UVA CENTER FOR DIABETES TECHNOLOGY

Adaptive Motif-Based Control (AMBC): Pilot 1 – Neural Net Implementation of Automated Insulin Delivery

Running Title: Neural Net Artificial Pancreas (NAP)

Protocol Principal Investigator

Sue A. Brown, MD

University of Virginia

Center for Diabetes Technology

NCT#05876273

Version Number: v1.3

19-Jun-2023

KEY ROLES

	Name, degree	Institution Name
Protocol Principal Investigator	Sue Brown, MD	University of Virginia Division of Endocrinology and Metabolism
Study Sponsor	Boris Kovatchev, PhD	University of Virginia Center for Diabetes Technology

PROTOCOL VERSION HISTORY

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0	Boris Kovatchev	Sue Brown	20-Feb-2023	Original Protocol
1.1	Mary Oliveri	Sue Brown	08-Mar-2023	FSDA Modifications
1.2	Sue Brown	Sue Brown	07-Apr-2023	Study team mods
1.3	Mary Oliveri	Sue Brown	19-Jun-2023	Study team mods • Revised Risk of Device Reuse section to identify equipment that may be reused during the trial after cleaning (section 9.1.6) • Added Device Cleaning Instructions (section 9.1.7)

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Adaptive Motif-Based Control (AMBC): Pilot 1 – Neural Net Implementation of Automated Insulin Delivery

Running Title: Neural Net Artificial Pancreas (NAP)

Protocol Version/Date: v1.3 19-Jun-2023

I have read the protocol specified above. In my formal capacity as a 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
ADE	Adverse Device Effect
AE	Adverse Event
AID	Automated Insulin Delivery
AMBC	Adaptive Motif-Based Control
AP	Artificial Pancreas
BG	Blood Glucose
CDCES	Certified Diabetes Care and Education Specialist
CDT	Center for Diabetes Technology
CF	Correction Factor
CGM	Continuous Glucose Monitoring
CIQ	Control-IQ AP system, Tandem Diabetes Care, San Diego, CA
CSII	Continuous Subcutaneous Insulin Injection
DCCT	Diabetes Control and Complications Trial
DiAs	Diabetes Assistant – the UVA algorithm prototyping system
DKA	Diabetic Ketoacidosis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
ICR	Insulin-to-carbohydrate ratio
iDCL	International Diabetes Closed-Loop trial
IDE	Investigational Device Exemption
IRB	Institutional Review Board
NAP	Neural Net Artificial Pancreas
NIDDK	National Institute for Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
PI	Principal Investigator
POC	Point-of-Care
SAE	Serious Adverse Event
T1D	Type 1 Diabetes
TAR	Time above range, above 180 mg/dL
TBR	Time below range, below 70 mg/dL
TIR	Time within the range 70-180 mg/dL
UMPC	UVA's Model-Predictive Control Algorithm
UADE	Unanticipated Adverse Device Effect
UVA	University of Virginia

PROTOCOL SUMMARY

PROTOCOL SECTION	DESCRIPTION
Title	Adaptive Motif-Based Control (AMBC): Pilot 1 – Neural Net Implementation of Automated Insulin Delivery
Investigational Devices	Neural Net Artificial Pancreas (NAP) implementation of the UVA model predictive control algorithm (UMPC); **Both NAP and UMPC are investigational devices.**
Objectives	The purpose of this study is to test the safety and feasibility of a neural net implementation of an established AP controller, known as UMPC, previously approved by IDE G200206, and tested in the following randomized controlled clinical trials: ClinicalTrials.gov NCT04545567, NCT04877730, and NCT05528770.
Study Design	A randomized cross-over trial assessing glycemic control on NAP, compared to the original UMPC algorithm, which includes two sessions studied in a supervised hotel setting: 1) using NAP – a neural net implementation of UMPC, and 2) using the original UMPC without modifications (see IDE G200206).
Number of Sites	One
Endpoint	The primary outcome will be time in range 70-180 mg/dL for an 18-hour period, 6 PM to 12 PM on the next day, including dinner and breakfast meals.
Population	Key Inclusion Criteria • Age ≥18 years of age • Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least 1 year • Currently using insulin for at least six months • Currently using the Control-IQ (CIQ) automated insulin delivery (AID) system.
Sample Size	Up to 20 participants
Treatment Groups	Randomized crossover: Participants will be randomized to two groups differing by the order of controller use: Group A: NAP first followed by UMPC; Group B: UMPC followed by NAP.
Participant Duration	Up to 6 weeks: Participants will be studied at a local hotel or rental house to test two algorithms, approximately 20 hours per each test. Prior to each hotel session, participants will passively collect CIQ data for a week. The two hotel sessions can be performed sequentially during the same hotel stay or in two hotel stays separated up to 28 days.
Protocol Overview/Synopsis	Following enrollment, 1 week of AID data will be downloaded from the participants' pumps or t:connect accounts and will be used to establish a baseline and initialize the control algorithms. Participants will be then studied at a hotel for 20 hours, including an 18-hour experiment, randomly receiving either NAP or UMPC. Participants will then receive the opposite intervention either sequentially during the same hotel stay, or in a second hotel stay up to 28 days following the first hotel stay (Figure 1).

STUDY VISITS AND PROCEDURES SCHEDULE

	Screening	Hotel Session 1			Hotel Session 2		
		Pre-Session Check-In	Hotel Session 1	Post-Session Check-In*	Pre-Session Check-In**	Hotel Session 2	Post-Session Check-In
Location	In person or Remote	Phone/ Email/ Text	Hotel/ Rental House	Phone/ Email/ Text	Phone/ Email/ Text	Hotel/ Rental House	Phone/ Email/ Text
Visit	1	2	3	4	5	6	7
Informed Consent	X						
Eligibility Assessment	X						
Medical History	X						
HbA1c	X						
Pregnancy test (if applicable)			X			X***	
Physical Exam	X						
Vital Signs (height/weight)	X		X			X***	
Demographic Survey	X						
Baseline data download (1 week of AID data)	X						
Randomization	X						
NAP / UMPC use			X			X	
Review diabetes management and AEs		X		X	X		X

* Post-session check-in Visit 4 will not occur, if the two hotel sessions are done sequentially

** Pre-session check-in Visit 5 will not occur, if the two hotel sessions are done sequentially

*** Pregnancy test and vital signs recheck will not occur during Hotel Session 2 if the two hotel sessions are done sequentially.

TABLE OF CONTENTS

Chapter 1 Background and Synopsis

1.1 Introduction

The National Institutes of Health's Strategic Plan for Fiscal Years 2021–2025 "outlines NIH's vision for biomedical research direction, capacity, and stewardship, by articulating the highest priorities of NIH over the next 5 years." [1] The Plan also highlights key accomplishments in the past 5 years. On page 13, under the heading "Giving the Right Treatment to the Right Patient at the Right Time," the Plan recognized the UVA CDT (Center for Diabetes Technology) for its research resulting in the clinical translation of innovative automated insulin delivery (AID) technology.[1] Indeed, the blueprint of the UVA-AID was created by our team over a decade ago[2-5] and, after a number of clinical trials, culminated in two large studies, part of the International Diabetes Closed-Loop (iDCL) Trial, grant UC4DK108483, led by our team and published in the *New England Journal of Medicine*.[6,7] As a result, FDA cleared Control-IQ (Tandem Inc.), derived from the UVA-AID, as "the first inter-operable, automated insulin dosing controller designed to allow more choices for patients looking to customize their individual diabetes management device system."[8] Control-IQ is now launched in over 24 countries and has over 400,000 users worldwide.

With the first-generation UVA-AID translated to routine clinical practice, we have developed a next-generation controller – University of Virginia's model-predictive control algorithm (UMPC) – which was approved by the FDA for investigational use with IDE G200206[38] and was then tested successfully in a randomized controlled clinical trial (NCT04545567), published in *Diabetes Care*.[9] Two other pilot studies tested glycemic disturbance anticipation (IDE #G210051[39], NCT04877730) and automated priming bolus (IDE #G220204,[40] NCT05528770). Most recently, in a grant application funded by the NIDDK (RO1 DK 133148-01, corresponding PI Kovatchev), we proposed using the data and experience amassed in our previous studies to design and test a new class of AID algorithms – Adaptive Motif-Based Control (AMBC), which blends Data Science methods with artificial pancreas (AP) control engineering.

The concept of AMBC is to enable a pathway towards adaptive AP algorithms which are capable of learning from a person's CGM and insulin delivery patterns, and from the patterns of others stored in databases. The first step towards this concept of the future, is translating a well-established AP control algorithm, e.g., UMPC into a Data Science "environment," i.e., creating a Neural Net adaptation of a model-predictive controller. This protocol intends to test such an adaptation – a Neural Net AP (NAP) – in a brief study in a well-controlled environment. Studies to follow will expand this concept further and will add elements of controller adaptation based on data accumulated in databases, labelled by prefixed "motifs" – a recently established structure of daily CGM profiles.[10] The latter would allow a finite table-lookup approach to real-time AP control adaptation; but, this is a subject of future studies. Now we focus on the first step only – translating a controller into a neural-net environment.

Thus, the only new AID algorithm tested in this study is NAP – a neural-net implementation of the UMPC – which produces insulin adjustment commands identical (within a small tolerance) to the original UMPC (see Appendix A-1: Algorithm Description). We should also emphasize that the two experimental algorithms used in this study, UMPC and NAP, modulate only the basal rate of insulin delivery. The other components, the Adaptive Bolus Priming System, the Hyperglycemia Mitigation System, and the Safety System Module dedicated to prevention of hypoglycemia – remain unchanged from previous studies and are described in IDE # G220204. In particular, the Safety System has been reviewed by the Agency in virtually all IDEs in the reference list.[15-36] *The Safety System Module has also been tested for its ability to prevent hypoglycemia in pivotal trials [IDE#G180053 and IDE#G180053] and in millions of days of routine home use, as part of the commercial Control-IQ AID device system.*[37]

1.2 Objective and Primary Outcome

Pilot test the safety and feasibility of a NAP implementation of an established AP controller – UMPC – in a crossover study. The primary outcome is percent TIR (70 to 180 mg/dL) on NAP vs UMPC. Secondary outcomes include frequency of hypoglycemia (TBR) and hyperglycemia (TAR), as well as other safety and control metrics. We will analyze non-inferiority of NAP compared to UMPC, but *this pilot feasibility study is not powered to formally test noninferiority*.

1.3 Study Design

We will consent up to 20 participants, ages ≥18.0, with a goal to have 15 participants complete the trial. The study randomized crossover design is presented in Figure 1 below, and includes screening, randomization, and two 18-hour hotel/rental house study sessions (heretofore referred to as "hotel"). The first hotel session will be preceded by a download of 1-week AID data:

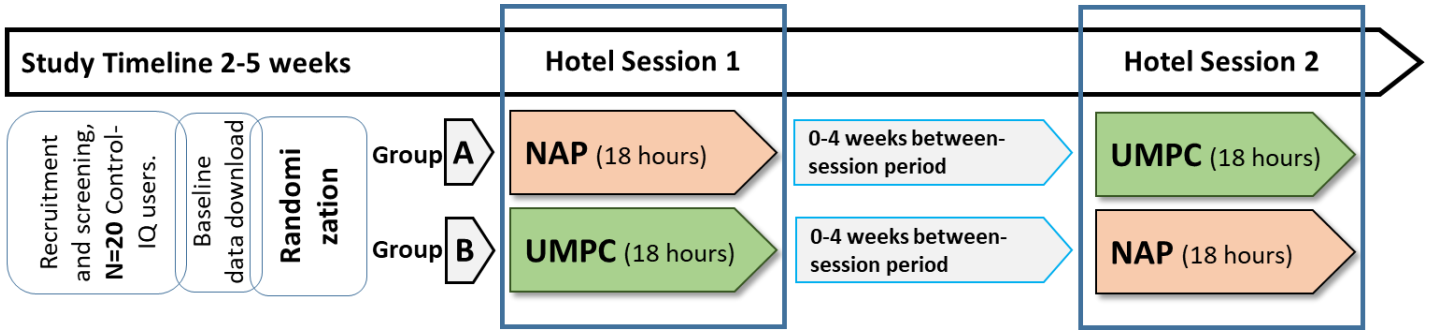

Figure 1: Timeline and randomized order of the hotel sessions. Group A will proceed with NAP first; Group B will use UMPC first; then the two groups will cross over after 0-4 week time period. In particular, the two hotel sessions can be combined into one, with two 18-hour periods alternating NAP vs UMPC.

1.4 Study Hardware/Software

The study will involve CIQ users who will continue to use their CIQ systems, except during the hotel sessions, which will use the DiAs prototyping platform (described in device master file MAF 2109), connected to a Tandem t:AP research pump and a Dexcom G6 sensor, and implementing NAP or UMPC. The study sensor will be the same sensor used by CIQ – it will be disconnected from CIQ and connected to DiAs.

1.5 Hotel Sessions

The participants will arrive to hotel and the experimental system will be set up and started within approximately two hours before dinner: participant's CIQ will be replaced by a Tandem research pump connected to the DiAs platform and their Dexcom G6 Transmitter will be linked with DiAs. The research pump will be programmed based on the individual's usual insulin parameters. Once started, the participants will have their blood sugar managed through this system during 18 hours of the time at hotel. A pre-meal bolus using the participant's normal insulin-to-carbohydrate ratio (ICR) will occur for dinner and breakfast after initiating the experimental system. Each participant will have two of these sessions: one on NAP and one on UMPC, in random order, separated by 0-28 days. In particular, the two hotel sessions can be combined into one, with two 18-hour periods alternating NAP vs UMPC. (see Figure 1).

During these 18-hour hotel sessions participants will be followed to compare blood glucose control on NAP vs. UMPC. The study meals and activities will be kept the same between study sessions. Study staff who will be present will include nursing and technical staff; a study physician/nurse practitioner/physician's assistant will be available either on-site or nearby off-site. Hyperglycemia and hypoglycemia treatment protocols will be followed per guidelines. UVa CDT study staff will monitor CGM output continuously and manage glucose control issues. At the end of the hotel stay, the participant will return to their home insulin management.

1.6 Device Download

Baseline data will be downloaded from the participants' CIQ pump or t:connect account. Before discharge from the hotel, DiAs will be turned in to study staff for device download, and the participants will return to their usual CIQ diabetes management. If the two hotel sessions are separated, a second CIQ pump or t:connect download will occur during Hotel Session 2.

1.7 Potential Study System Issues

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

pump will automatically revert to pre-programmed basal insulin delivery after 30 minutes without any need for instruction from the user.

Chapter 2 Study Devices

2.1 Insulin Pump

The study systems will utilize the Tandem t:AP research pump connected to the UVa DiAs system run on a dedicated external smart phone, running NAP or UMPC.

2.2 Continuous Glucose Monitor

A study Dexcom G6 CGM may be provided to study participants. . The study staff will remind the participant approximately 2-3 days before the hotel session to replace the sensor with a new one, so appropriate sensor warmup can occur prior to hotel session. If required, participants may use their personal CGM during the study session. The Dexcom G6 sensor is viable for up to 10 days.

2.3 Blood Glucose Meter and Strips

Blood glucose levels will be measured during the hotel sessions with the use of a Bayer Contour Next meter. The CGM device will be calibrated, if needed, using the study glucometer and strips in accordance with the manufacturer's labelling.

2.4 Ketone Meter and Strips

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

2.5 Study Devices Accountability Procedures

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

Chapter 3 Screening

3.1 Clinical Sites

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

3.2 Participant Recruitment and Enrollment

Enrollment in the study will proceed with the goal of completing up to 15 participants. Up to 20 participants may sign the consent form.

Recruitment, screening, and enrollment may be performed as an office visit, or via telecommunication.

3.3 Prescreening Procedures

Before informed consent, potential participants may be pre-screened by phone for eligibility. During pre-screening, potential subjects will be asked the Inclusion/Exclusion Questionnaire by study staff.

3.4 Informed Consent and Authorization Procedures

Before completing any procedures or collecting any data that are not part of usual care, written informed consent as described in section 14.3.1 will be obtained. Potential eligibility may be assessed as part of a routine-care examination.

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

Consenting procedures and documentation are defined in section 14.3.

3.5 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 at time of consent
2. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year
3. Currently using insulin for at least six months
4. Currently using the CIQ automated insulin delivery system for at least one month
5. Hemoglobin A1c ≤9%
6. Using insulin parameters such as ICR and CF consistently in order to dose insulin for meals or corrections
7. Access to internet and willingness to upload data during the study as needed

8. If female of childbearing potential and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of childbearing potential within 24 hours prior to initiating the experimental algorithms. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
9. Willingness to use the UVa DiAs system throughout study session
10. Willingness to use personal lispro (Humalog) or aspart (Novolog) during the study session.
11. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (including SGLT2 inhibitors, metformin/biguanides, GLP-1 receptor agonists, pramlintide, DPP-4 inhibitors, sulfonylureas and naturaceuticals)
12. Willingness to reschedule the hotel portion of the study if placed on systemic steroids (e.g. IV, IM, intra-articular or oral routes)
13. An understanding and willingness to follow the protocol and signed informed consent

3.6 Exclusion Criteria

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

1. History of diabetic ketoacidosis (DKA) in the 12 months prior to enrollment
2. Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment
3. Currently pregnant or intent to become pregnant during the trial
4. Currently breastfeeding
5. Currently being treated for a seizure disorder
6. Treatment with meglitinides/sulfonylureas at the time of hotel study.
7. Use of metformin/biguanides, GLP-1 agonists, pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, or naturaceuticals intended for glycemic control with a change in dose in the past month.
8. History of significant cardiac arrhythmia (except for benign premature atrial contractions and benign premature ventricular contractions which are permitted or previous ablation of arrhythmia without recurrence which may be permitted) or active cardiovascular disease
9. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
    a. Inpatient psychiatric treatment in the past 6 months
    b. Presence of a known adrenal disorder
    c. Uncontrolled thyroid disease (e.g. persistently abnormal TSH with hyperthyroid or hypothyroid symptoms in participants with known thyroid disease). Stable TSH suppression for prior thyroid cancer history for example could be enrolled.
    d. End-Stage Renal Disease (e.g. CKD Stage 4 or 5)

10. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol.

3.7 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by licensed personnel to screen for exclusionary medical conditions. A physical exam documented in the prior 9 months can suffice for the physical exam but will not serve as an exclusionary criterion if not available.

Up to 3 months of historical data from the participant's CIQ system may be downloaded or recorded. This data may be obtained through the commercial applications (e.g. t:connect).

Screening procedures will last approximately 1-2 hours. The visit may occur in-person or by telecommunication. 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. Current insulin pump model
    c. History of CGM use
    d. Current treatment
    e. Severe hypoglycemia history
    f. Severe hyperglycemia history
    g. History of seizures
    h. Loss of consciousness
    i. Pregnancy query
4. Basal rates
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 9 months of screening appointments may be used but is not required for eligibility. If vitals are not available, may include self-reported values.
    a. Weight (may be self-reported)
    b. Height (may be self-reported)
    c. Blood pressure
    d. Temperature (if available)
    e. Heart Rate
13. Labs
    a. Hemoglobin A1c, (not an eligibility criteria) and can be obtained within two weeks prior to screening and up until the start of the hotel sessions.

If needed based on medical history, investigators may include baseline chemistry panel to obtain creatinine/eGFR to determine stage of kidney disease 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) convenient to the participant.

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 his/her health during the study. The participant may have a copy of the screening tests to discuss with the personal physician. When the blood tests are completed, any blood left over will be thrown away. It will not be stored for any future testing.

The study physician or physician designee will have the discretion to repeat screening tests. The participant may request a copy of any of the results from the screening evaluation to review with their primary care provider.

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.

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

3.8 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.

a. Gender

b. Race
c. Ethnicity
d. Marital status
e. Level of education
f. Employment status
g. Household income
h. Health insurance status
i. Monthly insulin costs

Chapter 4 Randomization

Participants will receive the two different experimental conditions (NAP and UMPC) in random order. Once eligibility is met and screening procedures are completed, the participant may continue to randomization. Screening failures and dropout participants may be replaced.

Chapter 5 Pre-Hotel Schedule

Visit 2 and 4

5.1 Pre-Hotel Check-In

Participants will be contacted by the study team approximately 1-3 days prior to each hotel session if most recent contact with the study participant exceeds 10 days. The study team will verify the following information:

- Inquire about any changes to the participant's medical history
- Remind the participants to place a new sensor for proper warm-up prior to session
- Verify with the subject that the goal CGM reading at time of arrival is between 80-250 mg/dL; this may require contact with the study physician prior to arrival on the day of the study visit
- Should any concerns regarding medical history, pump information, or unforeseen issues arise, the session will be cancelled for that participant at the discretion of the investigator.

5.2 Other Issues

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

Chapter 6 Hotel Session

Visit 3 and 5

Each participant will have two hotel sessions. Each session will be of approximately 20 hours duration (see Figure 1). The sessions may occur sequentially within the same hotel stay or within 28 days of each other. If the hotel sessions are sequential, it is not required that the initial hotel check-procedures procedures be repeated.

6.1 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 (e.g. nurse, physician, nurse practitioner, physician assistant). There will be a physician at the hotel or nearby on call during the study. In addition, at least one engineer will be on call during the entire session. Participants will be remotely monitored by at least one study team member using a web-based remote monitoring system that has been previously established for DiAs. The web-based remote monitoring system will display real-time insulin delivery, CGM and other system information to allow for patient safety monitoring. Study team members will be trained in all protocol and glycemic treatment guideline procedures.

The study team will be responsible for monitoring and managing the study insulin pump during the hotel sessions. The participants may be provided a quick overview on its functionality to understand the equipment. The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters.

The participant will be instructed on charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc. The participant will be instructed to notify study staff if they experience any issues with the study devices during the hotel session. If insulin is delivered by any means other than the study pump (e.g. injection of subcutaneous insulin via syringe in the event of infusion site failure), the study team will be instructed to turn off closed-loop mode for approximately four hours.

The participant will also be asked to alert the study staff for technical issues with the Tandem research pump and/or the DiAs system, including component disconnections.

A glucagon emergency kit will be available at the hotel once the investigational system is in place.

Glycemic Treatment Guidelines will be available for staff use during the study sessions.

6.2 Session Check-In

Participants will arrive at the hotel around 4PM, approximately 2 hours before dinner. The study team will perform vital signs and inquire about any changes to the participant's medical history. Any changes to medical history will be communicated to the medical physician to ensure continued eligibility and participation.

A urine pregnancy test will be collected for female participants of childbearing age. The test must be negative for the participant to continue with the study.

The subject's CGM reading, and ketone concentration will be recorded. In the event that the participant's CGM reading is not between 80-250 mg/dL or ketone concentration is >0.6 mmol/L prior to initiation of DiAs, the study physician may recommend additional insulin dosing according to the participants' usual doses or glycemic treatments prior to initiating DiAs. Study physician may elect to cancel participant's participation in the hotel session if concerned about their medical safety. This participant will not be replaced but could be rescheduled for a later hotel session per investigator determination in the event of a modifiable factor that occurs early in the hotel session (e.g. severe migraine at the start of the hotel session).

The participant's CIQ will be discontinued, and the DiAs 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 are no protocol fingerstick blood glucose measurements other than at times of CGM calibration (if necessary) and if directed by the study team. Fingerstick blood glucose measurements may be taken whenever participants experience symptoms, if the CGM glucose is suspected to be erroneous, or any time the participant would like to be reassured.

6.3 Glycemic Treatment Guidelines during the Hotel Portion of the Study

The study physician will suggest appropriate treatment if the participant's CGM is <80 mg/dL or >250 mg/dL, or ketone test is >0.6 mmol/L at the start of the hotel session prior to the initiation of DiAs. The study subject may be initiated on DiAs at the start of the hotel study once CGM is between 80-250 mg /dL and ketone concentration is ≤0.6 mmol/L. Once DiAs is initiated, if CGM <60 mg/dL at any time, subjects will be given approximately 8-16 grams of fast-acting rescue carbohydrates. Study team will monitor CGM rise and will consider treating again if CGM <80 mg/dL after approximately 15-20 minutes. Hypoglycemic treatments can occur at any time per study physician request. Glucagon will be available at the study site and will be administered in the event of loss of consciousness or seizure related to hypoglycemia.

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

Once DiAs is initiated, if CGM is >250 mg/dL for more than 3 hours or >400 mg/dL at any time, study physician will be notified, and ketones will be checked. If ketone concentration is >0.6 mmol/L, the study team will notify the study physician and check the insulin pump infusion site and correction insulin will be administered via the subject's insulin pump or subcutaneous as needed. If subcutaneous injection is administered, closed-loop control will be stopped for up to 4 hours. The study team will monitor CGM changes and ketones will be checked every 60 minutes

until ketone concentration is ≤0.6 mmol/L. Closed-loop control using DiAs will be re-initiated once the participant's CGM reading is <250 mg/dL and ketones are <0.6 mmol/L. If ketone concentration is >1.0 mmol/L with significant symptoms, the study physician will recommend the appropriate medical treatment and the participant will be withdrawn from that portion of the study (the participant may possibly reinitiate the hotel portion of the study at a later date if a reversible cause)

6.4 Study Meals

Participants will eat dinner and breakfast during the session, with approximately the same amount of carbohydrate, protein, and fat for Sessions 1 and 2. Snacks with carbohydrates will not be allowed unless for the treatment of low blood sugars. Non-carbohydrates snacks may be allowed throughout the protocol per investigator discretion. Study staff will assist with bolusing decisions prior to all meals.

6.5 Hotel Activities

Generally, the daily routine of the participant will follow their usual daily routine as close as possible. Exercise will be permitted, to the extent it is typical for the participant and feasible for study staff to remotely monitor (e.g. would not allow a run outside).

If the hotel sessions are sequential within the same hotel stay, then the system algorithm will be changed by study staff to the second randomized condition at approximately 1 pm on the second day and the check-in procedures in section 6.2 do not need to be repeated. The hotel activities during the second session will be the same as the first (i.e. identical timing and content of meals, identical timing of activities).

6.6 Hotel Discharge

Discharge will be at approximately 1 pm. Discharge criteria is CGM value between 80-250 mg/dL with stable trend and ketones ≤0.6 mmol/L. If the CGM values are above 250 mg/dL and ketone values are >0.6 mmol/L, the study team will check the insulin pump infusion site and correction insulin will be administered per study physician judgement via the subject's insulin pump. The participant will not be able to be discharged from the study until the discharge criteria are met. The participant's CIQ will be reactivated and a qualified clinical study team member (e.g. MD, NP, PA, CDCES/RN) will assess and discuss the transition back to usual care.

Participants will be asked to continue monitoring ketone levels for 24-48 hours after the hotel session if ketones were >0.6 mmol/L within 12 hours prior to discharge. Urine ketone supplies may be provided for this testing. All study equipment will be returned at the time of study end.

6.7 Post Hotel Check-In Visit

Visit 5

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

Chapter 7 Medical Monitor 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 as soon as possible to the time of occurrence. The Medical Monitor also will be informed of any ADEs not meeting criteria for a UADE if the Study PI requests the Medical Monitor review. The Medical Monitor can request modifications to the study protocol or suspension or 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 document.

Chapter 8 Testing Procedures

8.1 HbA1c

A blood sample will be obtained to obtain a baseline hemoglobin A1c level by the start of the hotel visit. A blood test obtained within 2 weeks prior to enrollment may be used.

HbA1c level may be measured by study team using the DCA2000, or another comparable point of care device, at time of screening or by the start of the hotel visit.

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

8.2 Pregnancy Test

A urine pregnancy test will be required for women of childbearing potential within 24 hours prior to initiating the experimental algorithms during the hotel stay. Test must be negative to continue participation in the study.

Chapter 9 Risks Associated with Clinical Trial

9.1 Potential Risks and Benefits

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.

9.1.1 Venipuncture Risks

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

9.1.2 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.

9.1.3 Subcutaneous Needle Risks (CGM)

Participants using the CGM will be at low risk for developing a local skin infection at the site of the sensor needle placement. If a 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 needle is inserted 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 needle under the skin that may cause redness, swelling, or pain. The participants will be instructed to notify the study coordinator immediately if this occurs.

9.1.4 Risks of Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and that for a few days the participant may not be as aware of symptoms of hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery.

9.1.5 Risks of Hyperglycemia

Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period, e.g. if the pump or infusion set is not working properly, or a CGM functioning poorly significantly under-estimates glucose values.

9.1.6 Risks of Device Reuse

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

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

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

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

9.1.7 Device Cleaning Instructions

CGM cleaning instructions are provided in the Dexcom G4 Platinum (Professional) Cleaning and Disinfection manual (current edition) and a similar approach will be applied for the G6 version used in this study. The transmitter should be cleaned with Clorox Healthcare® Bleach Germicidal Cleaner or any disinfectant product in a spray bottle containing a bleach solution of 6500 parts per million with the EPA registration number 56392-7. The transmitter will be submerged in this solution and then placed on an absorbent wipe or clean surface. Two sprays will be dispensed from the Clorox cleaner onto each side of the transmitter. A nylon brush will be used to scrub the transmitter on all sides for 30 seconds. The transmitter will be placed in the Clorox Cleaner solution for one minute. Transmitter is then rinsed under flowing tap water for ten seconds. The transmitter will then be disinfected using a disinfectant product with EPA registration number 56392-7 using similar procedures as the cleaning process.

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

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

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

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

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

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

9.1.8 Risk of Exercise

While there are risks associated with physical activity, during the trial the participants will engage only in activities that are typical for them. No extra risks are added by the study protocol.

9.1.9 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 a sensor is used for longer than it is supposed to be used. Therefore, participants will be carefully instructed about proper use of the sensor.

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

9.1.10 Known Potential Benefits

It is expected that this protocol will yield increased knowledge about using a new neural-net based automated closed-loop system to control glucose levels. The individual participant may not benefit from study participation.

9.1.11 Risk Assessment

The risk to participants in this study are no higher than the risks associated with type 1 diabetes and the use of CIQ under normal outpatient conditions. This assessment is based on the following facts: (1) adults with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves automated insulin dosing that may increase the likelihood of hypoglycemia, and automated attenuation of insulin delivery that may increase the likelihood of hyperglycemia, (3) however, mitigations are in place that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4) rapid reversal of hypoglycemia and hyperglycemia can be achieved.

9.2 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 NAP and UMPC systems are experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

The study team will adhere to any CDC and local guidelines in effect at the time of the study.

Chapter 10 Adverse Events, Device Issues, and Stopping Rules

10.1 Definitions

10.1.1 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 10.2) for reportable adverse events for this protocol).

Positive pregnancy test will not be considered an adverse event.

10.1.2 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).

10.1.3 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)).

10.1.4 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.

10.1.5 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 work as intended. Performance specifications include all claims made in the labelling for the device. The intended performance of a device refers to the intended use for which the device is labelled or marketed. (21 CFR 803.3).

10.2 Reportable Events

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

- A SAE, as defined in section 10.1.2
- An ADE, as defined in section 10.1.4, unless excluded from reporting in section 10.7
- An AE, as defined in section 10.1.1 occurring in association with a study procedure
- An AE, as defined in section 10.1.1 which leads to discontinuation of a study device for 2 or more hours
- Hypoglycemia meeting the definition of severe hypoglycemia as defined in section 10.2.1
- DKA, as defined in section 10.2.2 or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria below

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

10.2.1 Hypoglycemia Event

Hypoglycemia not associated with an ADE is only reportable as an AE 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

10.2.2 Hyperglycemia Events/Diabetes Ketoacidosis

Hyperglycemia not associated with an ADE is only reportable as an AE when one of the following criteria is met:

- The event involved DKA, as defined by the DCCT and described below

- Treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis

Blood ketone level ≥1.0 mmol/L at any time during the study 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 AEs—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 AE form online. Each AE form is reviewed by the study investigator to verify the coding and the reporting that is required.

10.3 Relationship of AE to Study Device

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

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

- Related: There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon rechallenge.
- Unrelated: Evidence exists that the adverse event has an etiology other than the study intervention (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

10.4 Intensity of AE

The intensity of an AE 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 AE is not necessarily serious. For example, itching for several days may be 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 ameliorated by simple therapeutic measures.
- SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

10.5 Coding of AEs

AEs will be coded per the UVA IRB website instructions (i.e. mild, moderate, severe). AEs 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.

10.6 Outcome of AEs

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

- RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as SAE resulting in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing prior to 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 outcome (e.g., a participant lost to follow-up).

All clinically significant abnormalities of clinical laboratory measurements or AEs 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 AEs are present when a participant completes the study, or if a participant is withdrawn from the study due to an AE, the participant will be contacted for re-evaluation within 2 weeks. If the AE has not resolved, additional follow-up will be performed as appropriate. Every effort should be made to contact the participant until the AE has resolved or stabilized.

10.7 Reportable Device Issues

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

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

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

10.8 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 AEs, device malfunctions (with or without an AE) 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 Medical Monitor, IRBs, and FDA 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 Sponsor 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.

10.9 Stopping Criteria

10.9.1 Participant Discontinuation

Rules for discontinuing investigational device use are described below.

- 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.
- The participant tests positive for COVID-19 within 14 days of a hotel session.
- Any diagnosis of DKA meeting the definition in section 10.2.2 of the protocol.
- Any severe hypoglycemia event meeting the definition in section 10.2.1 of the protocol.
- Any ketone level >1.0 mmol/L with significant symptoms (e.g. nausea, vomiting, abdominal pain). The participant may be studied at a later date if due to a reversible cause (e.g. infusion site failure)

10.9.2 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 10.2.2), use of the study device system will be suspended while the problem is diagnosed.

In the event that two distinct episodes of DKA, two distinct severe hypoglycemia events, or one distinct DKA episode and one distinct severe hypoglycemia episode, as defined in section 10.2 occur, the overall study would be suspended while the underlying conditions are determined.

In addition, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension. The Medical Monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the safety data available.

10.10 Independent Safety Oversight

Detailed in Chapter 7.

10.11 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 11 Miscellaneous Considerations

11.1 Prohibited Medications, Treatments, and Procedures

Participants using insulins other than lispro and aspart 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 hotel sessions 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.

11.2 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.

11.3 Confidentiality

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

Chapter 12 Statistical Consideration

12.1 Design and Randomization

This is an early study intending to pilot test the safety and feasibility of a NAP implementation of an established AP controller – UMPC – in a crossover design (Figure 1).

The randomization list will use a sequence of computer-generated pseudorandom Bernoulli trials and will aim to balance age/gender and match groups by baseline HbA1c. The two groups will follow two different sequences of AID approaches: NAP followed by UMPC or UMPC followed by NAP.

12.2 Sample Size

We use pilot trials to introduce new technologies, test system component interoperability, and support regulatory approval of larger subsequent studies. Depending on the traceability of the system to previous established technology or components, the pilots can range from a small 5-person 3-day trial, such as the one we used to enable the pivotal trial of Control-IQ,[11] to a multi-center test of pump configurations.[12] In this study, NAP is directly traceable to UMPC in terms of its functionality; however, its implementation is qualitatively new. Thus, based on our experience, we estimate that the completion of N=15 (and recruitment of up to 20) CIQ users who will test NAP vs UMPC during two 18-hour hotel sessions, will be feasible, in terms of first regulatory approval, and sufficient to test the translation of the existing UMPC into neural-net framework.

12.3 Outcome Measures

The main purpose of this trial is initial system testing and receiving feedback form the participants regarding system functionality. Thus, we will observe, record, and tabulate any NAP errors that would inform us whether system fixes would be needed prior to deployment in a subsequent larger study. We will tabulate technical performance metrics including:

- Malfunctions requiring study team contact and other reported device issues;
- Percent time in closed-loop and any other relevant operational modes;
- Rate of relevant NAP and UMPC failure events and alarms per 24 hours;

In addition, descriptive glycemic analyses for certain efficacy measures recommended by a review written by the sponsor of this study[13] and by the International Consensus on Time-in-Range (TIR), to which we contributed,[14] will be tabulated for each subject based on CGM data, including:

- TIR, 70-180 mg/dL (primary outcome)
- percentage of readings in other ranges, including TBR, TAR, and 70-140 mg/dl;
- mean glucose; glucose variability measured by coefficient of variation;
- percentage of readings <54 mg/dl (i.e., level 2 hypoglycemia[14])
- percentage of readings >250 and >300 mg/dl (i.e., level 2 hyperglycemia[14])

The technical performance, errors, and glycemic analyses will be also split by time of the day: daytime vs. night-time.

12.4 Criteria for Success

The success criteria will include no critical system errors and the following performance criteria, which factor in likely inter-day variability for each participant and are consistent with the recommendations of the International Consensus on TIR:

- Difference in TIR between NAP and UMPC < 8 percentage points;
- Difference in TBR between NAP and UMPC < 3 percentage points;
- Difference in TAR between NAP and UMPC < 8 percentage points;

Formal power analysis is not applicable to this pilot study – 5-percent noninferiority hypothesis of NAP vs UMPC will be tested, but with this sample size a statistically significant result is not expected. The point of the study is to show feasibility of a neural-net implementation of an automated insulin delivery algorithm which, if shown, will open possibilities for control strategies based on machine-learning and artificial intelligence methods.

12.5 CGM data treatment

- Saturated CGM values “High” and “Low” will be replaced by 401mg/dL and 39mg/dL respectively.
- 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.
- CGM data following a pump/DiAs communication interruption >1h but less than 2h will be removed.

12.6 Safety Analyses and Participant Feedback

We will assess NAP functionality, including the ability of the system to run its code without error (deliver insulin safely, as planned), as well as its ability to avoid hypo- and hyperglycemia. Participants feedback will be informal, in the format of contrasting their experience with the commercial CIQ vs. the experimental NAP and UMPC.

12.7 Baseline Descriptive Statistics

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

- Age
- HbA1c
- Gender
- Race/ethnicity
- Diabetes duration

- BMI
- Total Daily Insulin

Chapter 13 Data Collection and Monitoring

13.1 Case Report Forms and Device Data

Data is 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. Records will be maintained in accordance with ICH E6 and institutional regulatory requirements for the protection of confidentiality of participants.

13.2 Study Records Retention

Study documents should be retained for a minimum of 6 years after the study completion, or until at least 2 years have elapsed since the formal discontinuation of development of the investigational product. Documents should be retained for a longer period, if required by local regulations. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study staff. In response to protocol deviations, corrective actions may be required and implemented as appropriate. Major deviations will be reported to the IRB within 7 calendar days of when the study team becomes aware of the event.

Chapter 14 Ethics/Protection of Human Participants

14.1 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.

14.2 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.

14.3 Informed Consent Process

14.3.1 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. Consent forms will be IRB approved, and the participant will be asked to read and review the document. The investigator or delegate will explain the study to the participant and answer any questions that may arise. 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 participant will sign the informed consent document prior to any procedures being done specifically for the study.

The potential participant will be provided 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 Questionnaire. 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 consenting process will involve discussing the study at length in a phone call/HIPAA compliant telecommunication method for consenting that is not face to face. 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 with the use of the Part 11 compliant version of DocuSign for both in-person and telecommunication screening visits. Note: For potential participants who are not able to use DocuSign, email, fax, or mail will be an option for receipt of the signed consent. A HIPAA compliant video conferencing tool 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. A copy of the informed consent document will be given to the participant for their records. 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.

14.3.2 Participant and Data Confidentiality

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

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

Participants' research data, which is for the purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the UVA CDT. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases may be de-identified and archived at the UVA CDT.

Chapter 15 References

1. https://www.nih.gov/about-nih/nih-wide-strategic-plan
2. Kovatchev BP, Patek SD, Dassau E, Doyle FJ III, Magni L, De Nicolao G, Cobelli C. Control-to-range for diabetes: functionality and modular architecture. J Diabetes Sci Technol. 2009; 3: 1058-1065. PMCID: PMC2769910
3. Hughes CS, Patek SD, Breton MD, Kovatchev BP. Hypoglycemia prevention via pump attenuation and red-yellow-green "traffic" lights using continuous glucose monitoring and insulin pump data. J Diabetes Sci Technol. 2010; 4: 1146-1155. PMCID: PMC2956822
4. Patek SD, Magni L, Dassau E, Karvetski CH, Toffanin C, DeNicolao G, Del Favero S, Breton M, Dalla Man C, Renard E, Zisser H, Doyle FJ III, Cobelli C, Kovatchev BP. Modular closed-loop control of diabetes. Transactions on Biomedical Engineering. 2012; 29: 2986-99. PMCID: PMC4607512
5. Keith Hynes P, Guerlain S, Mize LB, Hughes Karvetski C, Khan M, McElwee Malloy M, Kovatchev BP. DiAs user interface: a patient-centric interface for mobile artificial pancreas systems. J Diabetes Sci Technol. 2013; 7: 1416–1426. PMCID: PMC3876320
6. Brown SA, Kovatchev BP, Raghinaru D, et al, for the iDCL Trial Research Group. 6-month randomized multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med. 2019; 381: 1707-17. PMID: 31618560 PMCID: PMC7076915
7. Breton MD, Kanapka LG, Beck RW, et al, for the iDCL Trial Research Group. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. N Engl J Med. 2020; 383:836-845. PMID: 32846062; PMCID: PMC7920146.
8. U.S. Food & Drug Administration: FDA authorizes first interoperable, automated insulin dosing controller designed to allow more choices for patients looking to customize their individual diabetes management device system. https://www.fda.gov/news-events/press-announcements/fda-authorizes-first-interoperable-automated-insulin-dosing-controller-designed-allow-more-choices.
9. Garcia-Tirado J, Diaz JL, Esquivel-Zuniga R, Koravi CLK, Corbett JP, Dawson M, Wakeman C, Barnett CL, Oliveri MC, Myers H, Krauthause K, Breton MD, DeBoer MD. Advanced Closed-Loop Control System Improves Postprandial Glycemic Control Compared With a Hybrid Closed-Loop System Following Unannounced Meal. Diabetes Care. 2021 Aug 15:dc210932. doi: 10.2337/dc21-0932. Epub ahead of print. PMID: 34400480.
10. Lobo B, Farhy L, Shafiei M, Kovatchev B. A data-driven approach to classifying daily continuous glucose monitoring (CGM) time series. IEEE Trans Biomed Eng. 2021 Aug

10;PP. doi: 10.1109/TBME.2021.3103127. Epub ahead of print. PMID: 34375274.

11. Brown S, Raghinaru D, Emory E, Kovatchev BP. First look at control-IQ: a new-generation automated insulin delivery system. Diabetes Care. 2018 Oct 10. pii: dc181249, PMID: 30305346; PMCID: PMC6245207

12. Anderson SM, Dassau E, Raghinaru D, Lum J, Brown SA, Pinsker JE, Church MM, Levy C, Lam D, Kudva YC, Buckingham B, Forlenza GP, Wadwa RP, Laffel L, Doyle FJ 3rd, DeVries JH, Renard E, Cobelli C, Boscari F, Del Favero S, Kovatchev BP. The international diabetes closed-loop study: testing artificial pancreas component interoperability. Diabetes Technol Ther. 2019; 21: 73-80. PMCID: PMC6354594

13. Kovatchev BP. Metrics for glycaemic control: from HbA1c to continuous glucose monitoring. Nature Reviews Endocrinology. 2017; 13: 425-436. PMID: 28304392

14. Battelino T, Danne T, Bergenstal RM, Amiel SA, et al. for the International Time-in-Range Consensus. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019; 42: 1593-1603. PMID: 31177185.

15. IDE #G110095: Feasibility study of closed loop control in type 1 diabetes using heart rate monitoring as an exercise marker, approved 10/08/2011.

16. IDE #G120032: Early feasibility (pilot) study of outpatient control-to-range; 3/2/2012.

17. IDE #G120210: Early feasibility study 2 of outpatient control-to-range; 10/12/2012.

18. IDE #G130118: DiAs control-to-range nocturnal closed-loop camp study; 6/19/2013.

19. IDE #G130121: Optimizing closed-loop control of type 1 diabetes mellitus in adolescents; 6/19/2013; 05/01/13.

20. IDE# G130142: Closed loop control in adolescents using heart rate as exercise indicator; 7/16/2013.

21. IDE #G130143: Early feasibility study of adaptive advisory/automated (AAA) control of type 1 diabetes; 7/19/2013.

22. IDE #G140066: Full day and night closed-loop with DiAs platform; 5/9/2014.

23. IDE #G140068: Unified Safety System (USS) Virginia Closed Loop versus sensor augmented pump therapy overnight in type 1 diabetes; 5/14/2014.

24. IDE #G140119: Outpatient control-to-range: Safety and efficacy with day-and-night in-home use; 6/6/2014.

25. IDE #G140169: Unified Safety System (USS) Virginia Closed-Loop versus Sensor Augmented Pump (SAP) therapy for hypoglycemia reduction in type 1 diabetes; 10/3/2014.

26. IDE #G150221: Reducing risks and improving glucose control during extended exercise in youth with T1DM: The AP Ski Camp; 11/09/2015.

27. IDE #G150240: Project Nightlight: Efficacy and system acceptance of dinner/night vs. 24 hr closed loop control; 11/12/2015.

28. IDE #G160047: Closed-loop in young children 5-8 years old using DiAs platform; 03/29/2016.

29. IDE #G160097: Clinical Acceptance of the Artificial Pancreas: the International Diabetes Closed-Loop (iDCL) Trial/Research Site Training Protocol; 06/03/2016.

30. IDE#G160181: PROTOCOL 1 for "Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed Loop (iDCL) Trial; 09/21/2017.

31. IDE#G170255: Protocol 3 for "Pilot Trial of t:slim X2 with Control-IQ Technology";11/16/17 and IDE#G170255/S001 Protocol 3 for "Training Study of t:slim X2 with Control-IQ Technology"; 11/16/2017.

32. IDE#G170267 : "Real-Time Monitoring and Glucose Control During Winter-Sport Exercise in Youth with Type 1 Diabetes: The AP Ski Camp Continued"; Three 48-hour winter ski camps trial T1D participants; one site enrolled 13-18 years old participants in January 2018. The other two sites enrolled participants aged 6-12 years old. At the conclusion of these ski camps, subjects continued with the study device for 72 hours use at home; 11/21/17 & 01/10/18.

33. IDE#150240/S008: Project Nightlight: Efficacy and system acceptance of dinner/night vs. 24 hr closed loop control (Tandem t:slim insulin pump with Control-IQ Technology); 02/02/2018.

34. IDE#G180279: "Safety and Efficacy of Initializing the Control-IQ Artificial Pancreas System Using Total Daily Insulin." A safety and efficacy of using the Control-IQ artificial pancreas system using MyTDI in a randomized controlled trial; 12/19/2018.

35. IDE#G190205: "Safety of the Tandem t:slim X2 with Control-IQ Automated Insulin Delivery System in Preschoolers, age 2-6 Years Old"; 09/06/2019.

36. IDE#G190250: "SGLT2 Inhibitor Adjunctive Therapy to Closed Loop Control in Type 1 Diabetes"; 10/02/2019.

37. Kovatchev BP, Singh H, Mueller L, Gonder-Frederick LA. Biobehavioral Changes Following Transition to Automated Insulin Delivery: A Large Real-life Database Analysis. Diabetes Care. 2022 Nov 1;45(11):2636-2643. doi: 10.2337/dc22-1217. PMID: 36126177.

38. IDE # G200206: Fully Automated Closed Loop Control in Adolescents with Type 1 Diabetes (RocketAP). 08/20/2020.

39. IDE#210051: “Diabetes Closed-Loop Project 6 (DCLP6): Fully Automated Closed-Loop Control in Type 1 Diabetes Using Meal Anticipation”, 03/18/2021.

40. IDE#220204: “Evaluation of The Postprandial Impact of Automated Priming Bolus for Full Closed Loop Insulin Delivery”, 08/29/2022.