sensor data acquisition for more than three hours
3. If remote monitoring cannot be restored within 180 minutes, study staff will monitor it at least hourly.

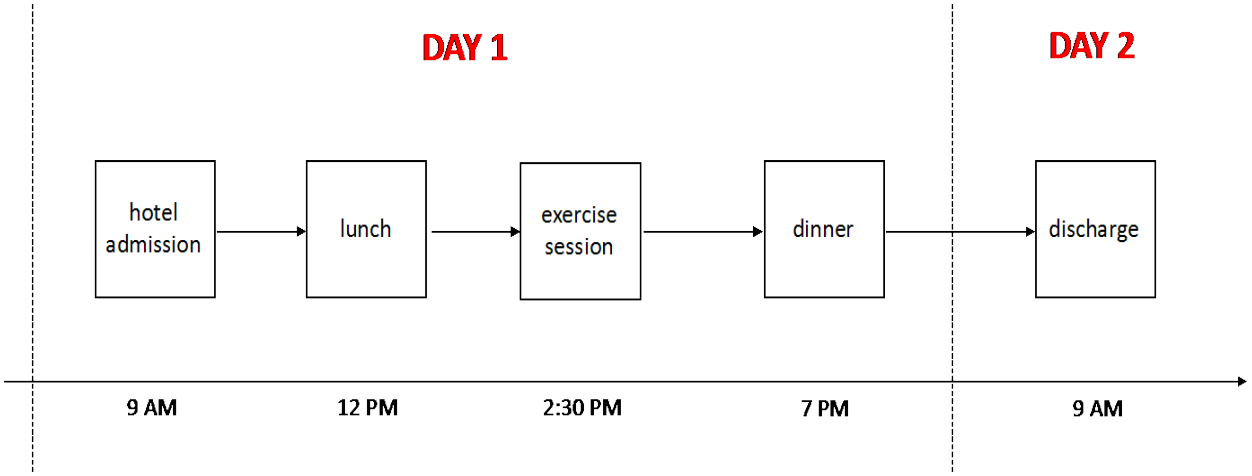

Figure 3: Diagram of the study research visit

2. **If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**
   The optimized bolus calculator will be used during the Experimental Admission (either Visit 3 or Visit 4, according to the randomization). After the Experimental Admission is completed, subjects will resume their usual insulin parameters.

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.** (e.g. study team will administer study drug/ study interventions, study drug inventory of dispensed and returned drug, diary etc.)
   Participants will be instructed to download and send data weekly during the 14-to-28-day Data Collection Period. Data download includes CGM and insulin pump records. The study staff will check for appropriate quality and quantity of data. If any problem in the quality or quantity of downloaded data is identified, the study staff will contact the subject to clarify the situation and try to gather the data needed for the study.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
   (e.g. subject returns more than 20% of the study drug, subject misses 20% of study visits)
   If data is not received in appropriate quality and quantity needed for the study, the participant will be asked to repeat the data collection period. Subjects will be considered not compliant after four repeated periods.

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