UNIVERSITY of VIRGINIA HEALTH SYSTEM | School of Medicine

UVA CENTER FOR DIABETES TECHNOLOGY

Hybrid Closed-Loop Control with Prandial Insulin Dosing Informed by Insulin Sensitivity in Adolescents with Type 1 Diabetes

Protocol Chair

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KEY ROLES

Protocol Principal Investigator	
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Institution Name	University of Virginia

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PROTOCOL VERSION HISTORY

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0	Melissa Schoelwer	Chiara Fabris	11-Mar-2021	Original Protocol
1.1	Mary Oliveri	Chiara Fabris	29-Mar-2021	FDA Modifications: • I/E modifications (section 3.4 & 3.5) • A1c lower limit • English proficiency • Additional restrictions of meds during study • Additional medical issues • Clarified insulin pump training (section 5.2) • Corrected CGM arrival values (section 6.2 & 6.3) • Added Meal Requirement to Pilot study (section 6.5) • Clarified discharge values of CGM reading is ≤250 mg/dL and ketones <0.6 mmol/L (section 6.7 and 8.5) • Added Admission(s) Discharge & Post-Study Check In Visit description (section 8.5 & 8.6)

				• Added additional possible occurrences of COVID-19 tests (section 9.1.3) • Added positive COVID-19 symptoms (section 10.3.1) • Added participant stopping criteria of positive COVID-19 test (section 11.10.1)
1.2	Mary Oliveri	Chiara Fabris	01-Apr-2021	FDA Modifications: • Removed 'if ketones were present at time of discharge' (section 6.7 and 8.5)
1.3	Jon Olson Mary Oliveri	Chiara Fabris	03-May-2021	IRB Full Board Mods: • Changed 1-2 pilot participants to up to 3 participants • Revised Statistical (section 13.3.2).
1.4	Mary Oliveri	Chiara Fabris Melissa Schoelwer	25-Jun-2021	Study Team mods: • Added copy of Covid vaccination record if available (section 3.4). • Modified Covid policy (section 10.3).
2.0	Chiara Fabris	Chiara Fabris	16-Aug-2021	Study Team mods: • Revised Protocol Summary Table to include change in study from a 6 day camp to a two 4-

				day camp study (Protocol Summary, section 1.3, Figure 1, 5.1, 8.4.4) • Hemoglobin A1C POC will be collected at the first study admission (Table 1) • Clarified that study is examining increased physical activity and exercise (aerobics) in T1DM adolescents (section 1.1, 1.2, 1.3) • Specified use of Dexcom G6 CGM (section 1.3, 3.4) – Please note, this use of Dexcom G6 CGM (section 1.3, 3.4) was not approved by the IRB Full Board with the approval of the other v2.0 edits. Therefore, it was removed. • Added inclusion criteria that participants must have completed COVID-19 vaccine at least 2 weeks prior to study admission(s) and provide the

				vaccination card (section 3.4, 10.3) • Added exclusion criteria of: • Known contact with COVID-positive individual within 14 days of any study admission(s) without a negative follow-up COVID test performed 3-5 days after the date of exposure • Symptoms of COVID-19 (e.g., fever, shortness of breath, unexpected loss of taste or smell) developed within 14 of any study admission(s) • Non-vaccinated participants will be excluded from participation (section 3.5, 10.3.1) • Added that basal rate will be reduced 10-20% by study physician (section 5.2.1) • Clarified specific COVID-19 symptoms that the study team will ask at pre-study admission(s) check-in visits (section 8.3.1)

				• COVID-19 Test section edited (section 9.1.3) • Study/camp staff will be full vaccinated (section 9.1.3, 10.3.1) • COVID-19 Risk Mitigation Plan and Justification section edited (section 10.3) • Staff at Camp Holiday Trails will work to reduce COVID exposures by following the guidelines in this protocol (section 10.3.2) • COVID-19 Transmission section edited (section 11.4) • Other minor clarifications made throughout document.
2.1	Mary Oliveri	Chiara Fabris	21-Sep-2021	IRB Modifications: • Removed requirement on use of Dexcom G6 CGM (section 1.3, 3.4) Study Team Modifications: • Removed reference to Accu-Chek Guide glucometer (section 2.3, 10.1.6) FDA Modifications

				• Increased enrollment of 35 people signing consent to 70 people signing consent (Protocol Summary, 1.4.1, 3.1, 4.2) • Reinstituted COVID-19 PCR testing 48-72h before camp for participants and staff (section 8.2, 9.1.3) • Participants with COVID-19 symptoms will be excluded from study admission(s) (section 8.2, 9.1.3) • No high-risk activities requiring sustained close contact will be conducted (section 10.3.3) • Participants with COVID-19 symptoms will be isolated until discharged and will be advised on appropriate isolation and testing to be completed (section 11.4) • Close contacts of a participant with symptoms will be

				discharged and will be advised on appropriate isolation and testing to be completed (section 11.4) • Universal masking and physical distancing will be mandated for the remaining participants and study staff in the event of a symptomatic case for the remainder of the study admission (section 11.4)
2.2	Mary Oliveri	Chiara Fabris	16-Nov-2021	Study Team mods: • Re-inserted that camp may be held over 6 days or two 4-day camp admissions (section 1.3)
2.3	Mary Oliveri	Mary Oliveri	02-Dec-2021	IRB Pre-Review: • Corrected session with sessions(s) throughout document • Added Participant Admission Itinerary for 6 night/5 day admission.
2.4	Mary Oliveri	Chiara Fabris	25_Mar-2022	Study Team mods: • Participants will sleep in cabins (section 10.3.1)

				• Revised COVID-19 policies (section 3.5, 8.2, 8.3, 9.1.3, 10.3, 10.3.1, 11.4) • Removed incorrect DSMB references; replaced with Medical Monitor (section 7.1, 7.2, Chapter 11:)
2.5	Mary Oliveri	Chiara Fabris	14-Apr-2022	FDA Modifications • Post study check in visit modified (section 11.4)

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SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Hybrid Closed-loop Control with Prandial Insulin Dosing Informed by Insulin Sensitivity in Adolescents with Type 1 Diabetes

Protocol Version: v2.5

Protocol Date: 14-Apr-2022

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
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
HCL	Hybrid closed-loop
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IS	Insulin sensitivity
JDRF	Juvenile Diabetes Research Foundation
LBGI	Low Blood Glucose Index
NIH	National Institutes of Health
POC	Point-of-Care
SAP	Sensor-Augmented Insulin Pump
QC	Quality Control
UI	User Interface

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Hybrid Closed-loop Control with Prandial Insulin Dosing Informed by Insulin Sensitivity in Adolescents with Type 1 Diabetes
Investigational Device	Smart bolus calculator informed by insulin sensitivity (SI)
Objectives	The objective of this study is to evaluate the safety and feasibility of a smart bolus calculator that adjusts insulin dosing for meals according to real-time SI in adolescents with type 1 diabetes (T1D) using a hybrid closed loop system during an active week of diabetes camp.
Study Design	Double-blind, randomized, crossover trial
Number of Sites	1
Endpoint	The primary endpoint is the low-blood glucose index (LBGI) in the four hours following dinner as measured by CGM, when using the hybrid closed-loop (HCL) system with the SI-informed smart bolus calculator compared to the standard HCL system alone.
Population	Key Inclusion Criteria • Age 12 - <18 years • Clinical diagnosis of T1D • Home use of an insulin pump and CGM for at least 3 months prior to study enrollment Key Exclusion Criteria • History of DKA in the past 6 months • History of hypoglycemic seizure or loss of consciousness in the past 6 months
Sample Size	• Pilot study: up to 3 participants • Main Study: 30 participants (up to 70 may be consented)
Treatment Groups	• All participants will be assigned to both treatment groups at differing points of the study (crossover) • Group 1: standard HCL (USS Virginia) • Group 2: HCL (USS Virginia) with smart bolus calculator informed by SI

Participant Duration	Pilot study: Up to 24 hours; Main study: 6 days or two 4-day camp admissions
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. Eligible participants will be screened, and data will be collected from their home pump and CGM from the preceding four weeks. Participants will then be randomized 1:1 to the use of the standard HCL system (USS Virginia) vs. the HCL system with a smart bolus calculator at the camp admission. Participants will crossover into the other group midweek OR at the second camp admission. Participants and study personnel actively involved in the study will be blinded to the treatment groups.

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Table 1. Schedule of Study Visits and Procedure

	Screening	Data Collection	Pre-Admission Check-in	Study Admission(s)s	Post Study Check-in
Location	Clinic/Remote	Remote (4 weeks historical data)	Phone/Email	Camp Holiday Trails	Phone/Email
Informed Consent	X				
Eligibility Assessment	X				
Medical History	X				
HbA1c (POC)				X (admission #1 only)	
Pregnancy test (if applicable)	X			X	
Physical Exam				X	
Vital Signs (height/weight)				X	
Randomization				X	
COVID-19 testing			X		
Wear Study CGM and Insulin Pump				X	
Review diabetes management and AEs	X	X		X	X
Check-In			X		X

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Chapter 1: Background

1.1 Introduction

The management of type 1 diabetes (T1D) involves close monitoring of blood glucose (BG) levels along with frequent administration of subcutaneous insulin, either with multiple daily injections or via continuous infusion from an insulin pump (1). The amount of insulin given to cover a meal is dependent upon several factors including the amount of carbohydrates consumed, the pre-meal BG level, the length of time since the last insulin administration, and how responsive or sensitive the person is to insulin (i.e., how much 1 unit of insulin is expected to drop his/her BG).

Notably, a person's insulin sensitivity (SI) is not constant, fluctuating throughout the day based on hormones and other factors such as physical activity (2-6). These fluctuations in SI make determining the appropriate insulin dosing at any given time quite challenging, particularly for meals following exercise. Despite the availability of guidelines for managing exercise with T1D (7), many adolescents with T1D report not making the appropriate insulin adjustments around exercise (8). While the use of continuous glucose monitoring (CGM) devices and hybrid closed loop (HCL) "artificial pancreas" systems have been shown to significantly improve glycemic control overall in people with T1D (9-11), daytime control remains suboptimal, largely due to the challenges surrounding meals and exercise. Accordingly, smart bolus calculators are under development to take into account changing metabolic needs and further improve glycemic control (12,13).

The proposed SI-informed bolus calculator was designed to adjust the insulin dosing for changes in SI at the time the bolus is delivered. If the real-time SI is estimated to be the same as the person's typical SI at that time, the administered bolus will remain unchanged. However, it will be increased/decreased if the participant is less/more sensitive than usual at the time the bolus is administered. Of note, the ratio used to modulate the bolus will be saturated in order to not allow for modifications larger than 30% of the original bolus amount (i.e., the dose suggested will be between 70% and 130% of the standard dose indicated by the bolus calculator implemented in the DiAs system using the participant's programmed insulin parameters).

The SI-informed smart bolus calculator was first tested *in silico* using the University of Virginia (UVA)/Padova Type 1 Diabetes Simulator, a simulation platform approved by the FDA as a substitute to preclinical trials in testing insulin-dosing algorithms (14), and a version has been successfully used in a decision support system found to decrease glucose variability (15). The smart bolus calculator was subsequently shown to be feasible and effective in a small clinical trial of 15 adults with T1D, decreasing postprandial hypoglycemia following one controlled meal after a standardized exercise period (16).

In this study, we propose integrating the SI-informed smart bolus calculator into a mobile platform (the DiAs, or Diabetes Assistant) running the UVA legacy HCL control algorithm (USS Virginia – which led to the FDA-approved Control-IQ HCL system), for extended use in adolescents with T1D in situations of increased physical activity and exercise.

1.2 Study Objective

The purpose of this study is to test the SI-informed smart bolus calculator when used repeatedly for all bolus insulin dosing over the course of several days, in adolescents with T1D using a HCL system and engaging in prolonged physical activity. The expected fluctuations in SI due to the increased physical activity will appropriately challenge the system.

1.3 Study Design

This is a single center, double-blind, randomized, crossover trial. The trial will be held at a local camp facility and will consist of EITHER a weeklong (6 day/5 night) camp OR two long weekends (4 day/3 night) separated by a washout period of about one week.

The study will deploy a control and an experimental system in random order. In the case of a weeklong camp, participants will be randomly assigned the first system to use and will crossover to the other system midweek; in the case of two long weekends, participants will be randomly assigned the system to use over the first weekend and will crossover to the other system during the second weekend. We will target enrollment of 30 adolescents (age 12- <18 years) with T1D who currently manage their diabetes with an insulin pump and a CGM system.

Participants will undergo an initial Screening Visit after which data from their personal insulin pump and CGM from the previous four weeks will be downloaded. This retrospective data collection period may be extended to gather more days of quality data if needed per the principal investigator's judgment. This data will then be used to determine each participant's typical daily fluctuations in SI.

After completion of the Screening Visit, if participants are eligible to take part in the study, they will undergo a Randomization Visit. Participants will be randomized 1:1 to two groups, either using USS Virginia (control system) or USS Virginia with the SI-informed smart bolus calculator (experimental system) first, and will crossover into the other treatment arm during the study. Participants and study personnel actively involved in the camp will be blinded to the assignment of study participants to treatment groups.

Upon completion of all visits leading up to camp visit(s), participants will present for study admission(s) at Camp Holiday Trails – a camp for children with chronic medical conditions, in Charlottesville, VA. At the time of the admission(s), a POC HbA1c will be obtained, and a physical

exam will be performed. During the entirety of camp admission(s) duration, participants will eat all meals at camp and participate in daily activities including hiking, aerobics, art, etc. Meals and activities will be kept similar during the use of the two systems (control and experimental), in order not to bias study outcomes.

Figure 1 below presents an overview of the timeline of the main study visits, in the case of two long weekends.

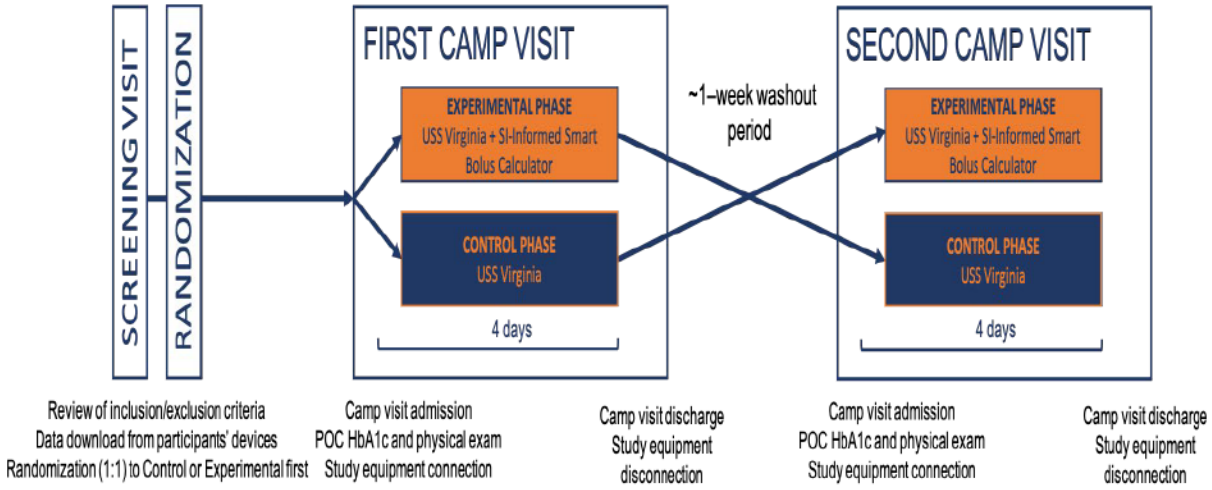

Figure 1: Study Diagram

1.4 Purpose/Objectives of Clinical Study

1.4.1 Study Participants

Enrollment in the study will proceed with the goal of completing approximately 30 participants. Up to 70 participants may sign the consent form.

1.4.2 Clinical Sites

The study will be performed at the University of Virginia.

1.5 Primary Specific Aim

- Demonstrate the safety and feasibility of using the SI-informed smart bolus calculator in an HCL system, over an extended period of time with multiple meals.

1.6 Secondary Specific Aim

- Demonstrate that the use of the SI-informed smart bolus calculator in an HCL system provides increased protection against hypoglycemia.

Chapter 2: Study Devices

2.1 Insulin Pump

The study system will include the Tandem t:ap research pump connected to the UVA DiAs system running on a dedicated external smartphone, implementing either the USS Virginia algorithm alone or the USS Virginia algorithm with the smart bolus calculator.

2.2 Continuous Glucose Monitor

The study CGM will include Dexcom G6 transmitter and sensors. The CGM sensor is viable for 10 days. Like the insulin pump, the CGM system will be connected to DiAs.

2.3 Blood Glucose Meter and Strips

Upon need, blood glucose levels will be measured using the study 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. Glucometers will be available during the study admission(s).

2.4 Ketone Meter and Strips

Upon need, 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. Ketone meters will be available during the study admission(s).

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

Participants will be recruited from the UVA Center for Diabetes Technology registry, social media advertisements, physician contacts at pediatric diabetes clinics in Virginia, and previous camp attendance data. The enrollment goal in the pilot study will be to complete up to three participants. Up to four participants may sign consent/assent forms. The enrollment goal for the main study is to complete 30 participants. Up to 70 participants may sign the consent form.

3.2 Informed Consent and Authorization Procedures

Before consent has been obtained, participants will be asked inclusion/exclusion criteria questions during prescreening to determine study eligibility. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. Informed consent will be obtained from a parent for participants <18 years old and assent will also be obtained from participants who are <18 years old. 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. The screening visit can be performed in clinic or by video conferencing.

3.4 Participant Inclusion Criteria

The participants must meet the following inclusion criteria in order to be eligible to participate in the study:

1. Age ≥12 and <18 years old at time of consent
2. Clinical diagnosis, based on investigator assessment, of T1D for at least one year
3. Currently using insulin for at least six months
4. Currently using an insulin pump for at least three months
5. Currently using a CGM system for at least three months

6. Having at least 75% of CGM data over the previous four weeks
7. Using insulin parameters such as carbohydrate ratio and correction factors consistently on their pump in order to dose insulin for meals or corrections
8. Access to internet and willingness to upload data during the study as needed
9. For females, not currently known to be pregnant or breastfeeding
10. A negative urine pregnancy test will be required for all females of childbearing potential
11. Willingness to suspend use of any personal CGM for the duration of the clinical trial once the study CGM is in use
12. 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
13. Total daily insulin dose (TDD) of at least 10 U/day
14. Willingness not to start any non-insulin glucose-lowering agent during the course of the trial (including metformin, GLP-1 agonists, pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals)
15. Willingness to eat at least 40 grams of carbohydrates per meal
16. An understanding and willingness to follow the protocol and signed informed consent
17. Participants and parent/legal guardians will be proficient in reading and writing in English
18. Willingness to comply with COVID-19 precautions as defined by the study team (study team will reference section 10.3)
19. Having completed a COVID-19 vaccination with an FDA-approved COVID-19 vaccine at least two weeks before the first study admission and willing to provide a copy of the COVID-19 vaccination card

3.5 Participant Exclusion Criteria

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

1. Hemoglobin A1c <6% or >10% if measured at screening or available from historical medical report performed within the last 6 months; in absence of a valid HbA1c measurement, average blood glucose estimated from CGM data to be approximately between 100 and 240 mg/dL
2. History of diabetic ketoacidosis (DKA) in the 6 months prior to enrollment
3. Severe hypoglycemia resulting in seizure or loss of consciousness in the 6 months prior to enrollment
4. Pregnancy or intent to become pregnant during the trial

5. Currently breastfeeding or planning to breastfeed
6. Currently being treated for a seizure disorder
7. Planned surgery during study duration
8. History of cardiac arrhythmia (except for benign premature atrial contractions and benign premature ventricular contractions which are permitted)
9. Current treatment with any non-insulin glucose-lowering agent (metformin, GLP-1 agonists, pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals)
10. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
    i. Significant chronic kidney disease (eGFR < 60) or hemodialysis
    ii. Significant liver disease
    iii. History of adrenal insufficiency
    iv. History of abnormal TSH consistent with hypothyroidism or hyperthyroidism that is not appropriately treated OR history of thyroid cancer
    v. Use of ongoing oral or injectable steroids in the last 8 weeks
11. Use of an insulin delivery mechanism that is not downloadable by the participant or study team
12. Known contact with COVID-positive individual within 7 days of any study admission(s)
13. Symptoms of COVID-19 (e.g., fever, shortness of breath, unexpected loss of taste or smell) developed after taking the mandatory COVID-19 PCR test prior to any study admission(s) or during study admission(s) participation
14. A positive COVID-19 test within 10 days of any study admission(s)
15. Not being fully vaccinated at the time of the first camp admission (according to CDC guidelines a person is intended to be fully vaccinated after two weeks from either the second dose of the Pfizer or Moderna vaccine, or the single dose of the Johnson & Johnson vaccine)

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. The following information will be collected during the screening procedures:

- Demographics
- Date of birth
- Gender

- Race
- Ethnicity
- Medical History
- Duration of disease (number of years)
- History of insulin pump use and current insulin pump model
- History of CGM use
- Current treatment
    i. Basal rates
    ii. Carbohydrate ratios
    iii. Insulin sensitivity factors
    iv. Target glucose
    v. Average daily insulin
- History of diabetic ketoacidosis
- History of severe hypoglycemia
- History of seizures
- Loss of consciousness
- Surgical history
- Allergies
- Concomitant medications
- Physical Examination – A historical history and physical report within 52 weeks of screening appointments may be used if available. Self-reported values are acceptable.
- Weight and height
- Blood pressure
- Pulse
- Temperature
- Screening Labs
- Hemoglobin A1c within past 6 months or average glucose on CGM
- History of pregnancy or intent to become pregnant during the study
- COVID-19 vaccination

Screening procedures will last approximately 1-2 hours. Screening can be performed via videoconference. 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.

Chapter 4: Randomization Visit

Once eligibility is met, the participant may continue with randomization at the conclusion of the screening appointment. Using a randomized block design, the participants will be randomly assigned to either one of the two treatment groups. Screening failures and study dropout participants may be replaced.

4.1 Pilot Participants

Participants will not be randomized in the Pilot Study.

4.2 Main Study Participants

Approximately 30 participants will be randomized 1:1 to use USS Virginia or USS Virginia with SI-informed bolus calculator first. Up to 70 participants may sign the informed consent form.

Chapter 5: Study Equipment Training

Participants will be trained on the use of the study CGM after study eligibility has been met. Additional equipment training may begin at arrival to study admission(s) after the system equipment has been put in place. The purpose of this training is to introduce the study insulin pump and study CGM to the participant.

5.1 CGM Training

A study CGM will be provided to all participants after meeting study eligibility. The participants will be provided with CGM equipment and instructed to place the study CGM ~24-48 hours prior to arrival to camp and 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 will have participants who are not familiar with the study CGM watch the Dexcom online training videos (https://www.dexcom.com/training-videos). Study staff will specifically identify how alarms are set using the app and the frequency that these alarms repeat. Parents may optionally use the Dexcom Share App for monitoring for the at-home use of the CGM. A study phone may be provided for this purpose.

5.2 Study Insulin Pump

The study team will be responsible for monitoring and managing the study insulin pump during the study admission(s). The participants will be provided a quick overview on its functionality.

5.2.1 Study Insulin Pump Topics

The study team will assist the participant in placing the study pump infusion site and will start the participant on the study pump. The study pump will be programmed by the study staff based on the participant's home parameters, with a 10-20% reduction of basal rate determined by the study physician to account for increased physical activity at the camp. The participant's personal pump and infusion site will be removed.

The participant will be instructed on placing infusion sites, cartridge/priming procedures, charging the pump, navigation through menus, and bolus procedures including stopping a bolus, etc.

5.2.2 Other Issues

The participant will be instructed to notify study staff if they experience any issues with the study devices during the study admission(s). Staff will be present in the even that 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, closed-loop mode will be turned off for approximately four hours.

The participant will be asked to alert the study clinical staff for any illness that develops during use of the study system. Participants will also alert the study staff for any technical issues or component disconnections with the study pump and/or the DiAs system.

A glucagon emergency kit will be available at all times during the study for use during emergencies. Glycemic Treatment Guidelines will be available for staff to use during the camp.

5.2.3 Optimization of Insulin Pump Settings

Optimization of pump settings can occur at any time during the study per the discretion of the study physician if there are concerns regarding recurring hypo- or hyperglycemia.

Chapter 6: Pilot Study

The Pilot Study will be performed at a local hotel. The study admission will take up to 24 hours with the intent of collecting appropriate safety data. Pilot study participants are eligible to enroll in the Main Study.

6.1 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 at the hotel or nearby on call during the study at all times. In addition, at least one senior engineer will be on call during the entire admission. Participants will be remotely monitored by at least one study team member using a web-based remote monitoring system that has been previously established for DiAs. The web-based remote monitoring system will display real-time insulin delivery, CGM and other system information to allow for patient safety monitoring. In addition, study team members will be trained in all protocol and glycemic treatment guidelines procedures. The closed-loop system will be managed by the participant with study-staff supervision, particularly at the time of insulin boluses. Glucagon for the emergency treatment of hypoglycemia will be available on-site.

6.2 Pre-Admission Check-In Visit

- Pilot participants will be contacted by the study team approximately 48 hours prior to the study admission to verify the following information:
- Confirm that the participant will insert a study CGM 24-48 hours prior to the study admission
- Inquire about any changes to the participant's medical history
- Inquire about the participant's possible COVID-19 exposures and study related initial COVID-19 testing
- Determine pump profile(s) the participant is currently using
- Verify with the participant that the goal CGM reading at time of arrival is less than 200 mg/dL
- 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.

6.3 Admission Check-In

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

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

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 the study pump initiation, the study physician may recommend corrective action as outlined in the Glycemic Treatment Guidelines. Study physician may elect to cancel participant's participation in the study 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 and insulin pump and will connect both of them to the DiAs device. The goal will be to initiate the study system by approximately 9-10 AM, running either USS Virginia alone or USS Virginia with the SI-informed smart bolus calculator in the DiAs platform.

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

6.4 Study Meals

Participants will eat study-provided meals during the admission. The estimated time of meals will be 8 AM, 12:30 PM, and 6 PM.

6.5 Meal Requirements

Study staff will confirm the carbohydrate content of all meals and snacks prior to entering into the bolus calculator. Participants will be required to consume a minimum of 40 grams of carbohydrate for each meal. All meal and correction boluses will be based on CGM readings.

6.6 Admission Activities

Participants will be free to engage in low-intensity activity (walking) during the morning and afternoon hours. Participants will enjoy quiet activities in the evening.

6.7 Admission Discharge

Discharge will be at approximately 10 AM if the CGM is between 80 and 250 mg/dL and ketones <0.6 mmol/L. Otherwise, the study team will reference the Glycemic Treatment Guidelines until the needed criteria for discharge are met.

A qualified clinical study team member (e.g., MD, NP, CDE) will assess and discuss the transition back to usual care with the study participant.

Participants will be asked to continue monitoring ketone levels for 24-48 hours after the hotel admission. Urine ketone supplies may be provided for this testing.

6.8 Post Admission Check-In Visit

Approximately 72 hours after the study admission, the study team will contact the participant via phone/email/text to assess for any adverse events, adverse device effects, and device issues.

Chapter 7: Medical Monitor

7.1 Study Safety Data Review

The Medical Monitor (MM) will be provided all adverse event data from the trial onset through the study admission(s) for review. The goal is to provide at least 75% of the data to the MM for review. Replacing dropped study participants will not be required in the Pilot Study. The MM will review data related to individual stopping criteria as detailed in the study protocol.

7.2 Medical Monitor Decisions

After their review, the MM 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 MM may recommend modifications to individual stopping rules if additional safety concerns arise during from their continuing reviews of the study data.

The study admission(s) will not be repeated unless required by the MM.

7.3 Medical Monitor Main Study Safety Data Review

A MM will review compiled safety data at the conclusion of the trial. In addition, the MM 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 MM also will be informed of any ADEs not meeting criteria for a UADE if the Study PI requests the MM review. The MM 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 8: Main Study

Study participants will be screened prior to arrival to camp.

8.1 Qualifications and Role of the Staff

Study staff will be present or on call at all times during the study admission(s), including study physicians, study nurses, technical support staff, and senior engineers. At least two medically-trained study staff members will be present on site at all times, including at least one study physician and one nurse. Camp personnel will direct the recreation activities with study staff support.

8.2 Pre-Admission(s) Check-in Visit

Participants will be contacted by the study team 24-48 hours prior to study admission(s). The study team will verify the following information:

- The participant will insert new CGM sensor approximately 24-48 hours prior to the camp
- Inquire about any changes to the participant's medical history
- Confirm the participant has completed COVID-19 PCR test as described in section 9.1.3
- Confirm the participant does not currently have any symptoms of COVID-19 (e.g., fever, shortness of breath, unexpected loss of taste or smell)
- Confirm the participant hasn't had known contact with COVID-positive individual within 7 days of any study admission(s)
    - Confirm the participants hasn't had a positive COVID-19 test results within 10 days of any study admission(s)
- Confirm pump parameter profiles the participant is currently using
- Verify with the participant that the goal CGM reading at the time of arrival is <200 mg/dL
- Should any concerns regarding medical history, pump information, or unforeseen issues arise, the admission(s) will be cancelled at the discretion of the investigator

8.3 Admission(s) Check-in Procedures

Participants will arrive at camp on the first day of each study admission(s).

8.3.1 Participant Check-in and Verification

At time of check-in, participants will undergo the following procedures/tests:

- Vital signs will be measured.

- It will be confirmed that the participant does not currently experience any symptoms of COVID-19; has not had any contact with a COVID-positive individual in the previous 7 days; and has not had a positive COVID-19 test result in the previous 10 days.
- Female participants of childbearing potential will be required to complete a urine pregnancy test. If positive, participant will be discontinued from the study.
- Confirm that the participant brought his/her personal insulin and regular medications.
- Participants will be asked to perform a blood ketone fingerstick. If ketones are not <0.6 mmol/L, study staff should treat with oral hydration and, if needed, the Glycemic Treatment Guidelines will be followed; ketones will be re-checked every hour until <0.6 mmol/L. The participant will be able to begin participation in the camp activities once the CGM reads between 80-250 mg/dL and ketones are <0.6 mmol/L.

8.3.2 Assignment to Randomization Group

Participants will be placed on the study CGM and insulin pump and the DiAs system implementing the algorithm of the specific arm (experimental or control) will be connected to the participant's CGM transmitter via Bluetooth connection. The study team will ensure the proper functioning of the CGM and insulin pump.

8.4 Main Admission(s) Activities and Procedures

8.4.1 General Admission(s) Overview

During the entire duration of each study admission(s), the study team will remotely monitor participants' real-time CGM readings. Study team members trained in all protocol interventions (including the hypoglycemia and hyperglycemia safety protocols) will be with the participants at all times during camp activities, with each member remotely connected to the participants CGM data. In addition, a study team physician trained in all protocol and glycemic treatment guideline procedures will be available at a central location on camp property.

All recreational activities will be managed by the staff and counsellors at Camp Holiday Trails with study staff supervision.

During the overnight hours, study staff will be actively monitoring real-time CGM data for all participants with direct access to the participants.

8.4.2 Device Procedures for Participants

The study insulin pump and DiAs device will be provided upon arrival to the camp. All participants will continue to wear the study CGM. When participants crossover into the other treatment group, they will continue to wear the same study CGM and study insulin pump with the change only made to the software that the system is running.

Participants will have all equipment with them at all times. Study staff will be available at all times to assure proper use of all study equipment.

8.4.3 Meal Requirements

Study staff will confirm the carbohydrate content of all meals and snacks prior to entering into the bolus calculator. Participants will be required to consume a minimum of 40 grams of carbohydrate for each meal. All meal and correction boluses will be based on CGM readings.

8.4.4 Participant's Admission(s) Itinerary

Participants will generally follow the below schedule during each study admission(s).

Participants will generally follow the below schedule during the 6 day/5 nigh admission:

Camp Check-in (all times are estimates):

1300-1600: Check-in and study equipment connection. Participants will undergo the check-in procedures as listed in section 8.3 and start use of study equipment.

1600-1800: Afternoon Camp Activity per Camp staff

1800: Dinner

1900-2030: Evening Camp Activity per Camp Staff

2030: Bedtime snack

2100-2300: Free time/Bedtime

Day 1 & 2

0800-0900: Breakfast

0900-1200: Morning Camp Activities. Participants will begin the activities if his/her CGM reads >90 mg/dL. If ≤ 90 mg/dL, the Glycemic Treatment Guidelines will be followed until cleared to begin activity. An optional morning snack will be provided between activities.

1230-1330: Lunch

1330-1500: Rest Hour

1500: Afternoon Snack

1515-1715: Afternoon Camp Activities. Participants will begin the afternoon activity if his/her CGM reads >90 mg/dL. If ≤ 90 mg/dL, the Glycemic Treatment Guidelines will be followed until cleared to begin activity.

1730-1830: Dinner

1830-2030: Evening Camp Activity per Camp Staff

2030: Bedtime snack

2100-2300: Free time/Bedtime

Day 3 & 4

Prior to breakfast on the morning of Day 3, all participants will crossover into the other treatment arm. The morning and afternoon activities that the participants performed on the first and second days of camp and the schedules will be identical on these days (i.e., Day 3 will be the same as Day 1 and Day 4 will be the same as Day 2). Provided meals will also be similar with regards to carbohydrate content.

Day 5

0800-0900: Breakfast

Participants will generally follow the below schedule during the 4 day/3 night admission:

Day 1 and Day 5 (i.e., first day of each camp admission)

1300-1600: Check-in and study equipment connection. Participants will undergo the check-in procedures as listed in section 8.3 and start use of study equipment.

1600-1800: Afternoon camp activity per camp staff

1800-1900: Dinner

1900-2200: Evening camp activity per camp staff

2200-2230: Preparation for bedtime and optional carb-free bedtime snack

Days 2&3 and Days 6&7 (i.e., second and third day of each camp admission)

0800-0900: Breakfast

0900-1230: Morning camp activities. Participants will begin the activities if their CGM reads >90 mg/dL. If ≤ 90 mg/dL, the Glycemic Treatment Guidelines will be followed until cleared to begin activity.

1230-1330: Lunch

1330-1430: Rest Hour

1430-1500: Optional afternoon snack

1500-1730: Afternoon camp activities. Participants will begin the afternoon activity if their CGM reads >90 mg/dL. If ≤ 90 mg/dL, the Glycemic Treatment Guidelines will be followed until cleared to begin activity.

17:30-1800: Shower time

1800-1900: Dinner

1900-2200: Evening camp activity per camp staff

2200-2230: Preparation for bedtime, optional carb-free bedtime snack, and back to tents

Day 4 and Day 8

0800-0900: Breakfast

0900-1200: Discharge procedures with support camp activities and lunch provided if needed

8.5 Admission(s) Discharge

Discharge will be at approximately 0900-1200 if the CGM are between 80-250 mg/dL and ketone values <0.6 mmol/L will be needed at time of discharge. Otherwise, the study team will reference the Glycemic Treatment Guidelines until the needed criteria for discharge are met.

A qualified clinical study team member (e.g., MD, NP, CDE) will assess and discuss the transition back to usual care with the study participant. Participants may continue wearing the study CGM between admission #1 and admission #2 if participating in the 4 day/3 night camp.

Participants will be asked to continue monitoring ketone levels for 24-48 hours after the admission(s). Urine ketone supplies may be provided for this testing.

8.6 Post Admission(s) Check-In Visit

Approximately 72 hours after the study admission(s), the study team will contact the participant via phone/email/text to assess for any adverse events, adverse device effects, and device issues. Post-discharge guidelines related to COVID are outlined in section 11.4.

8.7 Study System Issues

If the CGM signal becomes unavailable for more than 20 minutes consecutively, the HCL system 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 activate HCL for any reason, the pump will automatically revert to pre-programmed basal insulin delivery

without any need for instruction from the user. Study staff will be available at all times to assist with any issues in connectivity that arise.

Chapter 9: Testing Procedures

9.1 Laboratory / Point of Care Testing

9.1.1 HbA1c

- HbA1c level may be measured by study team using the DCA2000, a comparable point of care device at study admission #1.

9.1.2 Pregnancy Test

- Pilot study admission: A urine pregnancy test will be required for women who are in childbirth potential at the study admission. Test must be negative to participate in the study.
- A urine pregnancy test will be required for women of childbearing potential at the time of study admission(s). Test must be negative to participate in the study.

9.1.3 COVID-19 Test

- Main study admission(s): A COVID-19 PCR test will be required for participants and staff 48-72 hours prior to the study admission(s). Participants and staff with a positive test result within 10 days of the camp will be excluded from the study admission(s).
- Any appearance of COVID-19 symptoms in participants or staff members after the mandatory pre-admission COVID-19 PCR test will result in discharge from the study admission(s).

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 T1D and participants will be monitored for these symptoms.

10.1.1 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.

10.1.2 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.

10.1.3 Risks of Hypoglycemia

As with any person having T1D 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.

10.1.4 Risks of Hyperglycemia

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.

10.1.5 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 labeled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The transmitter and receiver 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 hand-held device.

The study insulin pumps are labeled 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 labeled for single-patient use. During the study, these devices may be reused after cleaning adhering to a hospital-approved cleaning procedure.

10.1.6 Device Cleaning Instructions

CGM cleaning instructions are provided in the Dexcom G4 PLATINUM (Professional) Cleaning and Disinfection manual (current edition). The transmitter should be cleaned with Clorox Healthcare® Bleach Germicidal Cleaner or any disinfectant product in a spray bottle containing a bleach solution of 6500 parts per million with the EPA registration number 56392-7. The transmitter will be submerged in this solution and then placed on an absorbent wipe or clean surface. Two sprays will be dispensed from the Clorox cleaner onto each side of the transmitter. A nylon brush will be used to scrub the transmitter on all sides for 30 seconds. The transmitter will be placed in the Clorox Cleaner solution for one minute. Transmitter is then rinsed under flowing tap water for ten seconds. The transmitter will then be disinfected using a disinfectant product with EPA registration number 56392-7 using similar procedures as the cleaning process.

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

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

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

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

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

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

10.1.7 Hb1Ac Risk

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

10.1.8 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, insulin pump, and glucose 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.

10.1.9 Known Potential Benefits

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

10.1.10 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

The study inclusion/exclusion criteria have been outlined to include only fully-vaccinated study participants. The presence of only vaccinated participants represents the main approach to COVID-19 risk mitigation. Further, all study/camp staff members will be fully vaccinated as well when the camp is scheduled to take place.

Additional layers to COVID-19 risk mitigation will also be implemented:

- Before admission(s), all participants and staff will take a COVID PCR test; a negative result is needed to be part of the study:
  - if any COVID symptoms develop after taking the test, the person will not be allowed at camp;
  - if any contact with a COVID positive person happens in the 7 days prior to camp, the person will not be allowed at camp;
  - if the person had a positive COVID test result in the 10 days prior to camp, the person will not be allowed at camp.
- During camp admission(s), participants will be grouped in small pods (5-6 participants each) for the daily activities; counselors will be assigned to a pod and maintained for the entire camp duration when possible.
- During camp admission(s), the majority of the activities will take place outdoor, and all efforts will be made to ensure physical distancing between members of different pods during the activities.
- During camp admission(s), participants will be sleeping in cabins according to the corresponding pod; counselors will be sleeping with the assigned pod for the entire camp duration; different pods will be assigned to different cabins with no indoor common parts.
- Meals will be consumed outdoor when possible.
- Social distancing between people not belonging to the same pod will be maintained when possible.
- Outdoor masking policy: no masking will be mandated; exception: if two people that do not belong to the same pod need to be less than 6ft apart for more than 5 consecutive minutes, masking will be required for both people.

- Indoor masking policy: universal masking will be mandated; exception: while eating, drinking, showering, and sleeping; during these times, physical distancing will be enforced between people not belonging to the same pod.
- If a person develops COVID symptoms during camp, the person will be discharged from the study. Before leaving camp site, the person will be tested for COVID using an antigenic rapid test that will be available on site.
- If a person within a pod (participant or counselor) tests positive, universal masking for the pod members will be mandated indoor and outdoor, with the exception of eating, drinking, showering, and sleeping; these activities will take place separately from other pods.
- Hand sanitizers will be available during the entire study duration and study participants and staff will be encouraged to frequently sanitize their hands.
- If the COVID-related situation changes before the camp admission, the study team will re-evaluate these guidelines in agreement with CDC recommendations, and this protocol may be changed if needed.

10.3.1 Participants and Study Personnel

The following guidelines will be followed during each camp admission:

- All participants will be ineligible if they have had known COVID-19 exposures in the 7 days prior to any admission(s).
- All participants will be ineligible if they have had a positive COVID test results in the 10 days prior to any admission(s).
- All participants will be ineligible if they develop symptoms of COVID-19 after taking the pre-admission mandatory COVID PCR test.
- Non-vaccinated participants will not be eligible for the study.
- Participants will sleep in cabins with members of the same pod; all meals will be eaten outdoor and provided in individual pre-packaged boxes.
- Participants will be assigned to small groups (pods), which will remain consistent throughout the study admission(s) for all activities. The study team will aim to limit changes in staffing among the pods.

Development of COVID-19 symptoms during study admission(s) is detailed in Section 11.4.

10.3.2 Environment

The staff at Camp Holiday Trails will work to reduce the risk of COVID-19 exposure by following the guidelines indicated in this protocol.

10.3.3 Activities

Group activities are an important part of a camp experience and will be done with the following precautions in place:

- All activities will be done outdoors
- Participants will be assigned to small groups or pods to limit exposures
- Staff will be maintained for the same pod as much as possible during each admission
- No high-risk activities requiring sustained close contact will be included and any higher risk contact-sport will be included in a skill building format so as to allow for adequate physical distancing and avoid unnecessary risk to study participants

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 11.1.2
- An Adverse Device Effect as defined in section 11.1.4, unless excluded from reporting in section 11.8
- An Adverse Event as defined in section 11.1.4 occurring in association with a study procedure
- An AE as defined in section 11.1.1 which leads to discontinuation of a study device for 2 or more hours
- Hypoglycemia meeting the definition of severe hypoglycemia as defined in section 11.2.1
- Diabetic ketoacidosis (DKA) as defined in section 11.2.2 or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

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

11.2.1 Hypoglycemia Event

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

- the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions;

- impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma;
- if plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

11.2.2 Hyperglycemia Events/Diabetes Ketoacidosis

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

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

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

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones ≥1.5 mmol/L or large/moderate urine ketones;
- 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-19 Transmission / Symptoms

While we are taking significant steps to prevent transmission of COVID-19 during this study, there is a possibility that participants are infected with COVID-19. The probability that infection is related to the study may be inferred in part by the timing, with symptoms beginning on days 1-2, or days 5-6 in a two weekend camp admission, of the study being more likely not related and onset of symptoms afterward being possibly related to exposure during the study.

- Participants or study staff who develop COVID-19 symptoms (e.g., fever, cough, shortness of breath (not related to camp activities)) during the study will be immediately isolated and discharged from the study. Before discharge, participants use of a facial masks will be mandated. Participants will not engage in further camp activities prior to discharge. At discharge, participants will be advised on appropriate isolation and testing to be completed.
- Before discharge, symptomatic participants will be tested with a rapid antigenic test; in the case of a positive test result, pod members of the symptomatic person will be wearing a mask at all times indoor and outdoor, except for eating, drinking, sleeping, and showering.
- All participants who develop symptoms of COVID 19 during camp, test positive for COVID 19 during camp, or are part of the same pod as a person who developed symptoms of COVID 19 or tested positive for COVID 19 during camp, will be asked to follow up via phone with the study team 5-7 days after discharge. All participants who develop symptoms of COVID 19 or test positive for COVID 19 within 7 days after discharge from the study admission will be asked to follow up via phone with the study team.

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 MMwill review the investigator's assessment of causality and may agree or disagree. Both the investigator's and MM's assessments will be recorded. The MM 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 MM within 10 working days of the study team becoming aware of the UADE per 21CFR 812.46(b) (2).
- The MM will determine if the UADE presents an unreasonable risk to participants. If so, the MM 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 MM 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
- One episode of DKA
- One episode of severe hypoglycemia as defined in section 11.2.1.
- Development of COVID-19 symptoms or positive COVID-19 test

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), use of the study device system will be suspended while the problem is diagnosed.

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

In addition, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g., product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension. The study MM 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 MM). The MM 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 MM 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 MM 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 MM review will be documented in a separate MM 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, participants 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 participant 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 study follows a double-blind randomized crossover design, comparing glycemic control obtained using the UVA HCL system – USS Virginia – alone (control) or in combination with a smart bolus calculator informed by real-time SI assessments (experimental). All study participants will undergo both treatment conditions, in different orders, defining two study arms as shown in Figure 1. Randomization (1:1) will determine whether a participant should undergo the control or experimental treatment condition first.

13.2 Sample Size

Sample size was determined by power analysis using G*Power 3.1 considering a paired t-test as the statistical test, comparing control group to experimental group on the primary efficacy endpoint. Effect size was determined based on the results obtained from the pilot clinical testing of the SI-informed bolus calculator in open-loop conditions to be dz=0.614. A total sample size of N=30 subjects was obtained considering a 0.66 correlation between groups, 90% power, and α=0.05.

13.3 Outcome Measures

13.3.1 Primary Efficacy Endpoint

The primary endpoint will be the low blood glucose index (LBGI) computed from CGM collected in the four hours following the dinner meal.

13.3.2 Secondary Outcomes

Secondary endpoints will include analysis over four different time intervals:

1. the dinner postprandial period (i.e., the four hours following dinner)
2. daytime, i.e., breakfast to bedtime
3. nighttime, i.e., bedtime to breakfast
4. 24 hours

The glycemic outcomes computed over the four horizons will be:

- percentage of time spent below 70 mg/dL
- percentage of time spent in 70-140 and 70-180 mg/dL
- percentage of time spent above 180 and 250 mg/dL
- the high blood glucose index

- average CGM
- CGM coefficient of variation
- Total number and amount of carbohydrate administered as rescue treatments

All glycemic outcomes (primary efficacy endpoint and secondary outcomes) will be computed based on CGM records. The primary analysis will focus on the postprandial period, but other analyses will evaluate different time intervals to assess whether the impact on the postprandial period will be influential enough to impact the overall daily control. Paired t-tests or non-parametric Wilcoxon signed-rank tests will be used to compare the control and experimental arms on the different glycemic outcomes, in case of normally/non-normally distributed samples respectively (Shapiro-Wilk test). Significance level will be set at a P value less than 0.05. All statistical analyses will be computed in SPSS Statistics 26 (IBM).

13.4 Safety Analyses

Safety endpoints are secondary outcomes addressing hypoglycemia and hyperglycemia, i.e., percentage of time below 70 mg/dL and above 250 mg/dL, and total number and amount of carbohydrate administered as rescue treatments.

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
- Diabetes duration
- BMI

13.6 Device Issues

The following tabulations and analyses will be performed by treatment group 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

The following tabulations will be performed for the Experimental arm only:

- Performance metrics, describing the 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

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 will sign the informed consent document prior to any procedures being done specifically for the study. 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. Children and Adolescents: Standards of Medical Care in Diabetes-2020. Diabetes care 2020; 43:S163-s182
2. Brown SA, Jiang B, McElwee-Malloy M, Wakeman C, Breton MD. Fluctuations of Hyperglycemia and Insulin Sensitivity Are Linked to Menstrual Cycle Phases in Women With T1D. Journal of diabetes science and technology 2015; 9:1192-1199
3. Carroll MF, Schade DS. The dawn phenomenon revisited: implications for diabetes therapy. Endocr Pract 2005; 11:55-64
4. Borghouts LB, Keizer HA. Exercise and insulin sensitivity: a review. Int J Sports Med 2000; 21:1-12
5. Maran A, Pavan P, Bonsembiante B, Brugin E, Ermolao A, Avogaro A, Zaccaria M. Continuous glucose monitoring reveals delayed nocturnal hypoglycemia after intermittent high-intensity exercise in nontrained patients with type 1 diabetes. Diabetes technology & therapeutics 2010; 12:763-768
6. Landt KW, Campaigne BN, James FW, Sperling MA. Effects of exercise training on insulin sensitivity in adolescents with type I diabetes. Diabetes care 1985; 8:461-465
7. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, Kowalski A, Rabasa-Lhoret R, McCrimmon RJ, Hume C, Annan F, Fournier PA, Graham C, Bode B, Galassetti P, Jones TW, Millán IS, Heise T, Peters AL, Petz A, Laffel LM. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol 2017; 5:377-390
8. Neyman A, Woerner S, Russ M, Yarbrough A, DiMeglio LA. Strategies That Adolescents With Type 1 Diabetes Use in Relation to Exercise. Clin Diabetes 2020; 38:266-272
9. Ekhlaspour L, Forlenza GP, Chernavvsky D, Maahs DM, Wadwa RP, Deboer MD, Messer LH, Town M, Pinnata J, Kruse G, Kovatchev BP, Buckingham BA, Breton MD. Closed loop control in adolescents and children during winter sports: Use of the Tandem Control-IQ AP system. Pediatric diabetes 2019;
10. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, Laffel LM, Levy CJ, Pinsker JE, Wadwa RP, Dassau E, Doyle FJ, 3rd, Anderson SM, Church MM, Dadlani V, Ekhlaspour L, Forlenza GP, Isganaitis E, Lam DW, Kollman C, Beck RW. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med 2019; 381:1707-1717
11. Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, Schoelwer M, Ruedy KJ, Jost E, Carria L, Emory E, Hsu LJ, Oliveri M, Kollman CC, Dokken BB, Weinzimer SA, DeBoer MD, Buckingham BA, Cherñavvsky D, Wadwa RP. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. N Engl J Med 2020; 383:836-845

12. Lopez PE, Evans M, King BR, Jones TW, Bell K, McElduff P, Davis EA, Smart CE. A randomized comparison of three prandial insulin dosing algorithms for children and adolescents with Type 1 diabetes. Diabet Med 2018; 35:1440-1447

13. Fabris C, Ozaslan B, Breton MD. Continuous Glucose Monitors and Activity Trackers to Inform Insulin Dosing in Type 1 Diabetes: The University of Virginia Contribution. Sensors (Basel) 2019; 19

14. Visentin R, Campos-Náñez E, Schiavon M, Lv D, Vettoretti M, Breton M, Kovatchev BP, Dalla Man C, Cobelli C. The UVA/Padova Type 1 Diabetes Simulator Goes From Single Meal to Single Day. Journal of diabetes science and technology 2018; 12:273-281

15. Breton MD, Patek SD, Lv D, Schertz E, Robic J, Pinnata J, Kollar L, Barnett C, Wakeman C, Oliveri M, Fabris C, Chernavvsky D, Kovatchev BP, Anderson SM. Continuous Glucose Monitoring and Insulin Informed Advisory System with Automated Titration and Dosing of Insulin Reduces Glucose Variability in Type 1 Diabetes Mellitus. Diabetes technology & therapeutics 2018; 20:531-540

16. Fabris C, Nass RM, Pinnata J, Carr KA, Koravi CLK, Barnett CL, Oliveri MC, Anderson SM, Chernavvsky DR, Breton MD. The Use of a Smart Bolus Calculator Informed by Real-time Insulin Sensitivity Assessments Reduces Postprandial Hypoglycemia Following an Aerobic Exercise Session in Individuals With Type 1 Diabetes. Diabetes care 2020; 43:799-805