University of Virginia
School of Medicine
Center for Diabetes Technology

Safety and Feasibility Testing of a Smaller Network Version of AIDANET

Running Title: Smaller Network Pilot

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Version Number:

v1.3 25-Oct-2024

KEY ROLES

	Name, Degree	Institution Name
Principal Investigator, IDE Chair	Marc D. Breton, PhD	University of Virginia Center for Diabetes Technology
Protocol Chair	Sue A. Brown, MD	University of Virginia Center for Diabetes Technology
Study Physician	Mark D. DeBoer, MD	University of Virginia Center for Diabetes Technology

PROTOCOL VERSION HISTORY

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0	Sue Brown	Sue Brown, Mark DeBoer	11-Sep-2024	Original Protocol
1.1	Mary Oliveri	Sue Brown, Mark DeBoer	24-Sep-2024	FDA Modifications: • Modified Glycemic Treatment Guidelines (section 7.6.1) • Modified Stopping Criteria (section 12.9.1)
1.2	Mark DeBoer	Sue Brown, Mark DeBoer	25-Sep-2024	FDA Modifications: • Modified Glycemic Treatment Guidelines (section 7.6.1)
1.3	Mary Oliveri	Mary Oliveri	25-Oct-2024	Study Team Modifications: • Added definition of AIDANET acronym (section 1.1) • Removed activity tracker (section 4.3) IRB Modifications: • Removed reference to assent (section 3.3) • Removed pregnancy test at hotel visit (section 7.3)

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Safety and Feasibility Testing of a Smaller Network Version of AIDANET

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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
ADA	American Diabetes Association
AE	Adverse Event
AID	Automated insulin delivery
AIDANET	Automated insulin delivery as Adaptive Network
AP	Artificial pancreas
AUC	Area Under the Curve
AYA	Adolescent and Young Adult
BDC	Barbara Davis Center
BG	Blood Glucose (as assessed by a blood glucose meter)
BGM	Blood glucose meter
CGM	Continuous glucose monitor
CSII	Continuous subcutaneous insulin infusion
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
FCL	Fully closed loop
HbA1c	Hemoglobin A1c
HCL	Hybrid closed loop
JDRF	Juvenile Diabetes Research Foundation
MDI	Multiple daily injections
NAP	Neural network artificial pancreas
SAE	Severe Adverse Event
SG	Sensor Glucose (as assessed by a continuous glucose monitor)
SH	Severe Hypoglycemia
T1D	Type 1 diabetes
TAR	Time above range
TBR	Time below range
TIR	Time in range 70-180 mg/dL

PROTOCOL SUMMARY

Participant Area	Description
Title	Safety and Feasibility Testing of a Smaller Network Version of AIDANET
Investigational Device	AIDANET algorithm as smaller network version with DiAs phone, Tandem t:AP insulin pumps, and Dexcom CGM
Objectives	The primary objective of the project is to demonstrate feasibility and safety of the Automated Insulin Delivery as Adaptive NETwork (AIDANET) system run in a new smaller network version, used in full closed loop (FCL) by adults with T1D.
Study Design	Randomized crossover, device safety/feasibility supervised house/hotel with transition to home use, interventional trial of AIDANET
Number of Sites	1
Endpoint	The primary metric for analysis will be change in mean CGM between the week of the control usual-care period and the one-week Remote Monitored At-Home Full Closed Loop period using AIDANET.
Population	Key Inclusion Criteria • Age 18-60 years at time of consent. • Clinical diagnosis of T1D, based on investigator assessment, of at least 1 year duration.
Sample Size	Complete 6 participants
Treatment Groups	Randomized Crossover: Participants will be randomized 1:1 to either conduct the control period before use of the AIDANET system (Group A) or after use of the AIDANET system (Group B).
Participant Duration	Approximately 3 weeks: approximately 1 week of usual care, 3 days/2 nights house/hotel in FCL, and 1 week At Home Remote Monitored FCL.
Protocol Overview/Synopsis	We will enroll up to 12 participants with a plan to complete 6 participants. The study will be performed for about 36 hours at a local hotel/rental. Following the house/hotel session, participants will undergo a 7 day/6-night Remote Monitored At-Home use session. We will also conduct a one-week control period gathering data on glycemic control and insulin administration with the participants usual care therapy. Participants will be randomized 1:1, to either Group A (control period prior to AIDANET use) or Group B (control period after AIDANET use).

TABLE 1. SCHEDULE OF STUDY VISITS AND PROCEDURES

	Screening	Randomization	Usual Care Data Collection	Pre-Hotel Check In	Hotel Admission with FCL	FCL Equipment Training	1-week at-home FCL	Post Study Check-In
Location	CV/R/Ph	CV/R/Ph	Home x 1 week	R/Ph	House/ Hotel	House/ Hotel	Home x 1 week	Home
Visit	1	2	3	4	5	6	7	8
Timeframe (days)	1	2	3-10	11	12-14	12	14-21	22
Informed Consent	X							
Eligibility Assessment	X							
Medical History	X							
HbA1c	X							
Pregnancy Test (if applicable)	X							
Blood Testing: BMP, Liver Functioning, Hematocrit, TSH (if requested by MD)	X							
Physical Exam (H&P within 6 months permitted as substitute)	X							
Vital Signs (including height/weight) (self-reported values permitted)	X				X			

Demographic Data Survey (if eligibility is met)	X							
Randomization		X						
Study Equipment Training						X		
CGM Use			X	X	X	X	X	
Fully Closed Loop (FCL) Use (e.g. AIDANET, DiAs, CGM)					X	X	X	
Questionnaires					X		X	
Concomitant Medication Review	X				X			
Review diabetes management and AEs			X	X	X	X	X	X

CV = Clinic Visit; R=Remote Visit; Ph=Phone which includes text messages and emails

Table 2. Metric Capture Timeline

	Enrollment	1-Week Usual Care	Hotel FCL	1-Week at-home FCL
Visit	1	3	5	7
Demographic Data	x			
HbA1c	x			
CGM Data				
Mean CGM		x	x	x
GMI		x	x	x
TIR 70-180 mg/dL		x	x	x
CGM StDev		x	x	x
CGM CV		x	x	x
CGM%<54 mg/dL		x	x	x
CGM%<70 mg/dL		x	x	x
CGM%>180 mg/dL		x	x	x
CGM%>250 mg/dL		x	x	x
Time in Automation			x	x
Total Daily Insulin Dose		x	x	x
Number of Boluses per Day		x	x	
Exercise: CGM %<70 mg/dL			x	
Unannounced Meals: % CGM>250 mg/dL			x	
Inspire Questionnaire			x	x
Technology Expectations Survey			x	x

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Chapter 1: Background

1.1 Introduction

A major impediment to maintaining blood glucose (BG) control in Type 1 diabetes (T1D) is missed meal boluses, which has been associated with significantly higher HbA1c levels.[1] While the advent of the artificial pancreas (AP) offers promise of safe reductions in HbA1c, our research group previously found that current AP systems only partly compensate for missed prandial insulin.[2] We thus designed a new system called Automated Insulin Delivery Adaptive NETwork, or AIDANET, to be fully automated, utilizing a Bolus Priming System (BPS) that recognizes meal ingestion and delivers a quick priming dose of insulin prior to extreme blood sugar excursions. When used as a fully automated closed loop (FCL) system (without any meal announcements to the controller), this system improves glucose time-in-target range (TIR) 70-180 mg/dL compared to a current commercially available system (Control-IQ). We subsequently incorporated this system in a neural net and found this to function as well as the previous model-predictive control algorithm. However, the long-term utility of such a system would have to be via use on an insulin pump, requiring a refined "smaller" code set to be able to run on internal pump software.

We have thus formulated a version of AIDANET that has a smaller coding footprint. The goal of the current project is to assess whether this "smaller" version of AIDANET continues to provide safe and effective glycemia management as seen in prior formulations. The current study is a randomized cross-over study comparing participants' usual care with one week at home on AIDANET. The week of control at home will follow a two-night hotel stay when participants will be taught how to operate the new system during the at-home portion of the study. The comparator usual care week will be randomly assigned to being before time on AIDANET (i.e., prior to the hotel stay) or after (i.e. time after the one-week home portion).

For the majority of time on AIDANET, participants will not announce meal ingestion to the system—using the system as an FCL system. However, the system is designed to also be able to be used as a hybrid system with carbohydrate announcement. Thus, as further assessment of the system, we will instruct participants to use the system as follows:

- For one of the dinners in the hotel participants will bolus for carbohydrate content of their meal, using their usual insulin-to-carbohydrate ratio (while the other dinner in the hotel will be fully FCL).
- For one full day while at home participants will bolus for carbohydrates for all ingestions (using their usual insulin-to-carbohydrate ratio).
- For another full day at home, participants will merely announce to the system each time they begin to eat a meal or snack; this will induce the system to deliver a rapid BPS dose (e.g. 10% of total daily insulin).

We hypothesize that performances of this smaller version of AIDANET will provide safe and effective care when used as FCL (with the exception of the hybrid use as just described). We expect

that this will constitute an important step toward having an AID system that has potential to be used embedded in insulin pumps.

1.2 Study Objective

This study aims to demonstrate the safety and feasibility of the Automated insulin delivery as Adaptive NETwork (AIDANET) system in a smaller software version, used as FCL. This study will also assess differences in glycemia outcomes on assigned days when the participant 1) enters total carbohydrate amount and 2) announces when food is started to be consumed.

1.3 Specific Aims and Hypotheses

Aim 1: To evaluate the performance (safety, efficacy) of the smaller version of AIDANET used as FCL.

Hypothesis: FCL use will provide as good or better mean CGM value and glucose TIR during 1 week of at-home use as compared to 1 week of standard care sensor data.

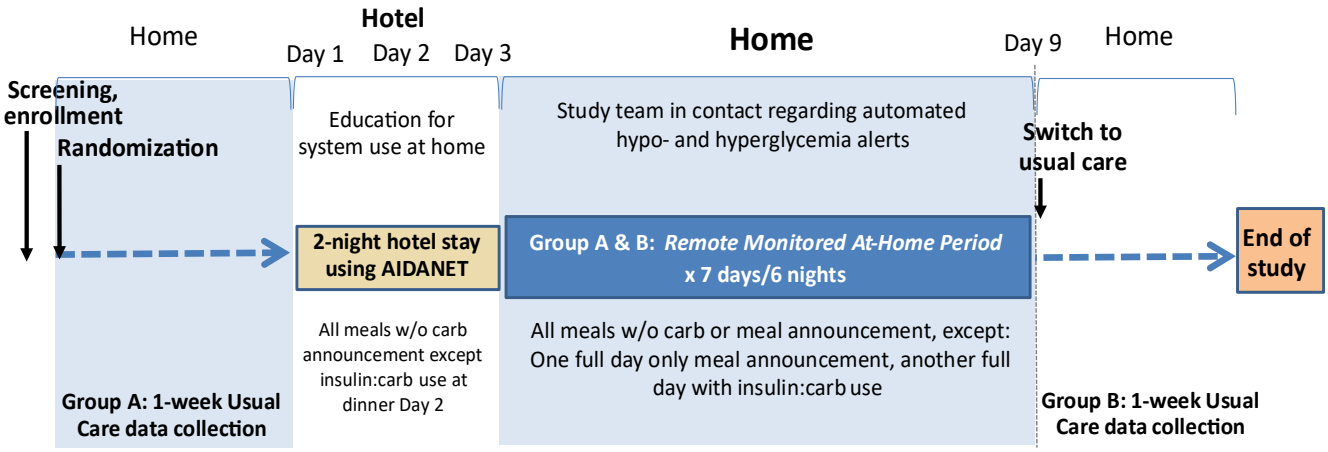
Aim 2: To evaluate the safety and efficacy of the smaller version of AIDANET during days where participants are assigned to 1) use usual insulin-to-carbohydrate ratio and 2) use meal announcement alone (triggering BPS).

Hypothesis: The AIDANET system will yield improved mean CGM glucose and TIR on days when meals are announced, both using insulin-to-carbohydrate ratio and simple meal announcement.

Chapter 2: Study Synopsis

2.1 Study Design

This study assesses adults with T1D on the AIDANET system during a 2-night house/hotel stay and during 1 week at home (Figure 1). Participants will use the system as FCL with the exception of using their insulin-to-carbohydrate ratio as usual during 1 dinner in the house/hotel and 1 day at home and announcing eating initiation for 1 day at home. We will aim to complete a total of 6 participants. We will also conduct an approximately 1-week control period gathering data on glycemic control and insulin administration with the participants' usual care therapy. Participants will be randomized 1:1 to either Group A (control period prior to AIDANET use) or Group B (control period after AIDANET use).



- Figure 1: Device Use Timeline

2.2 Study Hardware/Software

The study will involve testing a new AID system designed to enable full closed loop control and consisting of the following elements: the diabetes assistant (DiAs) prototyping platform, connected to a Tandem t:AP research insulin pump and a Dexcom G6 CGM, and implementing a new "smaller" coding version of the University of Virginia (UVA) AIDANET algorithm. Upon arrival at the hotel, participants will be taught how to use the Tandem t:AP pump as well as the DiAs system, including stopping the system.

2.3 Timing of Device Use

***One-Week Control Period*:** All participants will collect approximately one week of usual care data to serve as control data for cross-over testing as outlined in Section 6.1. During the control period, participants may use an insulin pump either in manual or automated mode that is capable of being downloaded. Participants will be randomized 1:1 to either conduct the control period before use of the AIDANET system (Group A) or after use of the AIDANET system (Group B).

***Hotel Period*:** Participants will arrive at the hotel prior to dinner on the afternoon of Day 1. They will be connected to the Tandem t:AP pump, which will be connected to the DiAs platform. A Dexcom G6 CGM may be placed on Day 1 or by the participant prior to Day 1 and will also be connected to the DiAs platform. The system will be started in the afternoon/evening with AIDANET enabled prior to dinner on Day 1. Participants will be taught how to use the DiAs in this configuration. The t:AP pump will be programmed with back up parameters determined by the study investigator(s). Once started, the participants will have their glucose values managed through use of this system during the hotel and Remote Monitored At-Home periods.

***Remote Monitored At-Home Period*:** Participants will continue to use the Tandem t:AP pump, DiAs platform running the AIDANET smaller network system, and Dexcom G6 CGM for glucose control for 7 days/6 nights during this period. At the end of the Remote Monitored At-Home period, participants will return to their usual diabetes therapy.

2.4 Meal and Exercise Testing

2.4.1 Meal Testing

During the supervised house/hotel period, participants will be instructed to eat approximately 3 unannounced meals per full day, with the exception of using their usual insulin-to-carbohydrate ratio with dinner one of the 2 nights. The time of completion for these meals will be recorded by study staff. The % CGM>250 mg/dL for the 4 hours after each meal will be recorded and specifically analyzed along with the CGM area under the curve (AUC) for the post-meal 4-hour period. Participants will be instructed to freely eat unannounced meals during the remote-monitored at-home stage but will not be required to record the timing of the meals. The exception is they will be instructed for 1 full day (from waking through bedtime) to announce usual insulin-to-carbohydrate for all ingestions and for another full day to announce when they begin to eat. Participants will be educated to consume their usual diet during both the at-home control period and the Remote Monitored At-Home FCL period.

2.4.2 Exercise Testing

During the supervised hotel period, participants will engage in mild activity (a walk of approximately 30 minutes) on Day 2. Study staff will set a Temporary Control Rate (TCR) of approximately 50-100% starting up to approximately one hour prior to exercise for approximately 2 hours, actual TCR settings will be tailored to an individual person. Study staff will record the duration, approximate intensity (low, moderate, or high intensity), the TBR <70 mg/dL, TBR <54 mg/dL, and any episodes of Severe Hypoglycemia (SH) during the walk and in the 2 hours after the exercise challenges. Participants will be provided with an exercise monitor (e.g., Fitbit) for use during the control and FCL periods. Participants will be allowed to practice their usual exercise routine during the control and remote-monitored at-home FCL periods with use of the TCR as needed. They will not be required to record exercise events during these periods.

2.5 Study Devices Download

Data from the study devices will be captured in real-time by the remote monitoring server for the DiAs system. In addition, study devices will be downloaded at the end of the Remote-Monitored At-Home FCL period.

2.6 Study System Issues

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

If the DiAs system is unable to maintain connectivity with the Tandem t:AP pump, the pump will automatically revert to the pre-programmed dosing parameters after 30 minutes without any need for interaction from the user.

Chapter 3: Study Screening

VISIT 1

3.1 Clinical Site

The study will be performed at the University of Virginia. Screening procedures will be performed either virtually or on site, at a clinical research unit, or at the hotel.

3.2 Participant Recruitment and Enrollment

We will enroll up to 12 participants who have been diagnosed with type 1 diabetes for at least one year. This enrollment number accounts for dropouts or screen failures that may occur. The goal is to complete a total of approximately 6 participants.

3.3 Informed Consent and Authorization Procedures

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

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

Consenting procedures and documentation are defined in section 16.3.

After informed consent has been signed, a potential participant will be evaluated for study eligibility through review of medical history, performance of physical exam by a licensed health care professional, and other testing as needed per the I/E criteria.

3.4 Participant Inclusion Criteria

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

1. Age ≥18.0 and ≤60 years old at time of consent
2. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year
3. Currently using insulin pump for at least three months; Any pump, either open loop or hybrid closed loop may be used.
4. Currently using insulin for at least six months.
5. Willingness to switch to use a commercially approved personal insulin (e.g., lispro or aspart, or biosimilar approved products) within the study pump as directed by the study team.

6. Currently using a Dexcom G6 or G7 CGM.
7. Has one or more supportive companions knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff that either lives with participant or located within approximately 30 minutes of participant and able to locate participant in the event of an emergency.
8. Participant not currently known to be pregnant or breastfeeding.
9. If participant capable of becoming pregnant, must agree to use a form of contraception to prevent pregnancy while a participant in the study (e.g. hormonal contraception, abstinence from heterosexual intercourse). A negative serum or urine pregnancy test will be required for all females of childbearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
10. Willingness to use the study FCL system (CGM, pump, and phone) during the relevant study period.
11. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial.
12. Willingness to participate in all study procedures including the house/hotel session, exercise challenges (e.g., one hour per day during hotel), and to consume approximately 3 unannounced meals per day during the relevant portion of the supervised hotel session.
13. Access to internet at home and willingness to upload data during the study as needed.
14. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol.
15. Participant is proficient in reading and writing English.

3.5 Participant Exclusion Criteria

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

1. Plans to start a new non-insulin glucose-lowering agent (e.g., GLP-1 receptor agonists, Symlin, DPP-4 inhibitors, sulfonylureas). Participants may be on a stable dose of such an agent for at least the past month.
2. Current use of an SGLT-2 or SGLT-1/2 inhibitor due to risk of euglycemic DKA.
3. Hemophilia or any other bleeding disorder.
4. History of severe hypoglycemic events with seizure or loss of consciousness in the last 12 months.
5. History of DKA event in the last 12 months.
6. History of chronic renal disease (Stage 4 or unstable Stage 3b per investigator judgment) or currently on peritoneal or hemodialysis.

7. History of adrenal insufficiency.
8. Currently being treated for a seizure disorder.
9. Hypothyroidism or hyperthyroidism that is not adequately treated.
10. Coronary artery disease or other heart condition that would prevent participation in moderate intensity exercise.
11. Use of oral or injectable steroids at the time of enrollment or within the last 4 weeks.
12. Planned surgery during the study period.
13. Known ongoing adhesive intolerance that is not well managed.
14. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk.
15. Participation in another interventional trial at the time of enrollment.
16. Participant with a direct supervisor involved in the conduct of the trial.

3.6 Screening Procedures

The participant will be evaluated for study inclusion and exclusion eligibility after the informed consent forms have been signed by the participant and the study team. Screening procedures will last approximately 1-2 hours. The visit may occur in-person or remotely by HIPAA compliant video communication (e.g., Zoom, Webex) The following procedures may be performed/data collected/eligibility criteria checked and documented:

1. Inclusion and Exclusion criteria assessed
2. Demographics, including:
    a. Date of birth
    b. Gender
    c. Race
    d. Ethnicity
3. Medical History, including diabetes history
    a. Duration of disease (number of years)
    b. History of pump use
    c. History of CGM use
    d. Current treatment
    e. Severe hypoglycemia history
    f. DKA history
    g. History of seizures
    h. Loss of consciousness
4. Basal rates or basal insulin dosing
5. Carbohydrate ratios
6. Insulin sensitivity factors
7. Target glucose
8. Average daily insulin

9. Surgical history
10. Allergies
11. Concomitant medications
12. Physical Examination – A historical history and physical report within 6 months of screening appointments may be used but is not required for eligibility. If vitals are not available, may include self-reported values of all available vitals.
    a. Weight
    b. Height
    c. Blood pressure
    d. Temperature
    e. Heart Rate
13. Screening Labs
    a. HbA1c point of care or laboratory; may use an HbA1c if obtained in the past month.
    b. Urine or serum pregnancy test for all women of childbearing potential (this test can be done remotely with results sent to the study team)

A physical exam documented in the prior 12 months can suffice for the physical exam but will not serve as an exclusion criterion if not available. Participants may self-report height, weight, blood pressure, temperature, and heart rate; or these may be obtained by study staff at the enrollment visit. An HbA1c value obtained in the previous one month may serve for the enrollment HbA1c value.

If needed based on medical history, investigators may include baseline chemistry panel, liver function tests, hematocrit, and thyroid stimulating hormone (lab results within one year of screening appointment may be used). Any labs required may be obtained at a local laboratory (e.g., LabCorp, Quest) convenient to the participant. The study physician or physician designee will have the discretion to repeat screening tests if applicable.

3.7 Screen Failures

If an exclusionary condition is identified, the study participant will be excluded from participation with follow up and referral to their primary care physician as needed.

If the study participant is pregnant, the study physician will discuss the results of the blood test with the participant and the participant will be asked to seek confirmation of the test and the appropriate medical care.

Participants may be re-screened if their clinical situation changes as determined by the study physician.

3.8 Personal Equipment Downloads

Up to 6 months of historical data from the participant's personal insulin pump, glucometer, or continuous glucose monitor may be downloaded or recorded. Data will be obtained from the participant's personal insulin pump, glucometer and CGM. This data may be obtained through the commercial applications (e.g., t:connect, Tidepool, and Dexcom).

3.9 Questionnaire

Participants will be asked to complete the Demographic Data Survey, as described in section 9.2, once eligibility has been met.

3.10 Other Considerations

This study is not meant to find out if the participant has any other disease or problem. The study leaders will alert the participant if any of the research results are important to the participant's health during the study. The participant may have a copy of the screening tests to discuss with the personal physician. If blood tests are completed, any blood left over will be thrown away. It will not be stored for any future testing.

Chapter 4: Study Devices & Training

The study system is designed to enable full closed loop control and consisting of the following elements: the diabetes assistant (DiAs) prototyping platform (smart phone), connected to a Tandem t:AP research insulin pump and a Dexcom G6 CGM, and implementing a new "smaller" coding version of the University of Virginia (UVA) AIDANET algorithm.

4.1 Insulin Pump

4.1.1 Equipment Description.

A study insulin pump will be provided to all participants at the training session. The participants will be trained in the basic functionality (e.g., bolus menu and infusion set change menu) for the study pump. For the Tandem pumps a training checklist is available on-line with relevant sections applicable to the study pump will be covered.

The t:AP research CSII pump will be programmed with the participants' usual pump parameters (basal insulin rate, insulin to carbohydrate ratio, and insulin correction factor) as determined by the study physician at the onset of the hotel phase. These parameters serve as backup-only settings for the system in open loop mode, and do not determine behavior of the AIDANET algorithm. The bolus priming system (BPS) profile determines the maximum fraction of total daily insulin (TDI) that can be injected by the BPS depending on the time of day (e.g., 8% between 06:00 and 10:00). The BPS profile is a setting on DiAs which can be modified by the provider to impact performance of the AIDANET algorithm. The study physician may alter the BPS profile during the hotel and at-home portions of the study to optimize participant safety with the experimental system.

4.1.2 Equipment Training

Training on the DiAs and study pump may begin at the hotel after the AIDANET system has been put in place. The purpose of this training is to introduce the study system to the participant. Insulin parameters will be determined by the investigator(s) and programmed into their study insulin pump and confirmed by two research staff. Participants will then switch to the study insulin pump. The participant's personal pump will be removed. The investigator may elect to use an existing personal pump infusion site at their discretion at the start of the study. The participant will be instructed on charging the pump, menu navigation, bolus procedures, and infusion site changes.

Data-driven optimization of pump settings can occur at any time prior to the hotel session, particularly if the participant contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia. During closed loop testing, study investigators may change pump settings as needed to optimize participant safety with the experimental system.

4.2 Continuous Glucose Monitor

4.2.1 Equipment Description

The study CGM will include the Dexcom G6 transmitter and sensor. Participants may elect to wear their personal Dexcom G6 CGM equipment throughout the study period. If currently wear a G7 CGM model, the participant will be provided with G6 CGM supplies. These sensors may be worn for up to 10 days of continuous wear. The G6 transmitter may be worn for 3 months.

4.2.2 CGM Training

A study CGM will be provided to all participants at the training session which is expected to occur prior to the hotel session or prior to the usual care period based on the current use of CGM and randomization. Participants using the Dexcom G6 may continue their personal CGM during the study session. The participants will be provided with CGM equipment and instructed to use CGM on a daily basis. If the participant has prior use of the G6, retraining will be specific to the individual. The study team may elect to have less frequent CGM users watch the Dexcom online training videos (https://www.dexcom.com/training-videos) to assist in the training session. Study staff training may include review of the study CGM in real-time to make management decisions and how to review the data after an upload for retrospective review. Study staff will specifically identify how alarms are set using the app and the frequency that these alarms will repeat.

For participants not using the Dexcom G6, the participants will be observed placing the sensor and will learn/review how to access the CGM trace via the Dexcom G6 commercial app (prior to the hotel session) and via the DiAs phone (during the hotel session). The participants will be asked to perform fingerstick blood glucose measurements (if needed) in accordance with the labelling of the study CGM device. An electronic copy of the CGM user's guide will be provided for these participants to read. The study team will be sure that the participants will leave the training session knowing how to properly use the CGM. The study team will be available for any questions.

The study team will ask participants to share their data to the study Dexcom clinical account. This requires a one-time confirmation of data sharing between either the participant's personal Dexcom account or the study Dexcom account and the study clinical account. Participants are identified in the study clinical account by their assigned participant number. The participant does not need to provide the study team with their own login information at any point in this process. The Dexcom clinical account allows the study team to remotely assess and download data as needed. Data sharing between the personal Dexcom account or study Dexcom account and the clinical account can be ended at any time by the participant.

During Usual Care phase, participants will have the option of using their personal smartphone or receive a study smartphone to use in order to collect the data from the devices. They may also use their own Dexcom G6 or G7 CGM. If the participant elects to use a personal device, the Dexcom app will be downloaded to their phone in order to monitor the participant's CGM values and alerts in real-time may be used prior to initiating DiAs.

4.3 Blood Glucose Meter and Strips

4.3.1 Equipment Description

A study glucometer will be provided to all participants to wear during the entire study to record any blood glucose levels measured during the study.

4.3.2 Equipment Training

Participants will be advised to use the study glucometer when experiencing a low or high glucose values as defined in the Glycemic Treatment Guidelines. The Dexcom CGM will be calibrated, if needed, using the study glucometer and test strips in accordance with the manufacturer's labeling.

If the study glucometer provides an app, the study team will request that the app be downloaded to the participant's personal phone. The app will permit continued visibility of blood glucose values to the participant and permit the study team to download the data without returning the glucometer at the end of the study.

4.4 Ketone Meter and Strips

Blood ketone levels will be measured during the hotel and at-home portions of the study with either the Abbott Precision Xtra Meter or the Ketomojo Meters and ketone test strips in accordance with the manufacturer's labeling. Urine ketone strips may be provided to the participant for the at-home data collection period. The glucometer component of either ketone meters will not be used.

4.5 Study Devices Accountability Procedures

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

Chapter 5: Randomization

VISIT 2

Once eligibility is met and screening procedures are completed, the participant will proceed to Randomization. Participants will be randomized 1:1 to assess a 1-week usual care period before use of the AIDANET system (Group A) or after use of the AIDANET system (Group B).

Participants who screen-fail or dropout will be replaced if it occurs prior to the Hotel Admission.

Randomization will occur via REDCap module.

GROUP A: Participants will complete one week at home usual care before the use of the AIDANET system at the hotel admission.

GROUP B: Participants will complete one week at home usual care after the use of the AIDANET system at the hotel admission.

Chapter 6: Usual Care Control Period

6.1 Usual Care Control Period

VISIT 3

During the usual-care control period, participants will continue to use their personal insulin pump in either manual or automated mode. The mode selected must be capable of downloading the data and sharing it with the study team. Participants using Dexcom CGM will continue to use their personal CGM or the study CGM and will share their CGM download data with the study team at the completion of the Usual Care period.

All participants will be provided with a study glucometer to collect blood glucose values during the study. This study team will download this glucometer at the conclusion of the study.

Participants will be instructed to follow their normal routine involving diet, exercise, and insulin administration.

Any relevant contacts will be recorded on the CRF and summarized as appropriate (e.g. contact that is not a scheduling or supplies issue will not be recorded).

6.2 Pre-Hotel Check-In Visit

VISIT 4

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

a. Inquire about any changes to the participant's medical history
b. Study equipment (e.g., CGM) has been initiated. A new CGM sensor will be placed approximately 24-72 hours prior to the hotel session for proper warm-up.
c. Verify with participant that the goal CGM reading at time of arrival is less than 200 mg/dL; this may require contact with the study physician prior to arrival on the day of the study visit.
d. Participants will be encouraged to complete the INSPIRE and Technology Acceptance surveys prior to the hotel admission but no later than the initiation of the study equipment at the hotel admission.

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.

Chapter 7: Supervised Hotel Fully Closed Loop Period

VISIT 5

7.1 Hotel Session

The study will be performed for about 36 hours at a local hotel/rental. Participants will use the AIDANET system in the hotel setting from the afternoon/evening of Day 1 through discharge in the morning of Day 3. They will then continue to use the system for the at-home period of the study.

7.2 Qualifications and Role of the Staff

There will be at least two study staff present at all times at the study site, at least one of whom will be clinical staff (e.g., nurse, physician, nurse practitioner, physician assistant). 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 hotel session. Participants will be remotely monitored by at least one study team member (maybe trained staff, nurse, physician, NP, or PA) using a web-based remote monitoring system that has been previously established for DiAs. The web-based remote monitoring system will display real-time insulin delivery, CGM and other system information to allow for patient safety monitoring. In addition, study team members will be trained in all protocol and Glycemic Treatment Guideline procedures. The closed-loop system will be managed by the participant with study-staff supervision, particularly at the time of insulin boluses (if needed). Glucagon for the emergency treatment of hypoglycemia will be available on-site. Participants will be instructed to bring their own rescue glucagon, though each site will also bring emergency rescue glucagon to the study.

7.3 Hotel Session Check-In

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

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

The participant's home insulin pump will be discontinued, and the study insulin pump will be initiated. The study team will ensure the proper function of the CGM and insulin pump. 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 is no required protocol fingerstick blood glucose measurements other than at times of CGM calibration (if necessary) and if directed by the study team. Fingerstick blood glucose measurements may be taken whenever participants experience symptoms, if the CGM glucose is suspected to be erroneous, or any time the participant would like to be reassured. Glycemic Treatment Guidelines to be used during the hotel admission are defined in section 7.6.

7.4 Study Meals

Participants will eat approximately 3 freely chosen unannounced meals per day during the supervised hotel session. Study staff will record the time the meal was eaten so that analysis of the AIDANET algorithm's performance around the mealtime may be conducted. Participants will use their usual insulin:carbohydrate ratio at dinner on Day 2. No other meal announcement will occur during the hotel stay. Snacks with carbohydrates will not be allowed unless for the treatment of low blood sugars. Non-carbohydrate snacks may be allowed throughout the hotel session per investigator discretion. Blood glucose levels will be followed via CGM with interventions for glucose extremes as per the Glycemic Treatment Guidelines.

7.5 Hotel Session Activities

Participants will engage in a walk of approximately 30 minutes on Day 2 of the hotel stay. Participants must have a CGM value of at least 80 mg/dL in order to begin the walk. The timing of exercise will be recorded by study staff so that analysis of the AIDANET algorithm's performance around exercise may be conducted. Participants will already be wearing an exercise monitor as part of the study protocol.

The walk will be terminated early with subjective symptoms such as shortness of breath, chest pain, dizziness, palpitations, or any such concerning symptoms reported by participants. Participants will stop their participation in the exercise portion of the study if reporting any concerning symptoms. Study physicians (or physician's assistants) will assess the participants for their need for additional care outside the study. If symptoms resolve entirely and there is no additional requirement for care outside the study, participants may then continue with the remainder of the study per investigator discretion.

Participants will also be free to engage in additional low-intensity activity (i.e., walking) during the hotel admission. Study staff will accompany participants if they leave the house/hotel.

7.6 Glycemic Treatment Guidelines

Hypo- and Hyperglycemia occurring while using the AIDANET system will be managed per the following protocol during both the hotel and at-home portions of the trial. Glycemic Treatment Guidelines will be available for staff use during the study sessions and will be provided to participants for the at-home phase of the study.

7.6.1 Hypoglycemia

a. If CGM falls below 70 mg/dL at any time, confirm <70mg/dL CGM readings and potential hypoglycemia symptoms with a fingerstick blood glucose. If blood glucose confirms <70mg/dL CGM reading, hypoglycemia will be treated with oral glucose of approximately 5-15 g. Participants will be encouraged to wait 15 min prior to giving a second glucose treatment. These fingerstick checks will be performed during the hotel stay and during the home portion if the participant chooses to do so. During the hotel stay we will also recheck a fingerstick blood glucose before retreatment.
b. If a participant experiences any symptoms of hypoglycemia (e.g., shakiness, dizziness, sweating, pallor, clumsiness, difficulty paying attention, or tingling around the mouth), then the participant should treat with oral glucose of 5-15 g. Participants will be encouraged to wait 15 min prior to giving a second glucose treatment. During the hotel portion of the study, a fingerstick blood glucose will be assessed before such treatment for symptoms and before any re-treatment.
c. If a participant displays any signs of neuroglycopenia (e.g., lethargy, disorientation, confusion, or inappropriate behavior) or severe hypoglycemia (e.g., hypoglycemic seizure, loss of consciousness, inability to properly consume treatment) hypoglycemia will be treated with either oral glucose or glucagon. The patient will be discharged from the study. The participant should consult with a study physician to discuss next steps for broader evaluation of symptoms unrelated to hypoglycemia.

7.6.2 Hyperglycemia

If CGM value is >300 mg/dL for 2 hours or >400 mg/dL at any time, check fingerstick BG and ketone level every 60±15 minutes. If unexplained hyperglycemia, evaluate the integrity of the insulin site, consider changing the site and providing a correction bolus as recommended by the bolus calculator. If insulin is given subcutaneous injection rather than through the DiAs, closed-loop control should be suspended for up to four hours unless directed by a study clinician.

7.7 FCL Equipment Training

VISIT 6

Participants will receive training on at-home use of the study system, safety protocols, and at-home study contacts on the day of discharge. Study equipment training is described in section Chapter 4:.

7.8 Hotel Session Discharge

Discharge will occur after breakfast on Day 3. After discharge, participants will proceed to the Remote Monitored At-Home Phase of the study.

7.9 Other Issues

The participant will be instructed to notify study staff if they experience any issues with the study devices. During the hotel phase, staff will provide hands-on support and troubleshooting training for any device issues. If subcutaneous insulin is needed, the participant will turn off closed-loop mode as instructed by study staff. During the at-home phase, participants will be instructed to contact the staff on-call in the event of subcutaneous insulin need. If insulin is delivered by any means other than the study pump, the participant will be instructed to turn off closed-loop mode for approximately four hours. This timeframe can be adjusted by the study physician.

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

Glucagon will be available at the hotel once the investigational system is in place. All participants will confirm that they have rescue glucagon available at home for the at-home phase.

Chapter 8: Remote Monitored At-Home Fully Closed Loop Period

VISIT 7

8.1 At Home Participant Plan

Upon discharge on day 3 of the hotel period, participants will begin a 7 day/6-night Remote Monitored At-Home stage of the study. Participants will continue to wear the FCL research system as initiated during the hotel period. Participants will be instructed to eat approximately 3 freely chosen meals per day without announcing them to the system. The exception is that on 2 separate days participants will 1) announce all food intake (triggering an immediate BPS dose) and 2) use their usual insulin-to-carbohydrate ratio for all food ingestion. Participants will be instructed to participate in their usual level of physical activity. Participants will complete the study after lunch on overall study day 9 (Day 7 of the home portion), at which point they will return to use of their usual diabetes care.

Participants in Group A will complete the study after this 1-week FCL data collection period. Participants in Group B will then begin the Usual Care control period for data comparison (see section 6.1).

8.2 Remote Monitoring

All participants will continue to be remote monitored during the At-Home period of the study using the connection between DiAs and Diabetes Web Monitoring (DWM) platform at UVA. Study staff may review the AID system data on the DWM platform as needed; in addition, at each site, a licensed medical provider (MD, PA, NP, RN, CDCES) will receive the following automated alerts from the DWM (automated notification system, ANS):

1. CGM > 300 mg/dL for 1 hour.
2. CGM < 70 mg/dL for 20 minutes.
3. CGM < 55 mg/dL at any point.
4. No sensor data for > 1 hour.

The provider on call will contact study participants (e.g., call, text, or video chat) and/or their companion for any of the above CGM alerts which are not resolved within a timely manner. Participants will be asked to manage glycemic extremes per the hyper- hypoglycemia safety protocol.

Contact (e.g., phone, text, email, etc.) with the study team will occur as needed. Any relevant contacts will be recorded on the CRF and summarized as appropriate (e.g. contact that is not a scheduling or supplies issue will not be recorded).

8.3 Questionnaires

All participants will complete the INSPIRE and Technology Acceptance survey:

- Prior to initiating the study equipment at the hotel admission
- At the conclusion of the one week of At-Home FCL data collection.

8.4 Post-Study Check-In

VISIT 8

Approximately 24-48 hours after the hotel session, the study team will contact the participant via phone/email/text/video to:

- Ask about any changes to the participant's medical history and medication.
- Review any hypoglycemic events that are less than 60 mg/dL.
- Review any hyperglycemic events that are more than 300 mg/dL .
- Verify that questions have been answered. The study physician or designee will be available for any questions related to insulin adjustments/parameters.

The study team may contact the participant for issues related to data collection and equipment issues.

8.5 Early Termination Visit (If Applicable)

Participants will be asked to attend the Post-Study Check-In Visit (visit 8) in the event of a withdrawal or early termination.

8.6 Unscheduled Visits

Participants may have unscheduled visits during the study period if required for additional device training or other unanticipated needs per the study investigator discretion.

Chapter 9: Medical Monitor Safety Review

The Medical Monitor will review compiled safety data at the conclusion of the trial. In addition, the Medical Monitor will review all DKA and severe hypoglycemia irrespective of relatedness to study device use, and all serious events (including UADEs) related to study device use at the time of occurrence. The Medical Monitor also will be informed of any Adverse Device Effects (ADE) not meeting criteria for a UADE if the Study PI requests the Medical Monitor review. The Medical Monitor can request modifications to the study protocol or suspension or stoppage of the study if deemed necessary based on the totality of safety data available.

Chapter 10: Testing Procedures

10.1 Laboratory and Point of Care Testing

10.1.1 HbA1c

A blood sample (either capillary or venous draw) will be obtained at screening to obtain a baseline Hemoglobin A1c level. A blood test obtained within 4 weeks prior to enrollment may be used. HbA1c level may be measured by the study team using the DCA2000, a comparable point of care device, at time of screening. Labs may be obtained at a local laboratory (e.g., LabCorp, Quest) convenient to the participant.

10.1.2 Pregnancy Test

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

10.2 Questionnaires

10.2.1 Demographic Data Survey

Research in diabetes technology has revealed significant disparities in minoritized population's representation in clinical trials and access to devices that improve diabetes outcomes. Collection of detailed demographic data regarding participants in technology trials has become essential. This includes data on race/ethnicity, income levels and insurance status, as well as education and other variables that describe the study population.

The Demographic Data Survey will be electronically administered once eligibility has been met. The below information will be gathered for all participants.

a. Age
b. Gender
c. Race
d. Ethnicity
e. Martial status
f. Level of education
g. Employment status
h. Household income
i. Health insurance status
j. Monthly insulin costs and co-payments

10.2.2 INSPIRE Questionnaire

The self-administered INSPIRE (INsulin Dosing Systems: Perceptions, Ideas, Reflections and Expectations) questionnaires have been developed to determine the psychosocial impact of AID

systems in a range of relevant factors specific to youth with T1D (8-17 years of age) and adults with T1D, as well as parents/caregivers of youth with T1D, and partners of adults with T1D.

The questionnaire will be administered at the onset of hotel admission and at the conclusion of the study.

10.2.3 Technology Expectations Survey

Participants will complete a Technology Expectation/Acceptance Survey which includes questions about attitudes, feelings, and behaviors related to the technology used in this study. AID Benefits and Burdens Scale Survey

The questionnaire will be administered prior to or at the onset of hotel admission and at the conclusion of the study.

Chapter 11: Risks Associated with the Clinical Trial

11.1 Potential Risks and Benefits of the Investigational Device

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

11.1.1 Venipuncture Risks

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

11.1.2 Fingerstick Risks

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

11.1.3 Subcutaneous Catheter Risks (CGM)

Participants using the CGM will be at minimal risk for developing a local skin infection at the site of the sensor needle placement. If a needle 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.

11.1.4 Risks of Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of having 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.

11.1.5 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.

11.1.6 Risks of Device Reuse

Participant will be informed that FDA or relevant national authorities have approved the insulin pump, CGM, glucometer and ketone meter for individual use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

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

CGM cleaning instructions are provided in the Dexcom G4 Platinum (Professional) Cleaning and Disinfection manual (current edition) and a similar approach will be applied for the CGMs used in this study.

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

The study-provided blood glucose meter will be returned to the study participant at the conclusion of the study after the study team has confirmed data collection. The study team will use cleaning procedures if it is necessary to be in physical contact with the equipment to download the device. The study team will clean the ketone meter per manufacturer directions.

11.1.7 Device Cleaning Instructions

Members of the study team will clean the study equipment after use as noted in these 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. The transmitter is then rinsed under flowing tap water for ten seconds. The transmitter will then be disinfected using a disinfectant product with EPA registration number 56392-7 using similar procedures as the cleaning process.

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

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

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

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

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

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

11.1.8 Hb1Ac Risk

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

11.1.9 Other Risks

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or to secure the insulin infusion sets for the continuous subcutaneous insulin infusion. If these reactions occur, different adhesives or "under-taping" (such as with IV 3000, Tegaderm,

etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

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

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

11.1.10 Known Potential Benefits

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

11.1.11 Risk Assessment

Based on the facts that (1) adults and adolescents with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may increase the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may increase the likelihood of hyperglycemia, (3) mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4) rapid reversal of hypoglycemia and hyperglycemia can be achieved, it is the assessment of the investigators that this protocol falls under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of the investigators that this study also presents prospects of direct benefit to the participants and general benefit to others with diabetes.

11.2 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.

Chapter 12: Adverse Events, Device Issues, and Stopping Rules

12.1 Definitions

12.1.1 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 12.2) for reportable adverse events for this protocol).

Positive pregnancy test will not be considered an adverse event.

12.1.2 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).

12.1.3 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)).

12.1.4 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.

12.1.5 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).

12.2 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 12.1.2.
- An Adverse Device Effect as defined in section 12.1.4, unless excluded from reporting in section 12.7.
- An Adverse Event as defined in section 12.1.1 occurring in association with a study procedure.
- An AE as defined in section 12.1.1 which leads to discontinuation of a study device for 4 or more hours during the hotel phase and 12 or more hours during the at home phase.
- Hypoglycemia meeting the definition of severe hypoglycemia as defined in section 12.2.1
- Diabetic ketoacidosis (DKA) as defined in section 12.2.2 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.

12.2.1 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.

12.2.2 Hyperglycemia Events/Diabetes Ketoacidosis

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

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

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

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

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

12.3 Relationship of Adverse Event to Study Device

The study investigator will review each adverse event and 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:

- 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.
- UNRELATED: 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.

12.4 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.

12.5 Coding of Adverse Events

Adverse events will be coded per standard categories (i.e., mild, moderate, severe). The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigators and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality.

Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

12.6 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 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 been 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.

12.7 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 report 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

12.8 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 Medical Monitor within 10 working days of the study team becoming aware of the UADE per 21CFR 812.46(b) (2).
- The Medical Monitor will determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than

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

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

12.9 Stopping Criteria

12.9.1 Participant Discontinuation

A participant will be discontinued if any of the following occur:

- The investigator believes it is unsafe for the participant to continue 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
- Two distinct episodes of DKA
- Two distinct severe hypoglycemia events as defined in section 12.2.1.
- Two events of any kind: severe hypoglycemia or DKA

12.9.2 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 12.2.2), use of the study device system will be suspended while the problem is diagnosed.

In the event that two distinct episodes of DKA or two distinct severe hypoglycemia events as defined in section 12.2.1 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 Medical Monitor will review all adverse events and adverse device events that are reported during the study and will review compiled safety data at periodic intervals. The Medical Monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

12.10 Independent Safety Oversight

A Medical Monitor will review all DKA and severe hypoglycemia irrespective of relatedness to study device use, and all serious events (including UADEs) related to study device use at the time of occurrence. The Medical Monitor can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available.

Details regarding the Medical Monitor review will be documented in a separate Medical Monitor document.

12.11 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 13: Miscellaneous Considerations

13.1 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.

13.2 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.

13.3 Confidentiality

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

13.4 Lost to Follow Up

If a participant is lost to follow up and participant outcome cannot be determined, outcome classification will be the last known outcome/contact with the participant. A participant will be considered lost to follow-up after three attempted contacts that do not result in any communication from the participant. A certified letter may be sent as the fourth and final attempt to communicate with the participant.

Chapter 14: Statistical Consideration

14.1 Design and Randomization

The proposed work is a safety and feasibility study of the FCL system and is not intended to be powered to fully demonstrate efficacy of the system. The sample size of up to 6 participants per session at each site was selected based on previous experience of the feasible number of individuals to supervise at one time under similar study conditions.

14.1.1 Planned Analysis

The primary outcome of interest will be the change in the mean CGM between the week of the Usual Care observational period and the week of AIDANET at-home. This study represents a small pilot study to assess the safety and efficacy of the small-version AIDANET system and is not formally powered. Nevertheless, the randomized crossover design will allow for analysis of period effects between Group A and Group B. Comparison between these groups will be made to determine if a period effect can explain part of the benefit of the FCL system during the at-home period.

a. Null Hypothesis: There is no difference in the mean CGM between the week of Usual Care observational period and the at-home FCL period.
b. Alternative Hypothesis: There is a difference in the mean CGM between the week of Usual Care observational period and the at-home FCL period.

Analysis will involve use of repeated measure ANOVA models to predict CGM average and TIR with the FCL status a fixed effect and baseline HbA1c and gender as covariates.

Secondary outcomes:
All secondary outcomes will be similarly analyzed. If an outcomes distribution is not suited for mixed model analysis (e.g., profound skewness, or large atom at boundary) we will perform paired Wilcoxon signed rank test (and loose the capacity to use covariate) to test difference in the median instead of the mean; this is expected for time below 70mg/dL, number of hypoglycemia, and possibly time above 250mg/dL.

We do not plan to correct for multiple comparisons.

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

14.2 Sample Size

As an early exploratory study, the goal will be to complete 6 participants to provide data from a variety of individuals. This number was chosen out of feasibility and not from a formal power calculation. The total sample size of 6 participants was selected based on previous experience of

the number of participants necessary to satisfy FDA requirements for a safety and feasibility study and move onto a larger out-patient efficacy study. While this sample size is thus a convenience sample, we may still determine the power to analyze each of the study hypotheses based on pilot trial data.

14.3 Outcome Measures

14.3.1 Primary Efficacy Endpoint

The primary metric for analysis will be change in mean CGM between the second last 7 days week of the control Usual-Care period and the one-week Remote Monitored At-Home FCL period.

14.3.2 Secondary Outcomes

Glycemic Metrics will be obtained directly from CGM data and will include the standard metrics recommended by the international consensus on CGM including mean CGM, GMI derived from mean CGM, time in range 70-180 mg/dL, CGM standard deviation (StDev), CGM coefficient of variation (CV), CGM %<54 mg/dL, CGM %<70 mg/dL, CGM %>180 mg/dL, and CGM %>250 mg/dL. For the Usual Care period, CGM data will be obtained from either the participant's personal CGM or a study provided CGM. Data for the control Usual-Care period will be analyzed by last available 7-day period. During the FCL period, CGM data will be obtained directly from the study device. As GMI is a linear transformation of mean CGM, this metric will have the same effect and will be presented as a primary outcome as well. All other glycemic metrics will be considered secondary outcome measures.

Device-Use Metrics will include time in automation, total daily insulin dose, and number of boluses per day. During the Usual Care period, participants using an insulin pump will have their pump uploaded at the end of the period to capture their insulin delivery and bolus data. The FCL period, insulin use, and bolus data (if any) will be captured from the experimental device.

Exercise Challenge Metrics will include the duration of exercise, approximate intensity of exercise (low, moderate, or high intensity), the % CGM<70 mg/dL, % CGM<54 mg/dL, and any episodes of SH (CGM<70mg/dL for more than 15 minutes with interruption, CGM≥70, of less than 15 minutes or CHO treatment) during and 2 hours after the exercise challenges.

Unannounced Meal Metrics during the supervised house/hotel FLC stage participants will be instructed to eat at least 3 meals per day. The time of completion for these meals will be recorded by study staff. The % CGM>250 mg/dL for the 4 hours after each meal will be recorded and specifically analyzed. Participants will be instructed to freely eat meals during the supervised at-home FCL stage but will not be required to record the timing of the meals for unannounced meals.

Patient Reported Outcomes will include several surveys aiming to capture participant satisfaction with the FCL device and any changes in distress or burden of diabetes management. See APPENDIX for survey tools. These surveys will include:

a. The INSPIRE Measures: A validated tool assessing the positive expectancies of AID systems for youth, adults, and parents and partners of people with diabetes. This tool has been specifically endorsed by the FDA for use with developing insulin-dosing systems.
b. Technology Expectations Surveys: A 25 question self-report measure of expectations from advanced technologies and perceived impact of the technology on quality of life. Validated to age 13+ years.

These surveys will be administered at baseline and then at the end of the prior to or at the start of the 1-week supervised House/Hotel FCL period and at the end of the 1-week remote-monitored at-home FCL study

14.3.3 CGM Data Treatment

a. Saturated CGM values "High" and "Low" will be replaced by 401mg/dL and 39mg/dL respectively.
b. Any CGM gaps shorter than 1 hour will be interpolated
c. CGM data during recorded occlusion event will be removed from analysis as follows: any measurement less than 2h before or after the time of record will be removed.
d. CGM data following a pump/DiAs communication interruption >1h by less than 2h will be removed

14.3.4 Outcome Computation Conditions

Outcomes will only be computed if at least 80% of the analysis window CGM measurements (after data treatment) are available.

14.4 Safety Analyses

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

14.5 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:

a. Age
b. HbA1c
c. Gender

d. Race/ethnicity
e. CGM use before enrollment
f. AID use before enrollment
g. Diabetes duration
h. BMI
i. Total Daily Insulin

14.6 Device Issues

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

a. Device malfunctions requiring study team contact and other reported device issues
b. % time CGM data available
c. % time with closed loop control

Chapter 15: Data Collection and Monitoring

15.1 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.

15.2 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.

15.3 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 16: Ethics/Protection of Human Participants

16.1 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.

16.2 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.

16.3 Informed Consent Process

16.3.1 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. The potential participant will be provided with a short overview of the study including its study goals, study procedures, and study timeline. If the potential participant remains interested, they will be asked permission to review inclusion/exclusion criteria to assess if they are eligible to participate in the study. If permission is granted, the study team will review the Inclusion/Exclusion criteria (section 3.4 and 3.5). If eligible, the study team member will provide a copy of the informed consent form (e.g., in person, email, fax, or mail) to the potential participant for their review. Potential participants may also elect to review the informed consent form prior to discussing pre-screening questions.

The potential participant will be provided with ample time to read and review the consent form. After their review, the study team will discuss the study at length in a phone call/HIPAA compliant telecommunication method for consenting that is not face to face. All participants will receive 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. Extensive discussion of risks and possible benefits of participation will be provided. The potential participant will be given an opportunity to ask the study team questions or may speak directly with the study physician. The potential participant's understanding of the information presented in the process of consent will be assessed by asking open-ended questions.

The consent form may be signed electronically for both in-person and telecommunication screening visits. Note: For potential participants who are not able to sign an electronic consent form, in-person, email, fax, or mail will be alternatives used to obtain a signed consent. A HIPAA

compliant video conferencing tool (e.g., Zoom, WebEx) will be utilized during the consenting process of the telecommunication screening visit to facilitate the FDA Part 11 compliant process of verification of reviewing two forms of identification if signing electronically off site. Participants can download a PDF copy of the signed consent and automatically receive a PDF via email from REDCap after the form is completed. CRCs also could download, print, and mail a paper copy for each participant. Study procedures may begin once the consent has been signed by the participant and a member of the study team.

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.

16.4 Participant and Data Confidentiality

The IRB-HSR Post Approval Monitoring (PAM) auditors, representatives of the IRB, or device company supplying study product may inspect 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. 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 will be archived at the UVA CDT.

Chapter 17: References

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