UNIVERSITY of VIRGINIA HEALTH SYSTEM | School of Medicine

UVA CENTER FOR DIABETES TECHNOLOGY

Fully Automated Closed Loop Control in Adolescents with Type 1 Diabetes (RocketAP)

Protocol Chair

Mark DeBoer, MD

University of Virginia

Center for Diabetes Technology

Version Number: v1.3

17-Nov-2020

KEY ROLES

Protocol Principal Investigator	
Name, degree	Mark DeBoer, MD, MSc., MCR
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			Original Protocol
1.1	Jon Olson	Mary Oliveri	10-Aug-2020	FDA Review: • Added stopping criteria of either one attributable DKA event or one attributable severe hypoglycemia event (section 11.9.1) • Added Definition of Data Breach (section 11.11)
1.2	Jon Olson	Mark DeBoer	21-Oct-2020	IRB FB Review: • Inserted Covid-19 Precautions (section 10.3)
1.3	Jon Olson	Mark DeBoer	11-Nov-2020	Follow-up Review: • Expanded on Covid-19 precautions

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Fully Automated Closed Loop Control in Adolescents with Type 1 Diabetes (RocketAP)

Protocol Version/Date: v1.2/17-Nov-2020

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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBGI	High Blood Glucose Index
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 in Adolescents with Type 1 Diabetes (RocketAP)
Investigational Device	Reactive Open-loop and Carbohydrate Kinetics EsTimation (Rocket) based Fully Automated Artificial Pancreas
Objectives	The purpose of this study is to show the safety and feasibility of a fully new fully automated AP controller based on automated meal priming and CHO kinetics estimation, within the UVA AP modular architecture.
Study Design	A randomized cross-over trial assessing glycemic responses to two different approaches to insulin dosing for carbohydrate ingestion (announced vs. unannounced), with two different AP systems (RocketAP vs. USS Virginia, aka Control-IQ, in random order)
Number of Sites	One
Endpoint	The primary outcome will be time in range 70-180 mg/dL from dinner time until midnight.
Population	Key Inclusion Criteria • Age 12-25 • 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 Key Exclusion Criteria • Hemoglobin A1c $\leq$ 12%
Sample Size	• Pilot Study: complete up to 3 participants • Main Study: complete up to 20 participants
Treatment Groups	• RocketAP • USS Virginia, aka Control-IQ
Participant Duration	Pilot Study: Participants will be admitted to a local hotel for approximately 42 hours and will have an experimental dinner with the RocketAP with no-carbohydrate announcement. Main Study: Participants will be admitted to a local hotel for approximately 64 hours.
Protocol Overview/Synopsis	Participants will be randomized to either the RocketAP experimental group or the Control-IQ control group. Each group will participate in two (2) ~64 hour admissions. During one admission, the RocketAP (Meal Control Module) group will have one dinner session with a normal carbohydrate announcement and one dinner session with no carbohydrate announcement. During the alternate admission, the participate will have the will have one dinner session with a normal carbohydrate announcement and one dinner session with no carbohydrate announcement while using the Control-IQ equipment. These studies will be performed under precautionary conditions where we will attempt to create a COVID-free "bubble" where participants and study personnel will have two rounds of testing to ensure that those in the "bubble" have very low risk of infection.

STUDY VISITS AND PROCEDURES SCHEDULE

	Screening	Study Equipment Training	CGM Run-In Phase	Pre-Admission Check-In	Study Admission #1	Post-Admission Check-In	Pre-Admission Check-In	Study Admission #2	Post-Admission Check-In
Location	**Clinic/ Remote**	**Clinic/ Remote Clinic/ Remote**	**Home**	**Phone/ Email/Text**	**Hotel**	**Phone/ Email/Text**	**Phone/ Email/Text**	**Hotel**	**Phone/ Email/Text**
Visit	**1**	**2**	**x**	**3**	**4**	**5**	**6**	**7**	**8**
Hotel Day	**NA**	**NA**	**x**	**NA**	**1-4**	**NA**	**NA**	**5-8**	**NA**
Informed Consent	X								
Eligibility Assessment	X								
Medical History	X								
HbA1c	X								
Pregnancy test (if applicable)	X	X			X			X	
Physical Exam	X								
Vital Signs (height/weight)	X								
Randomization					X				
COVID Testing				X	X			X	
CGM Run-In (non-G6 users)			~14 days if needed						
Study Dinner Sessions					Day 2 & 3			Day 6 & 7	
Survey / Questionnaires		X			Post			Post	X
Review diabetes management and AEs					X	X		X	X

Table of Contents

Chapter 1 Background 13
1.1 Introduction 13
1.2 Study Objective 13
1.3 Study Design 14
1.4 Study Device Download 17
1.5 Study System Issues 17
1.6 Purpose/Objectives of Clinical Study 17
Chapter 2 Study Devices 18
2.1 Insulin Pump 18
2.2 Continuous Glucose Monitor 18
2.3 Blood Glucose Meter and Strips 18
2.4 Ketone Meter and Strips 18
2.5 Study Devices Accountability Procedures 18
Chapter 3 Study Screening 19
3.1 Participant Recruitment and Enrollment 19
3.2 Informed Consent and Authorization Procedures 19
3.3 Screening Procedures 19
3.4 Participant Inclusion Criteria 19
3.5 Participant Exclusion Criteria 20
3.6 Eligibility Screening Procedures 21
3.7 Demographic Data Survey 22
Chapter 4 Randomization 23
4.1 Pilot Study Participants 23
4.2 Main Study Participants 23
Chapter 5 Study Equipment Training 24
5.1 CGM Training 24

5.2 Activity Tracker 25
5.3 Study Insulin Pump 25
Chapter 6 Pilot Study 27
6.1 Run-In Phase 27
6.2 Qualifications and Role of the Staff 27
6.3 Pre-Admission Check-In Visit 27
6.4 Admission Check-In 28
6.5 Hotel Admission Glycemic Treatment Guidelines 28
6.6 Study Meals 29
6.7 Admission Activities 29
6.8 Admission Discharge 29
6.9 Post Admission Check-In Visit 29
6.10 Medical Monitor Review 30
Chapter 7 Main Study 31
7.1 Run-In Phase 31
7.2 Qualifications and Role of the Staff 31
7.3 Pre-Admission Check-In Visit 31
7.4 Admission Check-In 32
7.5 Hotel Admission Glycemic Treatment Guidelines 32
7.6 Study Meals 33
7.7 Admission Activities 33
7.8 Admission Discharge 34
7.9 Post Admission Questionnaire 34
7.10 Post Admission Check-In Visit 34
7.11 Medical Monitor Review 34
Chapter 8 Medical Monitor Review 35
8.1 Medical Monitor Study Safety Data Review 35

8.2 Medical Monitor Decisions 35
8.3 Medical Monitor Main Study Safety Data Review 35
Chapter 9 Testing Procedures 36
9.1 Laboratory / Point of Care Testing 36
9.2 Questionnaire Schedule 36
Chapter 10 Risks Associated with Clinical Trial 37
10.1 Potential Risks and Benefits of the Investigational Device 37
10.2 General Considerations 41
10.3 COVID 19 Risk Mitigation Plan and Justification 41
Chapter 11 Adverse Events, Device Issues, and Stopping Rules 45
11.1 Definitions 45
11.2 Reportable Events 46
11.3 Relationship of Adverse Event to Study Device 47
11.4 COVID Transmission 48
11.5 Intensity of Adverse Event 48
11.6 Coding of Adverse Events 49
11.7 Outcome of Adverse Events 49
11.8 Reportable Device Issues 50
11.9 Timing of Event Reporting 51
11.10 Stopping Criteria 51
11.11 Independent Safety Oversight 52
11.12 Definition of a Data Breach 52
Chapter 12 Miscellaneous Considerations 53
12.1 Prohibited Medications, Treatments, and Procedures 53
12.2 Participant Withdrawal 53
12.3 Confidentiality 53
Chapter 13 Statistical Consideration 54

13.1 Design and Randomization 54
13.2 Sample Size 54
13.3 Outcome Measures 54
13.4 Safety Analyses 55
13.5 Baseline Descriptive Statistics 56
13.6 Device Issues 56
Chapter 14 Data Collection and Monitoring 58
14.1 Case Report Forms and Device Data 58
14.2 Study Records Retention 58
14.3 Protocol Deviations 58
Chapter 15 Ethics/Protection of Human Participants 59
15.1 Ethics Standard 59
15.2 Institutional Review Boards 59
15.3 Informed Consent Process 59
Chapter 16 References 61

Chapter 1 Background

1.1 Introduction

Maintaining blood glucose (BG) control among adolescents with Type 1 diabetes (T1D) is arguably the greatest challenge in entire field of T1D. While the reasons for this poor control are varied, a significant issue relates to missed meal boluses, which affects 65% of adolescents at least once weekly,[1] with 38% missing at least 15% of their boluses.[2] Adolescents who miss four boluses weekly experience an increase of 1% in their HbA1c.[1] While the advent of the artificial pancreas (AP) in this age range offers promise of safe reductions in HbA1c,[3] we previously found that the AP only partly compensates for missed prandial insulin[4]—demonstrating that some form of meal announcement is necessary for good BG control, even with an AP. One way to automate this process is by sharing the prandial dosing responsibilities between an automated insulin priming (based on CGM condition predictive of a safe situation for such insulin dosing) and a closed loop controller capable of reconstructing (estimating) the prevailing glucose rate of appearance from an unannounced meal. We have developed such an insulin priming schema and integrated it into a new version of the robust Model Predictive Controller UVa AP system (called the RocketAP).

In the current study, we are testing this new AP system in two configurations: hybrid and fully automated, among up to 20 adolescents. Our primary outcome will be one of efficacy in assessing how well the new system controls post-prandial blood sugar in the absence of carbohydrate announcement as compared to the same situation but using the Control-IQ closed loop algorithm, also designed at UVa and using the same modular architecture and safety system, but without insulin priming and with a less advanced model-based controller. Further comparisons will be made to blood sugar control on RocketAP with carbohydrate announcement and on Control-IQ with carbohydrate announcement. Adolescents will be started on the respective UVa artificial pancreas systems (RocketAP and Control-IQ in random order, both implemented on the DiAs platform, MAF 2109) and followed over the course of two dinners on each of the two platforms: a dinner where carbohydrate is announced as normal and the second where no announcement is made.

We hypothesize that performances of RocketAP in fully automated mode will lie in between Hybrid and Fully Automated Control-IQ. In time, this may provide an opportunity to improve blood sugar control among adolescents who miss meal announcement.

1.2 Study Objective

The purpose of this study is to test the RocketAP closed loop algorithm, a new algorithm leveraging the UVA modular architecture to insert a new basal rate modulator and a new insulin priming schema inside our validated framework including the UVA safety system module. We will

enroll up to 20 adolescents in a randomized cross-over trial, comparing blood glucose time in range 70-180 mg/dL following dinners consumed with or without announcement contrasting our currently approved algorithm (Control-IQ) with this new version.

1.3 Study Design

We will recruit approximately 30 participants, age 12-25 years, with a goal to have up to 20 participants complete the trial. The study will be performed overnight at a local hotel near the University Medical Center. This will be done under conditions where we will attempt to create a COVID-free "bubble," further described in section 10.3. The pilot study, which will have between 1 and 3 participants and be up to 2 days will be in a hotel/rented house. (Use of a rented house for a small group allows for more control over contact with non-study individuals.) Additional COVID-19 precautions are described below still apply.

1.3.1 Recruitment and Screening

Participants will be recruited from the UVa Center for Diabetes Technology registry, social media advertisements, physician contacts at pediatric diabetes clinics in Virginia (UVa, Virginia Commonwealth University, Children's Hospital of the King's Daughters) and camp attendance data. Potential participants will be informed of the study and offered a chance to have answered questions. Participants, and a parent if <18 years old, will provide written informed consent and, if participant is <18 years old, assent will also be obtained. Participants will be screened at a visit before the beginning of hotel stay to confirm eligibility. The screening visit can be performed by video conferencing. Prior to participation in the hotel study, participants will agree to self-isolate and have COVID testing.

1.3.2 CGM Data Collection

Following 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 can also be done via video conferencing, with supplies sent to the family. This study visit will be followed by 2 weeks of CGM and pump data collection at the participant's home/usual routine. Participants who have previously used a Dexcom CGM and have glucose data for the 2 weeks prior to the screening visit can skip the 2-week data collection. Participants will then be randomized to be on one artificial pancreas system or the other 1st (RocketAP or Control-IQ). This will be performed using two permuted blocks of 4 and one permuted block of 2.

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 either RocketAP or Control-IQ (in random order). Upon arrival at the hotel, participants will be instructed in how to

use the Tandem research pump as well as the UVa AP systems, including stopping the system and bolusing for food.

1.3.4 Timing of UVa Artificial Pancreas Use

Upon arrival to hotel, participants will be connected to a Tandem research pump connected to the UVa DiAs platform and their Dexcom G6 Transmitter will be linked with DiAs. Participants will then be taught how to use DiAs in this configuration. The research pump will be programmed with the adolescent'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 Dinner Sessions

Study dinners and timing: On four separate days (hotel days 2, 3, 6 and 7), participants will be followed for the experimental dinners as part of the Study Dinner Sessions to compare blood glucose control using four different approaches to insulin management for carbohydrate control (Figure 1). These Study Dinner Sessions start approximately 3-4 hours before the dinner and continue for approximately 12 hours after the dinner. During the Study Dinner Sessions, participants will consume structured dinners (with identical protein, fat, and carbohydrate content between the Study Dinner Sessions) while on the two UVa AP closed loop algorithms (RocketAP or Control-IQ—in random order); for each, insulin dosing on the first Study Dinner Session will be via normal carbohydrate announcement and the DiAs CGM-based bolus calculator, and on the second Study Dinner Session with no carbohydrate announcement (In the case of the RocketAP artificial pancreas system, the insulin priming will be in place to detect and dose for unannounced carbohydrate.) For other meals on the artificial pancreas system during the hotel stay, normal carbohydrate announcement will be performed.

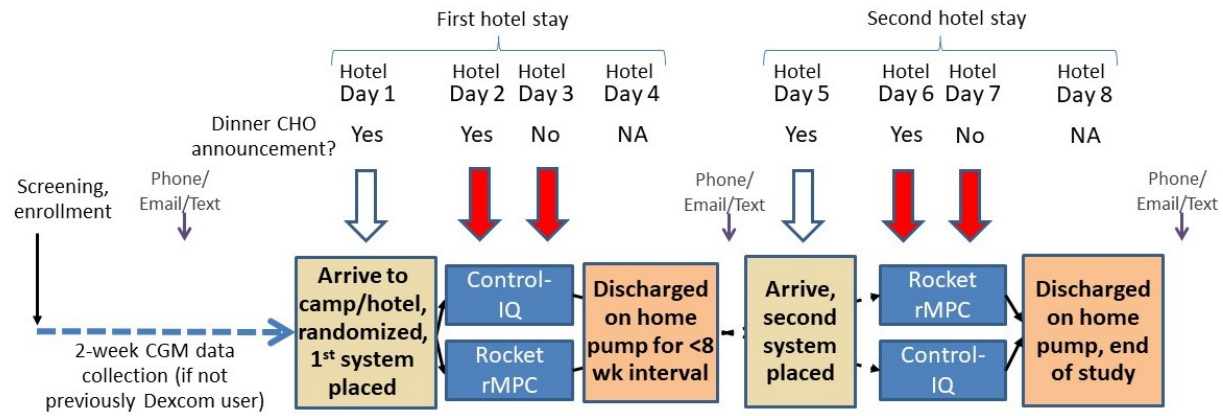

Figure 1: Timeline of the Study Dinner Sessions

The order of the AP system tested (RocketAP vs. Control-IQ) is determined randomly. The order of carbohydrate (CHO) announcement will be the same in both cases. Study Dinner Sessions will likely be performed during two hotel admissions separated by no more than 8 weeks.

Blood glucose levels will be followed via continuous glucose monitor, and the primary outcome will be percent time in blood glucose range 70-180 mg/dL during the 6 hours following start of the meal. 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 afternoon/evening before the first of the Study Dinner Sessions. UVa CDT study staff will monitor CGM output continuously and manage blood sugar control issues. At the end of the second Study Dinner Session, the participant will be placed on home insulin management (or adjustment based on diabetes camp management).

Stopping criteria for and individual study dinner session: A Study Dinner Session will be stopped for an individual participant for any of the following:

- Ketones >1.5 mmol
- Known site failure

- Two separate hypoglycemia events where the blood glucose falls below 50 mg/dL
- The behavior of the participant is such that there is concern about his/her ability to continue to adhere to the protocol
- At the discretion of the study physician.

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 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 30minutes 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 3 participants. Up to 6 participants may sign the consent/assent forms.

Enrollment in the Main Study will proceed with the goal of completing approximately 20 participants. Up to 30 participants may sign the Main Study consent/assent forms.

1.6.2 Clinical Sites

The study will be performed at the University of Virginia, with screening procedures taking place at the Clinical Research Unit or at a local hotel/rental house.

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 either the RocketAP control algorithm or the Control-IQ control algorithm (in random order).

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

Blood glucose levels will be measured using the Accu-Chek Guide blood glucose meter (glucometer). The CGM device will be calibrated, if needed, using the study glucometer and strips in accordance with the manufacturer's labeling.

2.4 Ketone Meter and Strips

Blood ketone levels will be measured using the Abbott Precision Xtra meters and strips in accordance with the manufacturer's labeling. The blood glucose meter component of the Precision Xtra Device will not be used. The ketone meter will be available for staff use during the study admissions.

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 participant. Up to 4 participants may sign consent/assent forms.

Main Study: Enrollment in the study will proceed with the goal of completing up to 20 participants. Participants will initially be randomized for the order of their 3 experimental meals use during the study. Up to 30 participants may sign the consent/assent forms.

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 (and assent, 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. A physical exam documented in the prior year can suffice for the physical exam. 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 ≥12.0 and ≤25 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 artificial pancreas system throughout study sessions.
11. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study
12. Total daily insulin dose (TDD) at least 10 U/day and not more than 100 U/d
13. 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)
14. Willingness to eat at least 1 g/kg of carbohydrate per day during the hotel (or rental house, in the case of the pilot) admission
15. Willingness to reschedule Study Dinner Sessions if placed on oral steroids
16. An understanding and willingness to follow the protocol and signed informed consent
17. Willingness to commit to self-quarantine for at least 5 days before COVID testing. The COVID testing will occur 2-3 days before the hotel study. Also, a willingness to comply with COVID precautions as outlined in section 10.3. The COVID test must be negative.

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-positive individual within 14 days of the hotel/rented house studies.
10. A positive COVID Test within 14 days of study participation, or during study participation.

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

3. Surgical history
4. Allergies
5. Concomitant medications
6. Physical Examination – A historical history and physical report within 52 weeks of screening appointments may be used
   - Weight
   - Height
   - Blood pressure
   - Temperature
   - Heart Rate
7. 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 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 self-quarantine and COVID testing as outlined above.

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 meals in random order as described below.

4.1 Pilot Study Participants

Pilot participants will not be randomized but will only undergo both a normal carbohydrate announcement and an experimental dinner with the RocketAP with no-carbohydrate announcement.

4.2 Main Study Participants

Once eligibility is met, the participant may continue to randomization following arrival to the first hotel visit. Screening failures and study dropout participants may be replaced. Randomization will determine the order of the Study Dinner Sessions, with potential order as shown in Table 1.

	Study Dinner Sessions #1 & 2 (Hotel days 2 and 3)		Study Dinner Sessions #3 & 4 (Hotel days 5 and 6)	
1.	**RocketAP**		**Control-IQ**	
	Study Dinner Session #1: Normal CHO announcement	Study Dinner Session #2: No announced CHO (insulin priming and automated AP correction boluses)	Study Dinner Session #3: Normal CHO announcement	Study Dinner Session #4: No announced CHO (automated AP correction boluses)
2.	**Control-IQ**		**RocketAP**	
	Study Dinner Session #1: Normal CHO announcement	Study Dinner Session #2: No announced CHO (automated AP correction boluses)	Study Dinner Session #3: Normal CHO announcement	Study Dinner Session #4: No announced CHO (insulin priming and automated AP correction boluses)

Table 1: Randomization Table

Randomization will occur via selection from the above list using permuted blocks in groups of 4, 4 and 2.

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 labeling 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 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 be asked to alert the study clinical staff during periods of illness that develops during use of the AP system (elevated temperature >101.5 degrees Fahrenheit [38.6 degrees Celsius], periods of significant illness, or during periods of use of medications such as epinephrine for the emergency treatment of a severe allergic reaction or asthma attack in addition to use of oral or injectable glucocorticoids to determine if closed-loop use should be temporarily discontinued.

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. Study staff contact information will be provided to the participant.

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

Glycemic Treatment Guidelines 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 during the study, particularly if the participant contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

Chapter 6 Pilot Study

In order to optimize the flow of the study visits during the Main Study, we will perform a Pilot Study at a local hotel. The duration of the hotel admission will be up to 48 hours with the intent of collecting appropriate safety data that will be presented to the study Medical Monitor for review. Pilot study participants are eligible to enroll in the Main Study.

6.1 Run-In Phase

Participants not familiar with the CGM will wear the CGM at home for approximately 14 days. Other participants who are familiar with the CGM will immediately proceed to the hotel/rented house admission. If currently using a Dexcom G6, up to 30 days of data may be obtained from the participant's personal CGM.

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 a 20-minute drive at all times. All study staff will have received COVID testing within 72 hours of the start of the pilot study. 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
- Inquire about the participant's self-quarantine, possible COVID exposures, and study-related initial COVID Testing.
- 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 participant will be assessed at a time. The participant will arrive at the hotel or rented house "bubble" on the first day of the admission. The study team will perform vital signs and inquire about the participant's self-quarantine, COVID Testing, 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.

Participants will at this point have the second COVID Test administered.

A urine pregnancy test will be collected. 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 3-4 pm, running the RocketAP system and 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.

6.5 Hotel Admission Glycemic Treatment Guidelines

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. The study team may request fingersticks as needed. 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 is >250 for more than 3 hours or >400 mg/dL at any time, study physician will be notified, and ketones will be checked. If ketone concentration is >0.6 mmol/L, the study team will check the insulin pump infusion site and correction insulin will be administered per study physician judgement via the subject's insulin pump. 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.

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 20 minutes. Hypoglycemic treatments can occur at any time per study physician request.

6.6 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 Meal Control Module on the RocketAP. During the time outside of the Study Dinner Sessions will continue in closed loop mode until it is time for discharge.

6.7 Admission Activities

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

6.8 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.

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.**

6.9 Post Admission Check-In Visit

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

6.10 Medical Monitor Review

At the conclusion of the Pilot Study, the medical monitor will review the data as referenced in Chapter 9.

Chapter 7 Main Study

Main Study participants will participate in two hotel admissions. Each admission will be up to 90 hours in duration. The two study admissions should be less than 8 weeks apart. The study physician will need to determine if second admission can be completed if greater than 8 weeks from the first admission.

7.1 Run-In Phase

Participants who are not familiar with the Dexcom G6 CGM will wear the equipment at home for approximately 14 days to ensure proper use of the equipment during the two hotel admissions. Other participants will immediately proceed to the hotel admissions.

7.2 Qualifications and Role of the Staff

There will be at least three 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 inside the "bubble" during the study at all times. In addition, at least one senior engineer will be on call during the entire admission. Glucagon for the emergency treatment of hypoglycemia will be available on-site.

7.3 Pre-Admission Check-In Visit

Participants will be contacted by the study team approximately 24-48 hours prior to each hotel admission if most recent contact with than study participant exceeds 10 days. This is in addition to the COVID testing for participants. The study team will verify the following information:

- Inquire about any changes to the participant's medical history
- Confirm participant has self-quarantined and study-related initial COVID testing.
- 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

7.4 Admission Check-In

Participants will arrive at the hotel "bubble" on the first day of the admission. As described in section 10.3, all participants will receive a second test for COVID-19 after arriving for the stduy. The study personnel will wear N95 masks and goggles when less than 6 feet from participants until this COVID test returns negative. The study team will perform vital signs and 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 urine pregnancy test will be collected. 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 artificial pancreas system, the study physician may recommended 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 insulin pump will be initiated. 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. Glycemic Treatment Guidelines to be used during the hotel admission are defined in Chapter 8.

7.5 Hotel Admission Glycemic Treatment Guidelines

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. The study team may request fingersticks as needed. 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 is >250 for more than 3 hours or >400 mg/dL at any time, study physician will be notified and ketones will be checked. If ketone concentration is >0.6 mmol/L, the study team will check the insulin pump infusion site and correction insulin will be administered per study physician judgement via the subject's insulin pump. 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.

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 20 minutes. Hypoglycemic treatments can occur at any time per study physician request.

7.6 Study Meals

Study Dinner Sessions start approximately 3-4 hours before the participant eats dinner and will continue for approximately 12 hours after the dinner. Participants will eat a structured dinner at approximately 6-7 pm during the admission. The order of the AP system tested (RocketAP vs. Control-IQ) is determined randomly. The order of carbohydrate (CHO) announcement will be the same in both cases (Table 1).

- Study Dinner Session #1 and #3: Normal CHO announcement
- Study Dinner Session #2 and #4: No announced CHO (Meal Control Module)

Blood glucose levels will be followed via continuous glucose monitor with the goal of maintaining a blood glucose range 70-180 mg/dL during the 6 hours following start of the meal. The closed loop session run between 3pm – 6 am and will be discontinued prior to time of discharge.

Breakfast and lunch will be announced into each system during the hotel admissions.

7.7 Admission Activities

Participants will be free to engage in low-intensity activity (i.e. walking, kicking soccer ball) during the hotel admission. If COVID precaution milestones are met (all participants and on-site study personnel are found to be COVID-negative on second study COVID test performed at entrance to the "bubble," see Section 10.3), limited activities with safe distancing and mask use may occur as described in Section 10.3. Participants will enjoy quiet activities in the evening.

7.8 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.

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 Questionnaire

Participants will complete questionnaire(s) at the completion of each admission. Questionnaires are described in section 9.2.

7.10 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 Medical Monitor Review

7.11 Medical Monitor Review

At the conclusion of the Pilot Study, the medical monitor will review the data as referenced in section 8.3.

Chapter 8 Medical Monitor Review

8.1 Medical Monitor Study Safety Data Review

The Medical Monitor will be provided all adverse event data from the Pilot Study for review prior to the main study. The Medical Monitor will review data related to individual stopping criteria as detailed in the study protocol.

8.2 Medical Monitor Decisions

After review, the Medical Monitor can recommend that the current study continue without modification, continue with specified modifications, discontinue one or more arms of the study, or halt or modify the study until more information is available.

The Medical Monitor may recommend modifications to individual stopping rules if additional safety concerns arise during from their continuing reviews of the study data.

The hotel admission will not be repeated unless required by the Medical Monitor.

8.3 Medical Monitor Main Study Safety Data Review

A Medical Monitor will review compiled safety data at the conclusion of the trial. In addition, the Medical Monitor 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 Medical Monitor also will be informed of any ADEs not meeting criteria for a UADE if the Study PI requests the Medical Monitor review. The Medical Monitor 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.

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. Blood test may be obtained within 2 weeks prior to enrollment may be used for eligibility purposes.
- 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.

9.2 Questionnaire Schedule

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

Participants will be provided a short questionnaire asking them to rate their experience with the study equipment.

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

759 solution and then placed on an absorbent wipe or clean surface. Two sprays will be dispensed
760 from the Clorox cleaner onto each side of the transmitter. A nylon brush will be used to scrub the
761 transmitter on all sides for 30 seconds. The transmitter will be placed in the Clorox Cleaner
762 solution for one minute. Transmitter is then rinsed under flowing tap water for ten seconds. The
763 transmitter will then be disinfected using a disinfectant product with EPA registration number
764 56392-7 using similar procedures as the cleaning process.

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

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

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

774 Equipment that touches intact skin will be cleaned with ethyl or isopropyl alcohol (70-90%),
775 quaternary ammonium germicidal detergent (i.e. Cavicide, EPA number 46781) or household
776 bleach. The contact time on the surface depends on the method used to clean the equipment.
777 Cavicide requires three minutes on the surface of the equipment. Clorox Germicidal Bleach Wipes
778 require two minutes on the equipment. The surface should remain wet (i.e. slightly damp) with
779 the disinfectant to be considered effective though not wet enough to leave drops of liquid.

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

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

789 ### 10.1.8 Hb1Ac Risk

790 An NGSP Point of Care analyzer (i.e. DCA Vantage Analyzer) will be utilized at the research site to
791 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 and adolescents 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, it is the assessment of the investigators that this protocol falls under DHHS 46.405 which is a minor increase over minimal risk. 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

To mitigate risk of exposure to COVID 19, we will attempt to create a COVID-free "bubble.". This plan involves renting an entire floor of a hotel for study purposes only and taking steps to only allow entrance to those who are reasonably likely to be COVID-free (participants and study personnel) and protecting a COVID-free space in which they can stay (Environment). Acknowledging that zero risk is not possible, we seek to take steps that in almost every case exceed the protection offered by the standard-of-care for clinical care and other research activities—and that very likely is safer than the usual activities of these adolescents, who in their current daily lives go to stores, participate in activities with friends, and in many cases attend school. Because of the restrictions that we will require, and testing we will employ, the participants are likely to be at lower risk for COVID transmission (during the study) than if they were pursuing their usual daily lives.

10.3.1 Participants and Study Personnel

We will follow a combination of self-isolation and testing to increase our likelihood of having all COVID-free entrants into the "bubble."

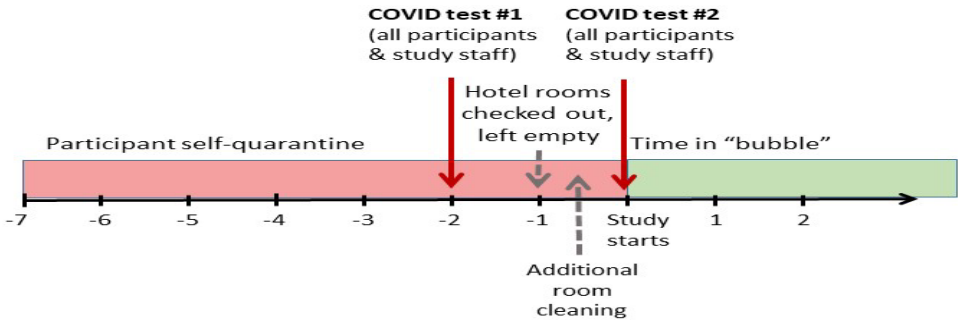

Figure 2: COVID Precautionary Timeline

As shown in the Figure 2 :

1. Participants will agree to stay quarantine for at least five days before being tested. This ensures that participants will be tested at least five days after their last possible exposure. "Quarantine" (or variations of this word) will be defined as: staying home with no close contact for more than 15 minutes, or contact only with an N95 or equivalent mask, with anyone who might have been exposed to COVID. Participants must get a nasal swab PCR test, this may be done at UVA or in their community.
2. All participants will be ineligible if they have had known COVID exposure or symptoms within 14 days of study start.
3. All participants, staff (research coordinators, technicians), nurses and physicians will be tested with a COVID PCR test 48-72 hours before being admitted to the study hotel. Those with positive tests will be excluded from the study. Participants will continue to self-quarantine in the time between testing and being admitted to the hotel. (This self-quarantine and testing regimen is well beyond the standard-of-care for current clinical care and most other research interactions, both of which involve repeated interactions with patients/participants who have neither self-isolated nor been tested for COVID.)
4. Upon admission to the hotel, all participants and staff will receive a second COVID PCR test. Following this test, all participants will stay quarantined in their hotel room without leaving until this second test returns negative. Until the second COVID tests return negative, all study staff who have to come within 6 feet of participants will wear N95 masks and goggles when doing so.
5. Any participants with positive test will be discharged from the study. Hotel rooms of these participants will not be used further. We will limit any personal interaction between study personnel and these individuals. Any interaction will be with N95 masks, hospital gown, gloves, and goggles. Study personnel will immediately change (and not reuse these clothes) and shower.
6. Participants will only share a room with a sibling or housemate that they are currently living with; otherwise, they must be alone in a room.
7. Study staff and physicians will stay in the "bubble" with the participants. The study team includes 2 study coordinator, 1 technician, 2 study physicians. Nurses will be assigned to shifts of up to 12 hours; there will be a minimum of 2 nurses on site at all times (and thus a total of 6 study personnel total). We anticipate up to 20 study participants in the "bubble." As described above, study staff that will be onsite will have COVID 19 negative test within 48-72 hours of the admission. All study staff onsite will abide by UVa clinical protocols currently in place for healthcare workers which stands as the standard-of care for those involved in patient care. This protocol includes use of the HOOS Health Check app and using masks at all times when with any other individual (participants or other study personnel). To minimize the number of staff members required to be present for

the study, monitoring of study equipment will be performed remotely. Remote and on-site staff will communicate via a dedicated study phone.

8. Because of the precautions we have put in place, we do not anticipate that participants or study personnel will have COVID during the study. However, participants or study personnel who develop symptoms of COVID during the study will be discharged from the "bubble" and receive COVID testing. In the case of study personnel, back-up team members who have received a negative COVID test hotel admission will replace the member who developed symptoms.

10.3.2 Environment

We are working to reduce risk of COVID exposure both by decreasing coronavirus on surfaces and avoiding any contact with hotel personnel. To do so, we will take the following precautions:

1. We will reserve the entire study floor of the hotel starting at least 24 hours before admission. While the rooms will have already been cleaned with the hotel's cleaning protocol, keeping the rooms empty for 24 hours further allows time for inactivation of any coronavirus. (This goes beyond the standard-of-care for clinical care and other research activities, which repeatedly utilize spaces throughout the day such as exam rooms and elevators, with cleaning of some surfaces but without allowing for inactivation of potential coronavirus on other surfaces not cleaned.)
2. We will further clean the surfaces of each hotel room with disinfectant wipes before participants are admitted.
3. The lobby of the hotel will be avoided, instead using the back stairwell. We will verify that there are no other users of the stairwell before using it.
4. Hotel staff will be instructed to avoid entrance to the study floor during the entirety of the stay. Housekeeping activities will be cancelled during the study. The only exception is breakfast delivery, which will be delivered by hotel staff in bags, either via the back stairwell and left on the floor at the entrance to the stairs or on the elevator and left right in front of the elevator (without having to step onto the study floor).
5. If hotel staff absolutely have to enter the floor for any purpose (e.g. plumbing failure), they will be requested to notify study personnel by phone before entering the study floor and will be asked to wear masks at all times while on the floor. If they need to enter a participant's room, the participant will first leave to a safe room. Following the hotel staff work, the participant's room will receive a thorough wipe by study staff before the participant can return.
6. Additional food will be dropped off by study staff (not in the hotel "bubble") via the back stairwell, and left on the floor.

7. Food will then be delivered one room at a time to individual participants by on-site study staff. Participants will eat their food in their rooms.

10.3.3 Activities

Group activities are important for this study, both for the physical activity (which is an important part of healthy diabetes control) and because of the otherwise completely confined space that constitutes the study. Again, we seek to only pursue safe situations that meet or exceed what is currently allowed inside the UVa Health System for faculty, staff, students and visitors. (For example, Internal Medicine Grand Rounds is permitted inside, in-person, with spacing and mask use—but does not require the self-isolating and testing that we will employ).

1. There will be no group activities until all COVID tests performed at study entry have returned negative. Study personnel will wear 95 masks during this period.
2. Group activities will involve the following precautions:
    - Study personnel will be stationed at intervals within the group to supervise that participants remain separated by 6 feet at all times.
    - Use of masks will be required by study staff and participants at all times. Participants caught without a mask during any part of the activity will be escorted back to the hotel and will not be able to participate in subsequent activities.
    - We will always use the back stairwell (not elevator, not lobby) to exit hotel.
    - We will utilize a staggered exit so that participants are always at least 6 feet separated from each other.
    - Walking will be the only form of transportation.
    - Preference for outdoor activities (e.g., walking, kicking soccer ball) will always be sought.
    - We will avoid congested areas where distancing is not possible.
    - Any indoor activities will be only be in a UVa facility that has been wiped down before use and has adequate space to permit separation by at least 6 feet between individuals at all times. Study staff will be present to observe and verify that all participants keep masks on and keep distanced. Entrance to the space will be via the shortest distance to the facility (e.g., direct entrance from outside or very short hallway that will only be used when there are no other individuals in the hallway.

      All activities will abide by statewide restrictions on numbers of individuals together.
    -

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).

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 labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled 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

- blood ketones ≥1.5 mmol/L or large/moderate urine ketones

- 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 Medical Monitor 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., preexisting 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 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 (in which case would be deemed not related to the study), testing at arrival to the hotel (again not related) or onset of new symptoms during the stay. The probability that infection is related to the study may be inferred in part by the timing, with symptoms beginning on day 1 or 2 of the study being more likely not related and onset of symptoms afterward being possibly related to exposure during the study. Any appearance of COVID symptoms in participants will be cause for repeat COVID testing and quarantine until test results are returned. If the positive, the participants will be discharged from the study. Study team will use N95 masks, gown, gloves, and goggles until test results are returned.

In the event of a COVID positive test in a participant, the study team will follow up with the participant via phone until conclusion of treatment for the COVID 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 per the UVA IRB website instructions (i.e. mild, moderate, severe). The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor 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 labeling

- 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 Medical Monitor will determine if the UADE presents an unreasonable risk to participants. If so, the DSMB 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 after the Medical Monitor 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 on either of the two scheduled COVID-19 tests 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 with BG <50 mg/dL and meeting the definition in section 11.2.1 of the protocol, or one distinct severe hypoglycemia event attributable to study device use, with BG <50mg/dL 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 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 Medical Monitor will review all adverse events and adverse device events that are reported during the study and will review compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the Medical Monitor). The Medical Monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

11.11 Independent Safety Oversight

A Medical Monitor 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 Medical Monitor 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 Medical Monitor review will be documented in a separate Medical Monitor 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 Design and Randomization

The main study is itself a pilot study to assess glycemic responses to four different approaches to insulin dosing for carbohydrate ingestion, with two different AP systems (RocketAP and Control-IQ, in random order) each in sessions involving normal carbohydrate announcement and no carbohydrate announcement (on successive nights). This information is detailed in Table 1.

Randomization will occur via selection from the above list using permuted blocks in groups of 4, 4 and 2.

13.2 Sample Size

As a Pilot Study, the goal will be complete up to 20 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. (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.)

13.3 Outcome Measures

13.3.1 Primary Efficacy Endpoint

The study design allows for multiple comparisons of blood glucose control during the Study Dinner Sessions, with for the primary comparison of interest being between the no carbohydrate announcement on the RocketAP (running the Meal Probability Detector and the Meal Control Module algorithms) compared to no carbohydrate announcement on the Control-IQ system. Our primary endpoint is time-in-range 70-180 mg/dL for the 6-hour period after dinner. Additional comparisons are made between the RocketAP system without vs. with normal carbohydrate announcement (which determines efficacy vs. premeal bolus), as well as the Control-IQ system without vs. with carbohydrate announcement (which determines risk of missed carbohydrate announcement in standard of care system).

13.3.2 Secondary Outcomes

For study period beginning after dinner and for 6h thereafter:

- Number of hypoglycemia events
- Time <70 mg/dL
- Time >180 mg/dL

- Time >250 mg/dL
- Units of insulin injected
- Area under the curve when accounting for starting BG

For study period beginning of dinner until 12 hours later:

- Time in range 70-180 mg/dL
- Number of hypoglycemia events
- Time <70 mg/dL
- Time >180 mg/dL
- Time >250 mg/dL
- Units of insulin injected
- Area under the curve when accounting for starting BG

We will also assess both safety and efficacy of the RocketAP in adolescents by assessing outcomes outside of the Study Dinner Sessions:

- Time in range 70-180 mg/dL
- Number of hypoglycemia events
- Time <70 mg/dL
- Time >180 mg/dL
- Time >250 mg/dL
- Units of insulin injected

13.4 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.

13.5 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:

- Age
- HbA1c
- Gender
- Race/ethnicity
- CGM use before enrollment
- Diabetes duration
- BMI

13.6 Device Issues

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

- Device malfunctions requiring study team contact and other reported device issues
- Sensor performance metrics (difference, absolute relative difference, and International Organization for Standardization criteria) – if applicable, by sensor version.
- % time CGM data available - overall and by month
- Performance metrics, describing the Closed Loop Control (CLC) system and its components like:
    a. % time CGM data were available to the CLC system – overall and by month
    b. % time in different operational modes per week - overall and by month
    c. Rate of different failure events and alarms per 48 hours recorded by the CLC system – overall and by month

Data will not be used on any night where there is a site failure for the insulin pump and/or malfunction of the CGM significantly effecting BG readings.

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

1. Burdick J, Chase HP, Slover RH, et al. Missed insulin meal boluses and elevated hemoglobin A(1c) levels in children receiving insulin pump therapy. *Pediatrics.* 2004;113(3):E221-E224.
2. Olinder AL, Kernell A, Smide B. Missed bolus doses: devastating for metabolic control in CSII-treated adolescents with type 1 diabetes. *Pediatric Diabetes.* 2009;10(2):142-148.
3. Brown SA. The International Diabetes Closed-Loop iDCL) Trial--Clinical Acceptance of the Artificial Pancreas. *The American Diabetes Association Scientific Sessions, San Francisco, CA.* 2019.
4. Cherñavvsky DR, DeBoer MD, Keith-Hynes P, et al. Use of an artificial pancreas among adolescents for a missed snack bolus and an underestimated meal bolus. *Pediatr Diabetes.* 2016;17(1):28-35.