UNIVERSITY of VIRGINIA HEALTH SYSTEM | School of Medicine

UVA CENTER FOR DIABETES TECHNOLOGY

Diabetes Closed-Loop Project 6 (DCLP6): Fully Automated Closed-Loop Control in Type 1 Diabetes Using Meal Anticipation

Protocol Chair

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KEY ROLES

Protocol Principal Investigator	
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Institution Name	University of Virginia Center for Diabetes Technology

PROTOCOL VERSION HISTORY

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0	Mark DeBoer	Sue Brown	11-Feb-2021	Original Protocol
1.1	Mary Oliveri		08-Mar-2021	FDA Review: • Removed Fiasp • Added monitoring description (section 7.4) • Added fingerstick blood glucose mitigation (6.4 and 7.6) • Updated Overall Study Stopping Criteria (section 11.10.2) • Clarified transition to personal equipment at study end (section 6.7 and 7.9 • Replaced Figure 1 and Figure 2

1.2	Mary Oliveri		21-Mar-2021	DSMB Review:
				• Mealtime clarifications (section 5.3.1. 6.5. 7.7)
				  ○ Minimum/maximum carbohydrate
				  ○ Bolus entry
				  ○ Carb counting
				• Discharge ketone values clarified (section Chapter 8)
				• Glycemic Treatment Guideline added as new chapter (Chapter 8) and removed as appendix item

1.3	Mary Oliveri			IRB FB Review:

				• Removed all references to Medical Monitor; replaced with study PI oversight. • ABACUS questionnaire removed from protocol. • Deleted DHHS 46.405 reference removed from protocol. • Added Statistical and Analytic Plans (section 14.1) and Statistical Hypotheses (section 14.2).
1.4	IRB Reviewer		14-May-2021	IRB FB Reviewer: • Removal of edit that was not required by the full board and could not be included in the conditional approval.
1.5	Mary Oliveri		24-May-2021	Study Team Modifications: • Protocol Table Endpoint correction: The primary outcome will be time in range 70-180 mg/dL for the period between breakfast and lunch (approximately 5h). • Inclusion criteria edit to clarification purposes (section 3.4) • Removed Accu-Chek study glucometer to remain consistent with informed consent form that states personal glucometer will be used in trial (section 2.3). • Removed questionnaire reference (Chapter 5).

				• Modified COVID policy to include CDC and local guidelines (section 10.3.1). • Modified several references to COVID-19 PCR test to FDA authorized COVID-19 test. • Moved Chapter 9 Medical Monitor details to Chapter 11 (section 6.9 & 7.10). • Deleted Medical Monitor chapter (formerly Chapter 9).
1.6	Mary Oliveri	Sue Brown	14-Jul-2021	Study Team Modifications: • Removed COVID-19 references in study design definition (section 1.3). • Added willingness to provide a copy of COVID-19 vaccination record if available (section 3.4). • Modified COVID-19 policy (section 10.3).
1.7	Mary Oliveri	Sue Brown	20-Jul-2021	Study Team Modifications: • Corrected definition of CDC
2.0	Mary Oliveri	Sue Brown, Mark DeBoer	10-Sep-2021	Study Team Modifications: • Increased enrollment goal from 18 participants to 36 participants; up to 60 participants may sign consent (Protocol summary, section 1.2, 1.3, 1.6.1, 3.1) • Increased from a 3-night overnight stay to a 4-night overnight stay; increased hotel admission from about 76 hours to about 92 hours (Protocol Summary, section 7.1)

				• Additional admission hours reflect increase in stabilization period (section 1.3.4) • Edited figure 2 (Figure 2) • Medical monitor and DSMB references removed (section 11.9
2.1	Mary Oliveri	Sue Brown	11-Nov-2021	IRB FB Reviewer (prior to meeting) / edited 10-Sep-2021 version: • Re-inserted DSMB monitoring (section 11.11) • Sample size description edited (section 13.4)
2.2	Mary Oliveri	Sue Brown	18-Nov-2021	IRB FB Review (prior to meeting/ edited 11-Nov-2021 version: • Deleted that phase 1 participants may participate in phase 2 (section 1.6.1)

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Diabetes Closed Loop Project 6 (DCLP6): Fully Automated Closed Loop Control in Type 1 Diabetes Using Meal Anticipation

Protocol Version v2.2

Protocol Date: 18-Nov-2021

I have read the protocol specified above. In my formal capacity as a Site Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature _____Date: _____ / _____ / _____

Investigator's Name: _____

Site Name: University of Virginia

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADRR	Average Daily Risk Range
AP	Artificial Pancreas
BG	Blood Glucose
BT/BTLE	Bluetooth, Bluetooth low energy
CGM	Continuous Glucose Monitoring
CLC	Closed-Loop Control
CiQ	Tandem t:slim X2 Insulin Pump with Control-IQ Technology
CSII	Continuous Subcutaneous Insulin Injection
DKA	Diabetic Ketoacidosis
DSMB	Data Safety Monitoring Board
FCL	Fully Closed Loop
FCL+	Fully Closed Loop with meal anticipation module
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBGI	High Blood Glucose Index
HCL	Hybrid Closed Loop
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
LBGI	Low Blood Glucose Index
POC	Point-of-Care
QC	Quality Control
rMPC	Regular Model Predictive Control
UI	User Interface

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Fully Automated Closed-Loop Control (FCL) in Type 1 Diabetes Using Meal Anticipation
Investigational Device	UVA Model Predictive Control Artificial Pancreas (RocketAP) with and without prandial excursion anticipation
Objectives	The purpose of this study is to show the safety and feasibility of a fully new fully automated AP controller based on meal anticipation and carbohydrate kinetics estimation, within the UVA AP modular architecture.
Study Design	A randomized cross-over trial assessing glycemic responses to three different approaches to insulin dosing for carbohydrate ingestion all run on an automated insulin delivery AP system: 1) FCL: without a meal anticipation module and without announced carbohydrate 2) FCL+: using a meal anticipation module without announced carbohydrate, and 3) HCL: without a meal anticipation module with announced carbohydrate
Number of Sites	One
Endpoint	The primary outcome will be time in range 70-180 mg/dL for the period between breakfast and lunch (approximately 5h)
Population	Key Inclusion Criteria • Age 18 and <70 years of age • Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year • Currently using insulin for at least six months • Currently using insulin pump for at least three months
Sample Size	• Pilot Study: complete up to 3 participants • Main Study: complete up to 36 participants
Treatment Groups	• Randomized cross over: RocketAP without meal anticipation module without meal bolus (FCL), RocketAP with meal anticipation module without meal bolus (FCL+), and RocketAP without meal anticipation module with meal bolus (HCL).
Participant Duration	Data Collection Phase of approximately 4 weeks followed by a hotel/rental house admission as follows: • Pilot Study: Participants will be admitted to a local hotel or rental house for up to approximately 92 hours and will have a dinner with the RocketAP with meal anticipation and no-carbohydrate announcement. • Main Study: Participants will be admitted to a local hotel for approximately 92 hours.
Protocol Overview/Synopsis	Participants will be followed for 4 weeks prior to the hotel study. During this data collection phase, they will wear the study CGM and be instructed to eat breakfast and dinner at approximately the same time 4-5 times per week. They will then be admitted to the hotel for a 4-night study, receiving the three controller sessions in random order: 1) FCL: without a meal anticipation module and without announced carbohydrate, 2) FCL+: with the meal anticipation module and without announced carbohydrate, and 3) HCL: without the meal anticipation module and with announced carbohydrate. During the admission, participants

	will receive structured meals and have blood glucose control followed to compare time in range 70-180 mg/dL between Controller sessions.

STUDY VISITS AND PROCEDURES SCHEDULE

	Screening	Study Equipment Training	CGM Run-In Phase	Data Collection	Pre-Admission Check-In	Study Admission	Post-Admission Check-In
Location	Clinic/ Remote	Clinic/ Remote	Home	Home	Phone/ Email/Text	Hotel/Rental House	Phone/ Email/Text
Visit	1	2	x	x	3	4	5
Informed Consent	X						
Eligibility Assessment	X						
Medical History	X						
HbA1c	X						
Pregnancy test (if applicable)	X	X				X	
Physical Exam	X						
Vital Signs (height/weight)	X					X	
Randomization						X	
COVID-19 Testing, non-vaccinated participants					X	X (main study only)	
CGM Use			~14 days if needed	X		X	
Survey		X	X			X	
Review diabetes management and AEs			X			X	X

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Chapter 1 Background

1.1 Introduction

A major impediment to maintaining blood glucose (BG) control in Type 1 diabetes (T1D) is missed meal boluses, which has been associated with significantly higher HbA1c levels.[1] While the advent of the artificial pancreas (AP) offers promise of safe reductions in HbA1c, our research group previously found that the AP only partly compensates for missed prandial insulin[2]—demonstrating that some form of meal announcement is necessary for good BG control, even with current AP systems. One way to automate this process is by having an AP system that is able to determine the usual timing of meals for a given individual and provides a small priming dose of insulin at this time—a process referred to as meal anticipation. We previously tested an AP system that was programmed to anticipate physical activity and successfully reduced insulin delivery during the time of usual exercise.[3] We have also recently tested a new artificial pancreas system composed of a robust Model Predictive Controller called the RocketAP. We now propose to test functionality of a module in RocketAP with anticipation of meal ingestion.

In the current study, we are testing this RocketAP system for BG response to three conditions:

1. FCL: without a meal anticipation module and without announced carbohydrate
2. FCL+: using a meal anticipation module without announced carbohydrate, and
3. HCL: without a meal anticipation module with announced carbohydrate.

We will test this system in up to 18 adults with T1D. Participants will first be asked during a 4-week period prior to the main study to eat breakfast and dinner at approximately the same time for 4-5 times a week to entrain the system regarding when these meals are anticipated. Participants will then be admitted to the in-person study and will be started on the RocketAP with approximately three 24-hour periods use of the three conditions described above, in random order, all implemented on the DiAs platform (MAF 2109). As an assessment of the efficacy of the system in maintaining BG control, participants will be followed for approximately 24 hours of use of each of three conditions noted above (FCL, FCL+ and HCL). As an assessment of safety (and efficacy), they will also be followed when a meal is consumed at a later time than expected (dinner will be consumed approximately 2 hours later than anticipated dinner time) as well as when a meal is not anticipated to occur at all (participants will receive a lunch which the system has not been anticipated to expect). Our primary outcome will be one of efficacy in assessing BG control (TIR 70-180 mg/dL) in the absence of carbohydrate announcement when the new meal anticipation module is on (FCL+) vs. off (FCL). Additional assessments of BG control will be made 1) comparing when there is no meal anticipation model and carbohydrate content is announced (HCL) vs. when carbohydrate content is not announced (FCL+), and 2) assessing the

safety of the system by having dinner later than the usual time—to ensure that this does not result excess insulin delivery and hypoglycemia, and 3) how the system responds to a lunch that has not been entrained or anticipated during each of the 3 conditions (FCL+, FCL without announced carbohydrate and during HCL with announced carbohydrate).

We hypothesize that performances of RocketAP with meal anticipation (FCL+) will result in significant improvement over not using the meal anticipation module (FCL) and without risk of significant hypoglycemia when meals are consumed later than expected. We expect that this will constitute an important step toward having a fully automated AP system.

1.2 Study Objective

The purpose of this study is to test the meal anticipation module on the RocketAP closed loop algorithm, assessing efficacy and safety. We will target completion of up to 36 adults in a randomized cross-over trial, comparing blood glucose time in range 70-180 mg/dL following meals with and without the meal anticipation module in use (FCL+ vs FCL), and comparing to a system with carb announcement instead of a meal anticipation module (HCL). We will further assess safety when dinner is consumed later than usual and when a lunch is consumed without having been entrained in the meal anticipation module.

1.3 Study Design

We will consent up to 60 participants, ages 18-70 years, with a goal to have up to 36 participants complete the trial. The study will be performed overnight at a local hotel/rental house (heretofore referred to as “hotel”). Enrollment in the Pilot Study will proceed with the goal of completing 1-3 participants. This admission will be up to 2 days will be in a hotel/rented house.

1.3.1 Recruitment and Screening

Participants will be recruited from the UVa Center for Diabetes Technology registry, social media advertisements, physician/health care provider contacts at diabetes clinics in Virginia. Potential participants will be informed of the study and will be encouraged to ask the study team questions about their study participation. Participants will provide written informed consent. The screening visit may be performed by telephone, video conferencing or in person.

1.3.2 CGM Data Collection

Following study enrollment, participants will be trained in use of the Dexcom G6 system, provided with adequate study supplies and have a Dexcom sensor placed. This training may be completed via video conferencing, with supplies sent to the participant in advance of the call. This study visit will be followed by 4 weeks of CGM and pump data collection at the participant’s

home/usual routine. Participants will be asked to have breakfast and dinner at approximately the same time at least 4-5 times per week during this period.

Participants will then be randomized to the order that they experience the three controller approaches (for 24 hours each): 1) without the meal anticipation module and without carbohydrate announcement (FCL), 2) with the meal anticipation module on and without carbohydrate announcement (FCL+), or 3) without the meal anticipation module on and with carbohydrate announcement (HCL). This will be performed using three permuted blocks of 6.

1.3.3 Study Hardware/Software

The study itself will involve use of the DiAs prototyping platform (MAF 2109), connected to a Tandem t:AP research pump and a Dexcom G6 sensor, and implementing RocketAP with or without the meal anticipation module. Upon arrival at the hotel, participants will be instructed in how to use the Tandem research pump as well as the UVa AP system, including stopping the system and bolusing for food.

1.3.4 Timing of UVa Artificial Pancreas Use

Upon arrival to hotel, participants will have a 12+ hour stabilization period. The participant will be connected to a Tandem research pump connected to the UVa DiAs platform and their Dexcom G6 Transmitter will be linked with DiAs on the morning of Day 1. Participants will then be taught how to use DiAs in this configuration. The research pump will be programmed with the individual's usual insulin parameters. Participants will have their blood sugar managed through this system during the entirety of the time at hotel.

1.3.5 Study Controller Sessions

Order and timing of controller sessions: During the hotel stay, participants will have three separate 24-hour periods during which they will receive three approaches to BG management (in random order): 1) without the meal anticipation module and without carbohydrate announcement (FCL), 2) with the meal anticipation module on and without carbohydrate announcement (FCL+), or 3) without the meal anticipation module on and with carbohydrate announcement (HCL). The timing and potential order of these sessions is shown in Figure 1.

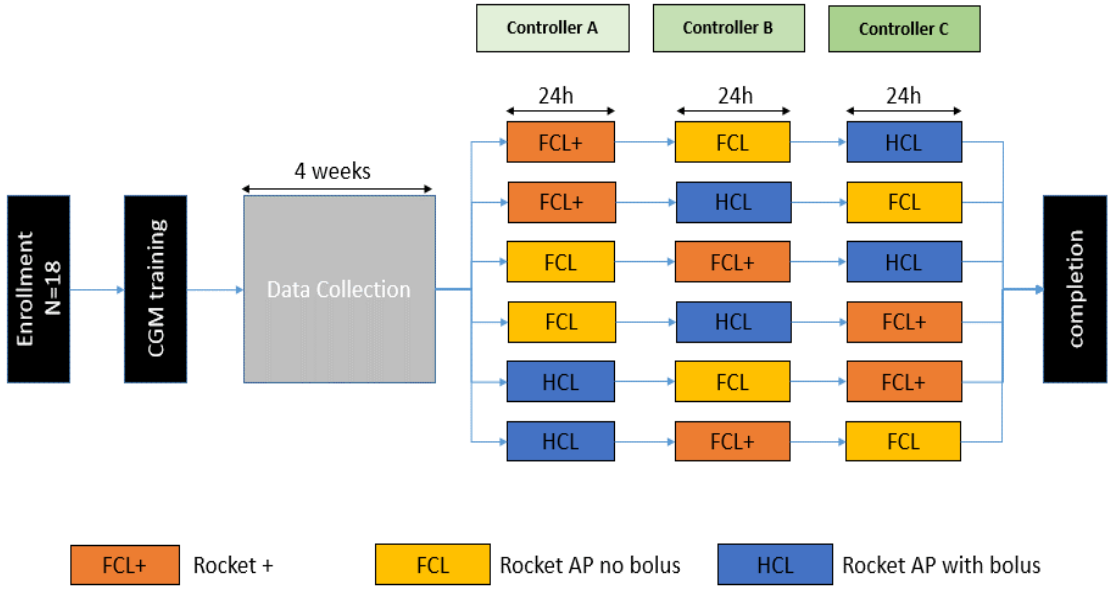

Figure 1: Timeline and randomized order of the Study Controller Sessions

During these 24-hour periods participants will be followed for the experimental meals as part of the Study Controller Sessions to compare blood glucose control using these three different approaches to insulin management for carbohydrate control (Figure 1). These study meals include a late dinner timed later than the participant's usual dinner time (to assess how the meal anticipation module handles a late meal), a lunch at a time when the system has not been entrained to expect it and a breakfast at the participant's usual breakfast time (see Figure 2).

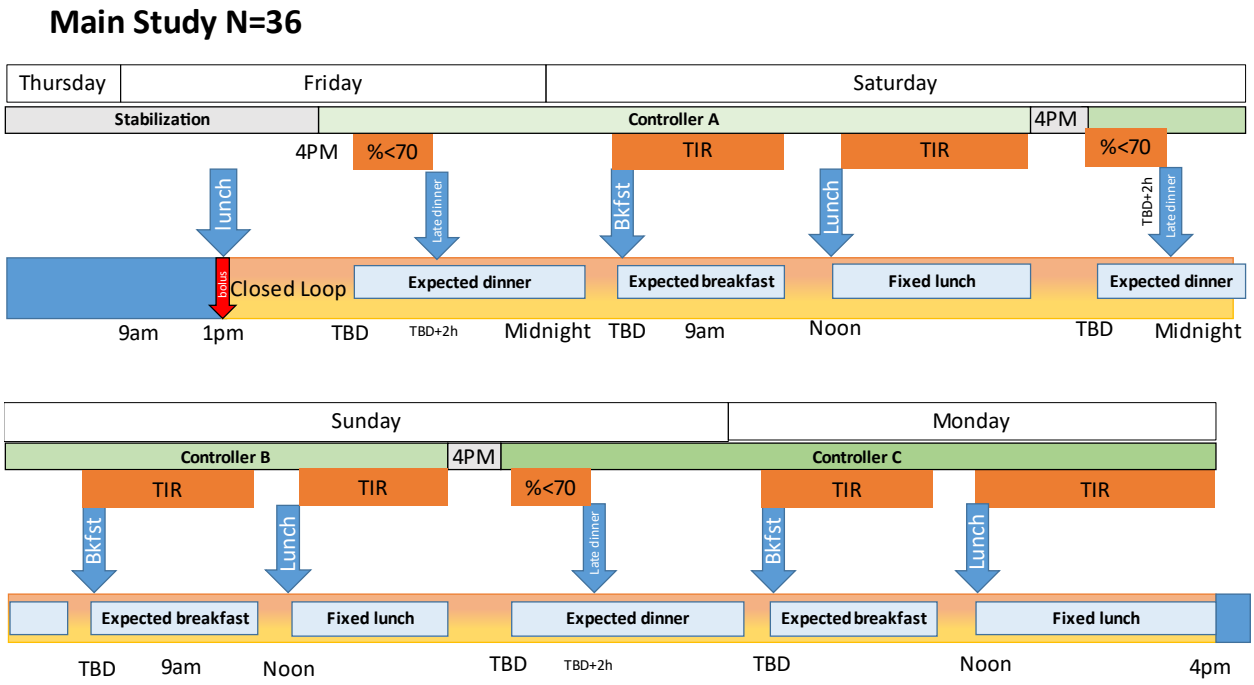

Figure 2: Timeline of Study Controller Sessions and Study Meals

The primary outcome will compare the percent time CGM is between 70 and 180 mg/dL after breakfast, starting at the time of breakfast and lasting approximately 5 hours afterwards (until noon). For study meals, participants will consume structured breakfast, lunch and dinner (with identical protein, fat, and carbohydrate content on each of the days). During the FCL and FCL+ sessions, participants will not announce the carbohydrate content in meals (and all additional insulin will be delivered by the AP system, without and with meal anticipation, respectively), while during the HCL session, participants will use insulin dosing via normal carbohydrate announcement and the DiAs CGM-based bolus calculator. Study staff who will be present will include nursing staff and technical staff; a study physician will be available either on-site or nearby off-site at all times. Hyperglycemia and hypoglycemia treatment protocols will be followed per CDT protocol. We anticipate more significant cases of hyperglycemia during dinners managed without carbohydrate announcement; participants will be encouraged to drink large amounts of non-caloric beverages, particularly after these meals.

The UVa AP systems will be initiated upon arrival to the hotel the morning before the first of the Controller Sessions. UVa CDT study staff will monitor CGM output continuously and manage glucose control issues. At the end of the hotel stay, the participant will return to their home insulin management.

1.4 Study Device Download

Before discharge from the hotel, all study devices will be turned in to study staff for device download and the participants will be placed on usual diabetes management.

1.5 Study System Issues

If the CGM signal becomes unavailable for more than 20 minutes consecutively, closed loop will not operate to automatically adjust insulin. If the CGM is not connected, the system will revert to usual function of the pump and deliver insulin with the insulin dosing parameters programmed in the system for that individual. Resumption of closed-loop control will occur automatically once CGM signal is available again.

If the study system is unable to maintain pump connectivity, the pump will automatically revert to pre-programmed basal insulin delivery after 30 minutes without any need for instruction from the user.

1.6 Purpose/Objectives of Clinical Study

1.6.1 Study Participants

Enrollment in the Pilot Study will proceed with the goal of completing 1-3 participants. Up to 6 participants may sign the consent form.

Enrollment in the Main Study will proceed with the goal of completing up to 36 participants. Up to 60 participants may sign the Main Study consent form.

1.6.2 Clinical Sites

The study will be performed at the University of Virginia, with screening procedures taking place either virtually, at the Clinical Research Unit, or at local hotel.

Chapter 2 Study Devices

2.1 Insulin Pump

The study systems will utilize the Tandem t:AP research pump connected to the UVa DiAs system run on a dedicated external smart phone, running the RocketAP control algorithm with the meal anticipation module (which will be turned on or off, depending on the Controller session, with the order of these sessions determined randomly).

2.2 Continuous Glucose Monitor

The study CGM will include Dexcom G6 transmitter and sensors. The CGM sensor is viable for 10 days.

2.3 Blood Glucose Meter and Strips

Study participants will use their personal glucometer during the study. A study glucometer will be provided in the event that the participant's glucometer cannot be downloaded.

2.4 Ketone Meter and Strips

Blood ketone levels will be measured during the hotel admission with the use of the Abbott Precision Xtra meters and strips in accordance with the manufacturer's labelling. The blood glucose meter component of the Precision Xtra Device will not be used.

2.5 Study Devices Accountability Procedures

Device serial numbers will be recorded and use of equipment will be tracked.

Chapter 3 Study Screening

3.1 Participant Recruitment and Enrollment

Pilot Study: Enrollment goal in the Pilot Study will be to complete 1-3 participants. Up to 6 participants may sign consent forms.

Main Study: Enrollment in the study will proceed with the goal of completing up to 36 participants. Participants will initially be randomized for the order of their 3 experimental meals use during the study. Up to 60 participants may sign the consent form.

3.2 Informed Consent and Authorization Procedures

Before consent has been obtained, participants will be asked inclusion/exclusion criteria questions during pre-screening to determine study eligibility. Before completing any procedures or collecting any data that are not part of usual care, written informed consent, when applicable) will be obtained. Potential eligibility may be assessed as part of a routine-care examination.

A participant is considered enrolled when the informed consent form has been signed by the participant and the study team.

Consenting procedures and documentation is defined in section 15.3.

3.3 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by licensed personnel, and pregnancy testing (if applicable) to screen for exclusionary medical conditions. If done remotely, a physical exam documented in the prior 18 months can suffice for the physical exam but will not serve as an exclusionary criterion if not available. If done remotely, participants may self-report height and weight. Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion.

3.4 Participant Inclusion Criteria

The participants must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1. Age ≥18.0 and ≤70 years old at time of consent
2. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year
3. Currently using insulin for at least six months
4. Currently using insulin pump for at least three months

5. Using insulin parameters such as carbohydrate ratio and correction factors consistently on their pump in order to dose insulin for meals or corrections
6. Access to internet and willingness to upload data during the study as needed
7. For females, not currently known to be pregnant or breastfeeding
8. If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of childbearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
9. Willingness to suspend use of any personal CGM for the duration of the clinical trial once the study CGM is in use
10. Willingness to use the UVa closed-loop system throughout study admission
11. Willingness to use lispro (Humalog) or aspart (Novolog) during the study admission.
12. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (including metformin, GLP-1 agonists, pramlintide, DPP-4 inhibitors, biguanides, sulfonylureas and naturaceuticals)
13. Willingness to eat at least 1 g/kg of carbohydrate per day during the hotel admission
14. Willingness to reschedule if placed on oral steroids
15. An understanding and willingness to follow the protocol and signed informed consent
16. Willingness to comply with COVID-19 precautions as defined by the study team. (Study team will reference section 10.3.)
17. Willingness to provide a copy of COVID-19 vaccination record, if available.

3.5 Participant Exclusion Criteria

The participant must not have any exclusion criteria in order to be eligible to participate in the study.

1. History of diabetic ketoacidosis (DKA) in the 12 months prior to enrollment
2. Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment
3. Pregnancy or intent to become pregnant during the trial
4. Currently being treated for a seizure disorder
5. Planned surgery during study duration

6. Treatment with any non-insulin glucose-lowering agent (including metformin, GLP-1 agonists, pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals)
7. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol.
8. Use of an automated insulin delivery mechanism that is not downloadable by the subject or study team
9. Known contact with a COVID-19 positive individual within 14 days of the hotel/rental house studies.

3.6 Eligibility Screening Procedures

The participant will be evaluated for study inclusion and exclusion eligibility after the informed consent form has been signed by the participant and the study team.

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion.

1. Demographics
    - Date of birth
    - Gender
    - Race
    - Ethnicity
2. Medical History
    - Duration of disease (number of years)
    - Current insulin pump model
    - History of CGM use
    - Current treatment
        i. Basal rates
        ii. Carbohydrate ratios
        iii. Insulin sensitivity factors
        iv. Target glucose
        v. Average daily insulin
    - History of diabetic ketoacidosis
    - History of severe hypoglycemia
    - History of seizures
    - Loss of consciousness

- Surgical history
- Allergies
- Concomitant medications

3. Physical Examination – If performed remotely, a historical history and physical report within 18 months of screening appointments may be used but is not required for eligibility. If vitals are not available, may include self-reported weight and height.

    - Weight
    - Height
    - Blood pressure
    - Temperature
    - Heart Rate

4. Screening Labs

    - Hemoglobin A1c point of care
    - Urine or serum pregnancy test for all women of childbearing potential

Screening procedures will last approximately 1-2 hours. Screening can be performed via telephone or video conference. Once all results of the screening evaluations are available, a decision will be made to determine the participant's eligibility for the study or if one or more part of the screening will have to be repeated. If at the first screening or repeat screening an exclusionary condition is identified, the participant will be excluded from participation with follow up and referred to their primary care physician as needed. The study physician may elect to rescreen participants if their clinical situation changes. Notably, screening is for determining study eligibility. Once participants are found to be eligible, they can begin their data collection phase as noted in Pilot Participants or Main Study.

3.7 Demographic Data Survey

The Demographic Data Survey will be electronically administered once eligibility has been met.

Chapter 4 Randomization

Participants will receive the three different experimental condition (FCL, FCL+, HCL) in random order as described below.

4.1 Pilot Study Participants

Pilot participants will not be randomized but will only use the meal anticipation module with an experimental meal without carbohydrate announcement and a study meal that is later than the usual entrained timing.

4.2 Main Study Participants

Once eligibility is met and the Data Collection Phase (CGM/Meal Entrainment) period is complete, the participant may continue to randomization. Screening failures and study dropout participants may be replaced. Randomization will determine the order of the Study Controller Sessions, with potential order as shown in Figure 1. Randomization will occur via permuted blocks of 6.

Chapter 5 Study Equipment Training

Equipment training may begin at arrival to hotel after UVa AP system has been put in place. The purpose of this training is to introduce the study insulin pump and study CGM to the participant.

The participant's insulin parameters will be programmed into their study insulin pump by two research staff. Subjects will then switch to the study insulin pump. The participant's personal pump and infusion site will be removed.

The participant will have the insulin pump and sensor on them at all times. Study supplied phones will be used if DiAs is the system utilized and otherwise upon participant request.

5.1 CGM Training

A study CGM will be provided to all participants at the training session. The participants will be provided with CGM equipment and instructed to use the study CGM on a daily basis. If the participant has prior use of the CGM, re-training will be specific to the individual. The study team may elect to have less frequent CGM users watch the Dexcom online training videos (https://www.dexcom.com/training-videos) to assist in the training session. Study staff training may include review of study CGM in real-time to make management decisions and how to review the data after an upload for retrospective review. Study staff will specifically identify how alarms are set using the app and the frequency that these alarms will repeat.

The participants personal CGM will be discontinued. The participants will be observed placing the sensor and will learn/review how to access the CGM trace via the DiAs phone or the Tandem research pump, as needed. The participants will be asked to perform fingerstick blood glucose measurements (if needed) in accordance with the labelling of the study CGM device.

An electronic copy of the CGM user's guide will be provided for the participants to read. The study team will be sure that the participants will leave the training session knowing how to use proper use the CGM. The study team will be available for any questions.

Participants will have the option of using their personal smartphone or receive a study smartphone to use in order to collect the data from the devices. If the participant elects to use a personal device, the Dexcom app will be downloaded to their phone in order to monitor the participant's CGM values and alerts in real-time may be used.

5.2 Activity Tracker

All participants may be asked to wear an activity tracker (e.g. Fitbit) during the entire study (home and hotel admissions) to record information about movement and heart rate though not an endpoint in this study.

5.3 Study Insulin Pump

The study team will be responsible monitoring and managing the study insulin pump during the hotel admissions. The participants may be provided a quick overview on its functionality if they understand the equipment.

5.3.1 Study Insulin Pump Topics

The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed.

The participant will be instructed infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including entering meals, stopping a bolus, etc.

5.3.2 Other Issues

The participant will be instructed to notify study staff if they experience any issues with the study devices during the hotel admission. Staff will be present in the event that if insulin is delivered by any means other than the study pump (e.g. injection of subcutaneous insulin via syringe in the event of infusion site failure). If insulin is delivered by any means other than the study pump, the study team will be instructed to turn off closed-loop mode for approximately four hours.

The participant will also be asked to alert the study clinical staff for technical issues with the Tandem research pump and/or the DiAs system, including use of the study pump and study CGM (open loop mode) during periods of component disconnections or technical difficulties.

A glucagon emergency kit will be available. Participants who currently do not have one will be asked to obtain a prescription for the glucagon emergency kit.

Glycemic Treatment Guidelines (Chapter 8) will be available for staff use during the study admissions.

5.3.3 Optimization of Insulin Pump Settings

Data-driven optimization of pump settings can occur any time prior to the hotel admission, particularly if the participant contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia. No pump settings changes can occur during closed loop testing.

Chapter 6 Pilot Study

In order to optimize the flow of the study visits during the Main Study, we will perform a Pilot Study with up to three pilot participants at a local hotel or rental house. Participants and staff will adhere to the COVID -19 Mitigation Plan as outlined in Section 10.3. The duration of the pilot admission will be approximately 24 hours with the intent of collecting appropriate safety data. Pilot study participants are eligible to enroll in the Main Study.

6.1 Data Collection Phase

Participants will wear the study CGM at home for approximately 28 days. If currently using a Dexcom G6, up to 30 days of data may be obtained from the participant's personal CGM and pump. The investigators may still ask G6 users to complete this run-in phase at their discretion.

6.2 Qualifications and Role of the Staff

For the pilot study, there will be at least two study staff present at all times at the study site, at least one of whom will be clinical staff (e.g. nurse, physician, nurse practitioner). There will be a physician available either on-site or off-site within an approximate 20-minute drive at all times. In addition, one of the study medical physicians and one senior engineer will be on call during the entire admission. Glucagon for the emergency treatment of hypoglycemia will be available on-site.

6.3 Pre-Admission Check-In Visit

Pilot participants will be contacted by the study team approximately 24-48 hours prior to the hotel admission to verify the following information:

- Inquire about any changes to the participant's medical history
- Study equipment (e.g. CGM and activity tracker) initiation has occurred
- Determine pump profile(s) the participant uses on certain days
- New CGM sensor has been placed approximately 24-72 hours prior to admission for proper warm-up
- Verify with the participant that the goal CGM reading at time of arrival is less than 200 mg/dL; this may require contact with the study physician prior to arrival on the day of the study visit
- Should any concerns regarding medical history, pump information, or unforeseen issues arise, the admission will be cancelled for that participant at the discretion of the investigator

6.4 Admission Check-In

For the pilot study, one to two participants will be assessed at a time. The participant will arrive at the hotel or rental house on the first day of the admission. The study team will perform vital signs, and any changes to the participant's medical history. Any changes to medical history will be communicated to the medical physician to ensure continued eligibility and participation.

A urine pregnancy test will be collected if relevant. The test must be negative for the participant to continue with the study.

The subject's CGM reading, and ketone concentration will be recorded. In the event that the participant's CGM reading is not between 80-250 mg/dL or ketone concentration is ≥0.6 mmol/L prior to initiation of the UVa AP system, the study physician may recommend additional insulin dosing according to the participants' usual doses. Study physician may elect to cancel participant's participation in the hotel admission if concerned about their medical safety. This participant will not be replaced.

The participant's home insulin pump will be discontinued, and the study Tandem research insulin pump will be initiated. The study team will ensure the proper function of the CGM, insulin pump, and activity tracker. The goal will be to initiate Closed-Loop Control by approximately lunch time, running the RocketAP system on the DiAs platform.

The CGM used in the study is FDA-approved for the non-adjunctive measurement of blood glucose (i.e. the CGM reading can be used for insulin dosing decisions). The CGM readings will be the primary source of blood glucose values. There are no protocol fingerstick blood glucose measurements other than at times of CGM calibration (if necessary) and if directed by the study team. Fingerstick blood glucose measurements may be taken whenever participants experience symptoms, if the CGM glucose is suspected to be erroneous, or any time the participant would like to be reassured.

6.5 Study Meals

Participants will eat a structured dinner at approximately 6-7 pm during the admission. The participant will not announce carbohydrate ingestion, allowing testing of the RocketAP controller. Throughout the Pilot study, the participant will remain in closed loop mode.

Participants will consume approximately 30-90 grams of carbohydrates at each meal. The study participant will determine the quantity of carbohydrates in each meal. Staff will separately record the calculated carbohydrate count. FCL and FCL+ will be tested during the pilot. Staff will continue to follow the Glycemic Treatment Guidelines detailed in Chapter 8.

6.6 Admission Activities

Participants will be free to engage in low-intensity activity (i.e. walking) during the admission. Participants will enjoy quiet activities in the evening.

6.7 Admission Discharge

Discharge will be at approximately 8 a.m. If the CGM values are above 300 mg/dL and ketone values are >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. A qualified clinical study team member (e.g. MD, NP, CDE) will assess and discuss the transition back to usual care with the study participant.

Participants will be asked to continue monitoring ketone levels for 24-48 hours after the hotel admission if ketones were present at time of discharge. Urine ketone supplies may be provided for this testing.

6.8 Post Admission Check-In Visit

Approximately 24-48 hours after the hotel admission, the study team will contact the participant via phone/email/text/text to assess adverse events, adverse device effects, and device issues.

Chapter 7 Main Study

7.1 Hotel Admission

Main Study participants will participate in hotel admission. Each admission will be up to approximately 92 hours in duration. Participants and staff will adhere to the Center for Disease Control and Prevention (CDC) and local guidance COVID -19 Mitigation Plan effective at the time of the study.

7.2 Data Collection Phase (CGM/Meal Entrainment period)

Participants who are not familiar with the Dexcom G6 CGM will have a run-in phase in which they wear the equipment at home for approximately 14 days to ensure proper use of the equipment. All participants will wear the CGM at home for approximately 28 days, with instructions to eat breakfast and dinner at approximately the same time 4-5 days each week. The timing of the breakfast will be requested to be at or before 8 am and the timing of the dinner will be requested to be between 6-9 pm. If currently using a Dexcom G6, up to 30 days of data may be obtained from the participant's personal CGM and pump. If participant reports consistent timing of meals in the 30 days before enrollment, these data may be used instead of the CGM/Meal Entrainment period at the discretion of the investigators. The investigators may ask current Dexcom G6 CGM users to complete this run-in phase at their discretion. Data-driven optimization of insulin dosing parameters can occur at any time during and immediately after the CGM/Meal Entrainment period.

7.3 Qualifications and Role of the Staff

There will be at least two study staff present at all times at the study site when the investigational device is active, with at least one of whom will be clinical staff (e.g. nurse, physician, nurse practitioner). There will be a physician at the hotel or nearby on call during the study at all times. In addition, at least one senior engineer will be on call during the entire admission. Participants will be remotely monitored by at least one study team member using a web-based remote monitoring system that has been previously established for DiAs. The web-based remote monitoring system will display real-time insulin delivery, CGM and other system information to allow for patient safety monitoring. In addition, study team members will be trained in all protocol and Glycemic Treatment Guideline procedures (Chapter 8). The closed-loop system will be managed by the participant with study-staff supervision, particularly at the time of insulin boluses. Glucagon for the emergency treatment of hypoglycemia will be available on-site.

7.4 Pre-Admission Check-In Visit

Participants will be contacted by the study team approximately 24-72 hours prior to each hotel admission if most recent contact with the study participant exceeds 10 days. The study team will verify the following information:

- Inquire about any changes to the participant's medical history
- Adhere to relevant sections of 10.3 COVID-19 Risk Mitigation Plan
- Study equipment (e.g. CGM and activity tracker) initiation has occurred
- Determine pump profile(s) the participant uses on certain days
- New CGM sensor has been placed approximately 24-72 hours prior to admission for proper warm-up
- Verify with the subject that the goal CGM reading at time of arrival is less than 200 mg/dL; this may require contact with the study physician prior to arrival on the day of the study visit
- Should any concerns regarding medical history, pump information, or unforeseen issues arise, the admission will be cancelled for that participant at the discretion of the investigator

7.5 Admission Check-In

Day 0 Arrival

Participants will arrive at the hotel on the first day of the admission. The study team will inquire about any changes to the participant's medical history. Any changes to medical history will be communicated to the medical physician to ensure continued eligibility and participation.

A new CGM sensor will be placed if the sensor has not been changed within the last 24-48 hours.

Participants will be provided unstructured dinner (no meal-time restrictions). Participants are on their home devices overnight and, therefore, no study staff are required to be present.

Day 1 Morning

The study team will perform vital signs. The subject's CGM reading, and ketone concentration will be recorded. In the event that the participant's CGM reading is not between 80-250 mg/dL or ketone concentration is ≥0.6 mmol/L prior to initiation of the UVa artificial pancreas system, the study physician may recommend additional insulin dosing according to the participants' usual doses. Study physician may elect to cancel participant's participation in the hotel admission if concerned about their medical safety. This participant will not be replaced. A urine pregnancy test will be collected for female participants of childbearing age within 24 hours prior to

transitioning to the AP Controller. The test must be negative for the participant to continue with the study.

The participant's home insulin pump will be discontinued, and the study insulin pump will be initiated. The insulin site will be changed and the participants may use the Tandem t:AP2 pump without the DiAs platform for basal delivery until transition to AP. The study team will ensure the proper function of the CGM, insulin pump, and activity tracker.

The CGM used in the study is FDA-approved for the non-adjunctive measurement of blood glucose (i.e. the CGM reading can be used for insulin dosing decisions). The CGM readings will be the primary source of blood glucose values. There are no protocol fingerstick blood glucose measurements other than at times of CGM calibration (if necessary) and if directed by the study team. Fingerstick blood glucose measurements may be taken whenever participants experience symptoms, if the CGM glucose is suspected to be erroneous, or any time the participant would like to be reassured. Glycemic Treatment Guidelines to be used during the hotel admission are defined in a separate document.

7.6 Study Meals

Participants will eat structured study meals during the admission, with the same amount of carbohydrate, protein, and fat for the same meals (breakfast, lunch, dinner) on different days (days 1, 2, and 3). Meal content may differ on the same day. The dinners will occur approximately 2 hours after the time that is usual for the participant from the Data Collection Phase (CGM/Meal Entrainment period, defined as the median time of recorded meals between 6 and 8pm). The breakfasts will occur at approximately the time that is usual for the participant from the Data Collection Phase (CGM/Meal Entrainment period, defined as the median time of recorded meals between 5am and 8am), and the lunches will occur at approximately noon (see Figure 2).

Participants will consume approximately 30-90 grams of carbohydrates at each meal. The study participant will determine the quantity of carbohydrates in each meal and will enter this information into the insulin pump with staff supervision during HCL. Staff will separately record the calculated carbohydrate count at each meal. The carbohydrate content of the system will only be announced during the HCL Controller period. During HCL, correction doses of insulin will also be calculated at the time of meals. During FCL and FCL+, study staff will be monitoring the closed-loop system as usual to identify insulin administration in the setting of postprandial hyperglycemia. Staff will continue to follow the Glycemic Treatment Guidelines detailed in Chapter 8. Snacks with carbohydrates will not be allowed unless for the treatment of low blood sugars. Non-carbohydrates snacks are allowed throughout the protocol. Blood glucose levels will

be followed via continuous glucose monitor and glucose values will be managed by the AP system as usual.

7.7 Admission Activities

Participants will be free to engage in low-intensity activity (i.e. walking) during the hotel admission. Participants may leave the hotel to be outside, provided they are accompanied by a study staff member and masking and distancing are observed, as described in Section 10.3. Participants will enjoy quiet activities in the evening.

7.8 Admission Discharge

Discharge will be at approximately 4 pm. If the CGM values are above 300 mg/dL and ketone values are >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. A qualified clinical study team member (e.g. MD, NP, CDE) will assess and discuss the transition back to usual care with the study participant. Study team will reference the Glycemic Treatment Guidelines.

Participants will be asked to continue monitoring ketone levels for 24-48 hours after the hotel admission if ketones were present at time of discharge. Urine ketone supplies may be provided for this testing.

7.9 Post Admission Check-In Visit

Approximately 24-48 hours after the hotel admission, the study team will contact the participant via phone/email/text to assess adverse events, adverse device effects, and device issues.

Chapter 8 Glycemic Treatment Guidelines

The following guidelines will be used for both the Pilot Study and the Main Study Admissions to the hotel/rental house.

The study physician will suggest appropriate treatment If CGM is <70 mg/dL or >250 mg/dL, or ketone test is >0.6 mmol/L at the start of the hotel admission. The study subject may continue participation in the trial once CGM is between 70-250 mg/dL and ketone concentration is ≤0.6 mmol/L.

If CGM <60 mg/dL at any time, subjects will be given 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 approximately 15-20 minutes. Hypoglycemic treatments can occur at any time per study physician request. Glucagon will be available at the study site and will be administered in the event of loss of consciousness or seizure related to hypoglycemia.

The study team may request fingersticks as needed. Any fingerstick readings obtained will be addressed the same way as the CGM values.

If CGM is >250 for more than 3 hours or >400 mg/dL at any time, study physician will be notified, and ketones will be checked. In addition, insulin administration by the closed-loop system will be evaluated and infusion sites assessed. If ketone concentration is >0.6 mmol/L, the study team will check the insulin pump infusion site and consider changing and correction insulin will be administered via the subject's insulin pump or subcutaneous as needed. If subcutaneous injection is administered, physician will determine if closed-loop control needs to be temporarily stopped for up to 4 hours. The study team will monitor CGM changes and ketones will be checked every 60 minutes until ketone concentration is ≤0.6 mmol/L. If ketone concentration is ≥3.0 mmol/L, the study physician will recommend the appropriate medical treatment.

The study physician will suggest appropriate treatment If CGM is <70 mg/dL or >300 mg/dL and ketone test is >0.6 mmol/L at the conclusion of the hotel admission. The study subject may be discharged home once CGM is between 70-300 mg/dL and ketone concentration is ≤0.6 mmol/L.

Chapter 9 Testing Procedures

9.1 Laboratory / Point of Care Testing

9.1.1 HbA1c

A blood sample will be obtained at screening to obtain a baseline hemoglobin A1c level. A Blood test obtained within 2 weeks prior to enrollment may be used.

HbA1c level may be measured by study team using the DCA2000, a comparable point of care device, at time of screening

Labs may be obtained at a local laboratory (e.g. LabCorp) convenient to the participant.

9.1.2 Pregnancy Test

A serum or urine pregnancy test will be required for women of childbearing potential at in person visit and admission. Test must be negative to participate in the study.

9.1.3 COVID-19 Testing (Non-vaccinated participants/staff)

Non-vaccinated participants and study staff (research coordinators, technicians, nurses, and physicians) will be tested with an FDA authorized COVID-19 test approximately 72 hours before starting the study hotel, and upon admission to the study hotel (main study only). Individuals with COVID-19 positive tests will be excluded from the study.

9.1.4 Demographic Data Survey

The Demographic Data Survey will be asked at only the screening appointment and will reflect the status of the participant.

Chapter 10 Risks Associated with Clinical Trial

10.1 Potential Risks and Benefits of the Investigational Device

Risks and Benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia, hyperglycemia and ketone formation are always a risk in participants with type 1 diabetes and participants will be monitored for these symptoms.

10.1.1 Venipuncture Risks

A hollow needle/plastic tube may be placed in the arm for taking blood samples (e.g. external HbA1c measurements for inclusion criteria). Blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

10.1.2 Fingerstick Risks

About 1 drop of blood will be removed by fingerstick for measuring blood sugars and sometimes HbA1c or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as finger sticks are part of the usual care for people with diabetes.

10.1.3 Subcutaneous Catheter Risks (CGM)

Participants using the CGM will be at low risk for developing a local skin infection at the site of the sensor needle placement. If a catheter is left under the skin for more than 24 hours it is possible to get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causes a bruise (1 in 10 risk).

Study staff should verbally alert the participant that on rare occasions, the CGM may break and leave a small portion of the sensor under the skin that may cause redness, swelling, or pain at the insertion site. The participant should be further instructed to notify the study coordinator immediately if this occurs.

10.1.4 Risks of Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less

than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and that for a few days the participant may not be as aware of symptoms of hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery.

10.1.5 Risks of Hyperglycemia

Hyperglycemia is likely because of the study design including unannounced carbohydrate ingestion. Also, hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. A CGM functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery.

10.1.6 Risks of Device Reuse

Participant will be informed that FDA or relevant national authorities have approved the insulin pump, CGM, glucometer and ketone meter 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.

The study CGM system is labelled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The transmitter and receiver may be reused during the study after cleaning the device using a hospital-approved cleaning procedure. The transmitter is attached to the sensor but does not enter the skin and the receiver, if used, is a handheld device.

The study insulin pumps are labelled for single-patient use. During the study, this device may be reused after cleaning adhering to a hospital-approved cleaning procedure. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.).

The study blood glucose meter and blood ketone meter are labelled for single-patient use. During the study, these devices may be reused after cleaning adhering to a hospital-approved cleaning procedure.

10.1.7 Device Cleaning Instructions

CGM cleaning instructions are provided in the Dexcom G4 Platinum (Professional) Cleaning and Disinfection manual (current edition) and a similar approach will be applied for the G6 version used in this study. The transmitter should be cleaned with Clorox Healthcare® Bleach Germicidal Cleaner or any disinfectant product in a spray bottle containing a bleach solution of 6500 parts per million with the EPA registration number 56392-7. The transmitter will be submerged in this

solution and then placed on an absorbent wipe or clean surface. Two sprays will be dispensed from the Clorox cleaner onto each side of the transmitter. A nylon brush will be used to scrub the transmitter on all sides for 30 seconds. The transmitter will be placed in the Clorox Cleaner solution for one minute. Transmitter is then rinsed under flowing tap water for ten seconds. The transmitter will then be disinfected using a disinfectant product with EPA registration number 56392-7 using similar procedures as the cleaning process.

Per the pump manufacturer, the insulin pump will be cleaned with a damp lint-free cloth. Use of household or industrial cleaners, solvents, bleach, scouring pads, chemicals, or sharp instruments are prohibited. The pump should never be submerged in water. If needed, use only a very mild detergent, such as a bit of liquid soap with warm water. A soft towel will be used to dry the pump.

The glucometer is cleaned and disinfected with two separate Super Sani-Cloths (EPA number 9480-4). The entire surface will be cleaned, making sure the surface stays wet for 2 minutes. This step is repeated with a clean cloth for disinfecting the device.

The Precision Xtra User's Guide suggests that healthcare professionals use 10% bleach, 70% alcohol or 10% ammonia to clean the device.

Equipment that touches intact skin will be cleaned with ethyl or isopropyl alcohol (70-90%), quaternary ammonium germicidal detergent (i.e. Cavicide, EPA number 46781) 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 of the equipment. 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.

In the event a manufacturer updates cleaning procedures for their device, the study team will adhere to the most current recommendations.

There is the risk of blood sampling collection and 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 subject's protection (i.e. hand washing, changing gloves frequently, disposing needles properly). Gloves will be removed, and hands washed or sanitized prior to leaving and upon return to the subject's room. Soiled linen will be changed to minimize the transfer of pathogenic organisms.

10.1.8 Hb1Ac Risk

An NGSP Point of Care analyzer (i.e. DCA Vantage Analyzer) will be utilized at the research site to obtain the subject's HbA1c level.

10.1.9 Other Risks

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or to secure the insulin infusion sets for the continuous subcutaneous insulin infusion. If these reactions occur, different adhesives or "under-taping" (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

Whenever the skin is broken there is the possibility of an infection. The CGM and pump infusion sites are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection. These occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. The risk of skin problems could be greater if you use a sensor for longer than it is supposed to be used. Therefore, participants will be carefully instructed about proper use of the sensor.

Data downloaded from the CGM, pump, glucometer, and ketone meter will be collected for the study as measures of diabetes self-management behaviors. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

10.1.10 Known Potential Benefits

It is expected that this protocol will yield increased knowledge about using an automated closed-loop system with anticipatory action to control glucose levels. The individual participant may not benefit from study participation.

10.1.11 Risk Assessment

Based on the facts that (1) adults with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may increase the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may increase the likelihood of hyperglycemia, (3) mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4) rapid reversal of hypoglycemia and hyperglycemia can be achieved.. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the participants and general benefit to others with diabetes.

10.2 General Considerations

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

Whenever possible, data will be directly collected in electronic case report forms, which will be considered the source data.

The protocol is considered a significant risk device study, due to the fact that the closed-loop system is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

10.3 COVID-19 Risk Mitigation Plan and Justification

The study team will follow CDC guidelines that are in effect at the time of the study admission. Participants who do not provide a copy of their COVID-19 vaccination record will be considered not vaccinated.

10.3.1 Participants and Study Personnel

We will follow a combination of approaches to increase our likelihood of having all COVID-free environment:

- We will follow CDC and local guidelines in effect at the time of the study.
- All participants will be ineligible if they have had known COVID-19 exposure or symptoms within 14 days of hotel admission.
- Non-vaccinated participants and study staff (research coordinators, technicians, nurses, and physicians) will be tested with an FDA authorized COVID-19 test approximately 72 hours before their participation in the study hotel. Those with positive tests will be excluded from the study.
- Any participants with positive test will be discharged from the study. Hotel rooms of these participants will be restricted from future use. We will limit any personal interaction between study personnel and these individuals. We will follow local guidelines in effect at the time of study to guide interactions.
- All study staff onsite will abide by UVa clinical protocols currently in place at the time of the study for healthcare workers which stands as the standard-of care for those involved in patient care. This protocol may include use of the HOOS Health Check app.

10.3.2 Environment

The study team will adhere to current hotel guidelines.

Chapter 11 Adverse Events, Device Issues, and Stopping Rules

11.1 Definitions

11.1.1 Adverse Events (AE)

Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation (section 11.2) for reportable adverse events for this protocol).

Positive pregnancy test will be not considered adverse event.

11.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (life threatening).
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

11.1.3 Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

11.1.4 Adverse Device Effect (ADE)

Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed.

11.1.5 Device Complaints and Malfunctions

A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labelling for the device. The intended performance of a device refers to the intended use for which the device is labelled or marketed. (21 CFR 803.3).

11.2 Reportable Events

For this protocol, a reportable adverse event includes any untoward medical occurrence that meets one of the following criteria:

- A serious adverse event as defined in section 11.2
- An Adverse Device Effect as defined in section 11.1.4, unless excluded from reporting in section 11.7
- An Adverse Event as defined in section 11.1.1 occurring in association with a study procedure
- An AE as defined in section 11.1.1 which leads to discontinuation of a study device for 2 or more hours
- Hypoglycemia meeting the definition of severe hypoglycemia as defined in section 11.2.1
- Diabetic ketoacidosis (DKA) as defined in section 11.2.2 or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events unless associated with an Adverse Device Effect. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

11.2.1 Hypoglycemia Event

Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when the following definition for severe hypoglycemia is met:

- the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions
- impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ 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

11.2.2 Hyperglycemia Events/Diabetes Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following four criteria is met:

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis
- blood ketone level ≥1.5 mmol/L and communication occurred with a health care provider at the time of the event
- blood ketone level ≥3.0 mmol/L, even if there was no communication with a health care provider

Hyperglycemic events are classified as DKA if the following are present:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting
- Serum ketones ≥1.5 mmol/L or large/moderate urine ketones
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15
- Treatment provided in a health care facility

All reportable Adverse Events—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—will be reported on an adverse event form online. Each adverse event form is reviewed by the study PI to verify the coding and the reporting that is required.

11.3 Relationship of Adverse Event to Study Device

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

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

- There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the

participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

- Evidence exists that the adverse event has an etiology other than the study intervention (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

11.4 COVID-19 Transmission

While we are taking significant steps to prevent transmission of COVID-19 during this study, there is a possibility that participants, based either on exposure before the hotel admission or during the stay, are infected with COVID-19. Infection with COVID-19 could be determined by testing 48-hours prior to study admission and the day of admission for participants (in which case would be deemed not related to the study) or onset of new symptoms during the stay. Any appearance of COVID-19 symptoms in participants will be cause for repeat COVID-19 testing and quarantine until test results are returned. If this COVID -19 test is positive, the participant will be discharged from the study. Study team follow applicable local guidelines in effect at the time of study.

In the event of a COVID-19 positive test in a participant, the study team will follow up with the participant via phone until conclusion of treatment for the COVID-19 related symptoms. All participants will be asked to follow up via phone with the study team in the event of a positive test within 14 days after discharge from the hotel.

11.5 Intensity of Adverse Event

The intensity of an adverse event 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.

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities but is usually ameliorated by simple therapeutic measures.
- SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

11.6 Coding of Adverse Events

Adverse events will be coded by the Study PI per the UVA IRB website instructions (i.e. mild, moderate, severe). The study PI will review the investigator assessment of causality and may agree or disagree. The study PI assessments will be recorded. The study PI will have the final say in determining the causality.

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.

11.7 Outcome of Adverse Events

The outcome of each reportable adverse event will be classified by the investigator as follows:

- RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
- An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
- The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

All clinically significant abnormalities of clinical laboratory measurements or adverse events occurring during the study and continuing at study termination should be followed by the participant's physician and evaluated with additional tests (if necessary) until diagnosis of the underlying cause, or resolution. Follow-up information should be recorded on source documents.

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be

contacted for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

11.8 Reportable Device Issues

All UADEs, ADEs, device complaints, and device malfunctions will be reported irrespective of whether an adverse event occurred, except in the following circumstances.

The following device issues are anticipated and will not be reported but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than the number of days expected per CGM labelling
- CGM tape adherence issues
- Pump infusion set occlusion not leading to ketosis
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement or pump infusion set placement that do not meet criteria for AE reporting

11.9 Timing of Event Reporting

- UADEs must be reported within 10 working days to the FDA after the sponsor first receives notice of the adverse effect.
- Other reportable adverse events, device malfunctions (with or without an adverse event) and device complaints should be reported promptly, but there is no formal required reporting period.
- The IDE Sponsor will investigate the UADE and if indicated, report the results of the investigation to the IRBs FDA and DSMB within 10 working days of the study team becoming aware of the UADE per 21CFR 812.46(b) (2).
- The FDA and DSMB will determine if the UADE presents an unreasonable risk to participants. If so, the Study PI must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5

working days makes this determination and no later than 15 working days after first receipt notice of the UADE.

- In the case of a device system component malfunction (e.g. pump, CGM, control algorithm), information will be forwarded to the responsible manufacturer by the study personnel.

11.10 Stopping Criteria

11.10.1 Participant Discontinuation

Rules for discontinuing study device use are described below.

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- The participant tests positive for COVID-19 (during study testing or otherwise within 14 days of study start) or subsequently develops symptoms for COVID-19 and tests positive.
- Two distinct episodes of DKA, or one distinct episode of DKA attributable to study device use.
- Two distinct severe hypoglycemia events meeting the definition in section 11.2.1 of the protocol, or one distinct severe hypoglycemia event attributable to study device use and meeting the definition in section 11.2.1 of the protocol.

11.10.2 Suspending/Stopping Overall Study

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in section 11.2.2), use of the study device system will be suspended while the problem is diagnosed.

In the event that two distinct episodes of DKA or two distinct severe hypoglycemia events as defined in section 11.2 occur, the overall study would be suspended while the underlying conditions are determined.

In addition, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The affected study activities 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 Study PI will review all adverse events and adverse device events that are reported during the study. The

Study PI may request suspension of study activities or stoppage of the study is deemed necessary based on the totality of safety data available.

11.11 Independent Safety Oversight

A Data and Safety Monitoring Board (DSMB) will review compiled safety data at periodic intervals. In addition, the DSMB will review all DKA and severe hypoglycemia irrespective of relatedness to study device use, and all serious events (including UADEs) related to study device use at the time of occurrence. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding DSMB review will be documented in a separate DSMB document.

11.12 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.

Chapter 12 Miscellaneous Considerations

12.1 Prohibited Medications, Treatments, and Procedures

Participants using glulisine at the time of enrollment will be asked to contact their personal physician to change their prescribed personal insulin to lispro or aspart for the duration of the trial.

The study devices (study insulin pump, study CGM) must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or diathermy treatment. Participants may continue in the trial after temporarily discontinuing use if requiring one of the treatments above.

12.2 Participant Withdrawal

Participation in the study is voluntary. Participant may withdraw at any time. For participants who do withdraw from the study, the study team will determine if their data will be used in analysis.

12.3 Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study may be shared with the third-party collaborators. De-identified subject information may also be provided to collaborators involved in the study after the appropriate research agreement has been executed.

Chapter 13 Statistical Consideration

13.1 Statistical and Analytical Plans

We will conduct a paired comparison of outcomes between each admission (FCL vs. FCL+, HCL vs FCL, and FCL+ vs HCL), using Student paired t-test for percent in ranges and average CGM, and Wilcoxon test for overtly non normally distributed residuals (which often occur with outcomes such as % time below 70mg/dL, as well as 50, or 60mg/dL, and % time above 250mg/dL). Furthermore, we will use repeated measure ANOVA 3x2 with within factors and contrasts (to differentiate the repeated measures) if covariates are deemed necessary in the analysis.

We do not plan to correct for multiple comparisons.

We do not expect substantial missing values in this highly supervised study, but if more than 3 subjects have one or more missing admissions, we will consider switching from RANOVA to mixed model repeated measures.

13.2 Statistical Hypotheses

The hypotheses for the primary outcome are:

a. Null Hypothesis: There is no difference in the time spent in the 70-180mg/dL range within the breakfast postprandial period (mealtime to mealtime+5h) between FCL and FCL+ (without and with anticipation respectively)

b. Alternative Hypothesis: There is a difference in the time spent in the 70-180mg/dL range within the breakfast postprandial period (mealtime to mealtime+5h) a between FCL and FCL+ (without and with anticipation respectively).

13.3 Design and Randomization

The main study is itself a pilot study to assess glycemic responses to three different approaches to insulin dosing for carbohydrate ingestion, with different approaches to the RocketAP system (1) without the meal anticipation module and without carbohydrate announcement (FCL), 2) with the meal anticipation module on and without carbohydrate announcement (FCL+), or 3) with the meal anticipation module on and with carbohydrate announcement (HCL), in random order). This information is detailed in Table 1.

Randomization will occur via selection from the above list using permuted blocks in groups of 6.

13.4 Sample Size

As a Preliminary Study, the goal will be to complete up to 36 participants in the main study to provide data from a variety of individuals. This number was chosen out of feasibility and not from

a formal power calculation, and revised when new data (see reference 5) indicated that the outcome variance was likely to be greater than originally assumed. The pilot study for this proposal will assess ease of system use in up to 3 individuals prior to the beginning of the main study. Based on this empirical sample size, we would detect an effect size of approximately 0.5 at 80% power, and 0.6 at 95% power. Based on the recommended MCID of 5% TIR over a day, and assuming no influence of meal on overnight (midnight-6AM) control at TIR=90%, this would lead to an improvement in TIR of approximately 11% during the breakfast regimen. Considering the broad variability observed during un-bolused prandial control (SD_{TIR}≈22% from Garcia-Tirado et al 2021, reference 5), this leads to a MCID-derived Cohen-d effect size of approximately 0.5

13.5 Outcome Measures

13.5.1 Primary Efficacy Endpoint

The study design allows for multiple comparisons of blood glucose control during the study meals and treatment sessions, with for the primary comparison of interest being between the RocketAP with and without the meal anticipation module, without announcement of carbohydrate. Our primary endpoint is CGM time-in-range 70-180 mg/dL for the period between breakfast and lunch (approximately 5h). Additional comparisons are made between the RocketAP system without vs. with normal carbohydrate announcement (which determines efficacy vs. premeal bolus).

13.5.2 Secondary Outcomes

Each admission is separated in 5 windows of analysis:

1. The entirety of the admission (24h: 4pm to 4pm)
2. The 2 hours between expected dinner time and actual dinner time (day 1).
3. The overnight period (midnight to 6am day 2)
4. The window between the expected breakfast time and noon on day 2, ~5h (primary outcome)
5. The 4h following lunch (noon-4pm day 2)

For each of these periods we will compute the following outcomes:

5. Number of hypoglycemia events defined as at least two consecutive CGM values <70mg/dL or a hypoglycemia treatment (two events separated by less than 30 minutes are counted as one).

6. Percent CGM time <70 mg/dL
7. Percent CGM time between 80-140mg/dL
8. Percent CGM time between 70-180mg/dL
9. Percent CGM time >180 mg/dL
10. Percent CGM time >250 mg/dL
11. Units of insulin injected
12. Area under the curve when accounting for starting BG
13. Low Blood Glucose Index
14. High Blood Glucose Index
15. CGM coefficient of variation

13.6 Safety Analyses

We will assess for the system's functionality, including the ability of the system to run its code without error (delivering insulin safely, as planned), as well as its ability to avoid low BG <70 mg/dL.

13.7 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all randomized participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. Descriptive statistics will be displayed overall and by treatment group.

Will include:

1. Age
2. HbA1c
3. Gender
4. Race/ethnicity
5. CGM use before enrollment
6. AID use before enrollment

7. Diabetes duration
8. BMI
9. Total Daily Insulin

13.8 Device Issues

The following tabulations and analyses will be performed during time on the UVa AP systems to assess device issues:

1. Device malfunctions requiring study team contact and other reported device issues
2. % time CGM data available
3. % time with closed loop control

Chapter 14 Data Collection and Monitoring

14.1 Case Report Forms and Device Data

The study data are collected through a combination of case report forms (electronic and paper) and electronic device data files obtained from the software and individual hardware components. These electronic device files and electronic CRFs are considered the primary source documentation.

When data are directly collected in electronic case report forms, this will be considered the source data. Records will be maintained in accordance with ICH E6 and institutional regulatory requirements for the protection of confidentiality of participants.

14.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practices (GCP), or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions may be developed by the site and implemented as appropriate. Major deviations will be reported to the IRB-HSR within 7 calendar days of when the study team becomes aware of the event.

Chapter 15 Ethics/Protection of Human Participants

15.1 Ethics Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

15.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

15.3 Informed Consent Process

15.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to an individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator or their delegate will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participant will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participant and the parent(s)/legal guardians will sign the informed consent document prior to any procedures being done specifically for the study. The consent forms may be signed electronically with the use of the HIPAA compliant version of DocuSign. A copy of the informed consent document will be given to the participant for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.3.2 Participant and Data Confidentiality

The study monitor, representatives of the IRB or device company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Virginia Center for Diabetes Technology. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases may be de-identified and archived at the University of Virginia Center for Diabetes Technology.

Chapter 16 References

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