UNIVERSITY of VIRGINIA HEALTH SYSTEM | School of Medicine

UVA CENTER FOR DIABETES TECHNOLOGY

Adaptive Biobehavioral Control (ABC) of Automated Insulin Delivery: A Randomized, Controlled Pilot Study

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30-Jun-2021

KEY ROLES

Protocol Principal Investigator	
Name, degree	Sue A. Brown, MD
Institution Name	University of Virginia Center for Diabetes Technology

PROTOCOL VERSION HISTORY

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0	Jon Olson, Mary Oliveri	Sue Brown	17-Nov-2020	Original Protocol
1.1	Jon Olson	Mary Oliveri	20-Nov-2020	FDA modifications • Added "Participants will be notified that eA1c is for informational purposes only and not to be used for short-term changes to insulin settings (section 5.3). • Modified study stopping criteria to include three severe hypoglycemia events or three DKA events (section 9.9.2)
1.2	Jon Olson	Sue Brown	11-Jan-2020	IRB Pre-Review • Corrected visit numbering (section 6.7)
1.3	Mary Oliveri	Sue Brown	30-Jun-2021	Study Team • Modified use of personal CGM equipment (Section 3.2 & 5.1) • Added Participant Compliance definitions (section 6.5)

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Adaptive Biobehavioral Control (ABC) of Automated Insulin Delivery: A Randomized, Controlled Pilot Study

Protocol Version/Date: v1.3/30-Jun-2021I 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
ABC	Adaptive Biobehavioral Control
AID	Automated Insulin Delivery Device
ATM	Auto Titration Module
ADRR	Average Daily Risk Range
AP	Artificial Pancreas
APG	Ambulatory Glucose Profile
API	Application Programming Interface
AWS	Amazon Web Services
BAM	Behavioral Anticipation Module
BG	Blood Glucose
BT/BTLE	Bluetooth, Bluetooth low energy
CF	Insulin sensitivity factor
CGM	Continuous Glucose Monitoring
CLC	Closed-Loop Control
Control-IQ	Tandem t:slim X2 Insulin Pump with Control-IQ Technology
CR	Carbohydrates Ratios Profile
CSII	Continuous Subcutaneous Insulin Injection
DKA	Diabetic Ketoacidosis
DSMB	Data Safety Monitoring Board
eA1c	Estimated Hemoglobin A1c
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBGI	High Blood Glucose Index
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
LBGI	Low Blood Glucose Index
NIH	National Institutes of Health
O/P	Office Visit / Phone Visit
POC	Point-of-Care
SAP	Sensor-Augmented Insulin Pump
QC	Quality Control

UI	User Interface
WIT	Web Information Tool
WST	Web Simulation Tool

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Adaptive Biobehavioral Control (ABC) of Automated Insulin Delivery: A Randomized, Controlled Pilot Study
Investigational Device	Web Information Tool (WIT) - A web-based software providing additional information regarding glucose variability, estimated A1c, risks for hypo- and hyperglycemia, and potential changes of insulin pump parameters, to users of the Control-IQ system. The WIT is the clinical implementation of the ABC concept, which includes the following modules: • Behavioral Anticipation Module (BAM) - an app running on a smart phone which provides on-demand information to the participant primarily on glycemic risks. • Auto Titration Module (ATM) that provides recommendations to the participant to periodically update insulin parameters. • Web Simulation Tool (WST) - is intended to allow users of the Control-IQ system replay treatment scenarios in computer simulation, thereby allowing user training with carbohydrate and insulin action.
Investigational Medication	None
Objectives	Assess the safety and feasibility of two modules (BAM and ATM / WST) used in conjunction with an FDA approved automated insulin delivery system (t:slim X2 with Control-IQ technology)
Study Design	Randomized parallel group trial.
Number of Sites	1
Endpoint	Primary Outcome: Safety assessment of ATM / WST and BAM modules. Secondary Outcomes: • Percent of readings in the target ranges of 70-180 and 70-140 md/dL • Other CGM-based metrics; • Questionnaires addressing BAM and participant preferences for system/technology use.
Population	Key Inclusion Criteria • Age 18-70, inclusive, with Type 1 Diabetes for at least one year • Current user of t:slim X2 insulin pump with Control-IQ Technology Key Exclusion Criteria • Recent severe hypoglycemic event or DKA during the past one year
Sample Size	Recruit up to 45 participants of Control-IQ with the objective of randomizing 30 subjects
Treatment Groups	• Group 1: Control-IQ + Auto Titration Module (ATM) and Web Simulation Tool (WST) for 6 weeks • Group 2: Control-IQ + Auto Titration Module (ATM) and Web Simulation Tool (WST) +Behavioral Adaptation Module (BAM) for 6 weeks
Participant Duration	8 weeks

Protocol Overview/Synopsis	Two-week baseline use of personal Control-IQ system followed by randomization 1:1 into two groups. Group 1 will use their personal Control-IQ system and add an auto titration module ATM) and web simulation tool (WST) in which insulin parameters may be adjusted on a weekly basis. Group 2 will use their personal Control-IQ system and add the ATM / WST on a weekly basis as well as a behavioral adaptation module (BAM). The BAM will consist of information modules in which information only is given to participants (e.g. hypoglycemic risks, daily glycemic profiles, eA1c, and variability tracker).

Table 1 Schedule of Study Visits and Procedures

Visit Name	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Description	**Screening Visit**	**Device Training & Run-In**	**Randomization**	**Weekly Check-In**	**Weekly Check-In**	**Weekly Check-In**	**Weekly Check-In**	**Weekly Check-In**	**Final Visit**
Timing	-8 to -2 weeks	-28 to -14 days	Day 1	Day 7±3	Day 14±3	Day 21±3	Day 28±3	Day 35±3	Day 42±3
Location	O/P	O/P	O/P	O/P	O/P	O/P	O/P	O/P	O/P
Informed Consent	X								
Eligibility Assessment	X								
Medical History	X								
HbA1c	X								X
Screening Blood Testing: CMP, TSH if applicable	X								
Pregnancy test (if applicable)	X	X	X						X
Physical Exam	X								
Vital Signs (including height/weight)	X								
Training on Relevant Devices or Modules		X	X						
Randomization			X						
Questionnaires			X						X
Review diabetes management and AEs	X	X	X	X	X	X	X	X	X

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Chapter 1: Background

1.1 Introduction

Large-scale artificial pancreas studies, including two multi-center pivotal trials recently completed by our team, have established the current capabilities of closed-loop control (CLC) and identified its deficiencies, e.g. inferior control during the day due to slow insulin response to fast biobehavioral perturbations. We therefore propose to pilot test *elements of a next-generation CLC system – Adaptive Biobehavioral Control (ABC) based on the novel concept of human-machine co-adaptation* – which uses a stochastic-process approximation of the day-to-day variation in human physiology and behavior to individualize and optimize CLC. The ABC concept recognizes *both* the necessity for the control algorithm to adapt to changes in human physiology *and* the necessity for the person to adapt to CLC action. This pilot-feasibility study is intended to test the Web Information Tool (WIT), a web-based software that provides additional information regarding glucose variability, estimated A1c, risks for hypo- and hyperglycemia, and potential changes of insulin pump parameters, to users of the Control-IQ system (Tandem Diabetes Care, San Diego, CA).

The ABC concept was conceived during our extensive studies carried under NIH/NIDDK project UC4DK108483 "Clinical Acceptance of the Artificial Pancreas: the International Diabetes Closed Loop (iDCL) Trial." The iDCL Trial became most successful study funded by NIDDK under RFA-DK-14-024 "Advanced Clinical Trials to test Artificial Pancreas Device Systems in Type 1 Diabetes (UC4)." We completed three clinical protocols, DCLP1, DCLP3, and DCLP5, which became three of the largest closed-loop control studies attempted to date:

1) Protocol 1 (DCLP1, NCT02985866, IDE#G160181) established that a mobile Artificial Pancreas (AP) system using a smart phone as a computational hub running the control algorithm, is a viable treatment for T1D. This protocol was executed at seven U.S. sites and was coordinated by the Jaeb Center for Health Research. DCLP1 recruited N=127 subjects randomized to AP vs. sensor-augmented pump (SAP). The results were published in *Diabetes Care*, showing that the study met its predefined criteria for success.[1]
2) Protocol 3 (DCLP3, NCT03563313, IDE #G180053) was a pivotal trial which, responding to the requirements of RFA-DK-14-024, aimed at regulatory clearance of Control-IQ – a system that includes a Dexcom G6 sensor and a t:slim pump (Tandem Diabetes Care). This system is based on a control algorithm developed at the University of Virginia under the NIDDK-funded grant RO1 DK 085623. DCLP3 randomized N=168 participants to Control-IQ vs. SAP, *all* of whom completed the 6-month trial and then continued with a 12-month study extension. DCLP3 met *all* of its predefined primary and secondary outcomes. The results were published in the *New England Journal of Medicine.*[2] As a result, the Control-IQ system received FDA clearance for clinical use by children and adults ages 14 and up.

3) Protocol 5 (DCLP5, NCT03844789, IDE #G180053/S008) was also a pivotal trial, which aimed at regulatory clearance of Control-IQ in children ages 6-13 years old. DCLP5 randomized N=101 participants to Control-IQ vs. SAP, and met *all* of its predefined primary and secondary outcomes. The results were also published in the *New England Journal of Medicine.*[3] As a result, the Control-IQ system received FDA clearance for clinical use by children ages 6-13 years old as well.

Defining the ABC Process: The ABC process consists of interacting cycles developing on different time scales:[4] (1) First, it is initialized by individual characteristics, such as HbA_{1c}, history of severe hypoglycemia, or hypoglycemia unawareness that sets the stage for further control adaptation; this initialization is slow, develops over months or years, and can be favorable or unfavorable to CLC (e.g. individuals at overall good vs. poor control would fare differently using CLC;[2] (2) Natural variation in a person's metabolic parameters occurs within a day (e.g. circadian rhythms) and between days; slower changes are possible, e.g. due to illness; (3) Behavioral perturbations challenge the metabolic system with meals or physical activity, which may trigger low BG events and escalate to recurrent hypoglycemia; this cycle includes significant randomness and is therefore best described by a stochastic process (dotted lines–clockwise cycles in Figure 1). This bio-behavioral interplay amplifies or attenuates the BG fluctuations of a person and is detected as degree of GV by CGM and/or other signals. (4) In this context, the control co-regulation objective is two-fold: gradual and safe stabilization of the metabolic system by adapting control parameters to the specifics and physiological variation of the metabolic system, and fast response to biobehavioral challenges that may require behavioral adaptation by the user, e.g. around meals and exercise (solid lines–counterclockwise cycles in Figure 1).

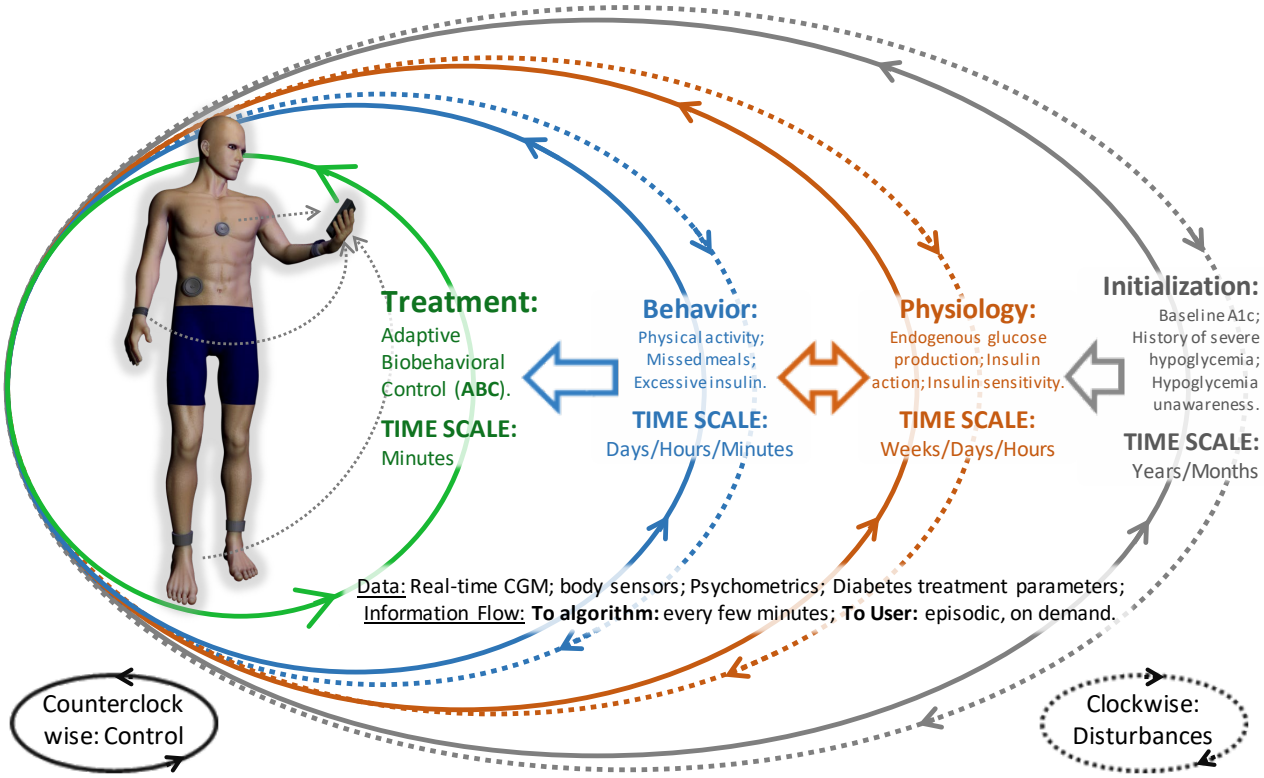


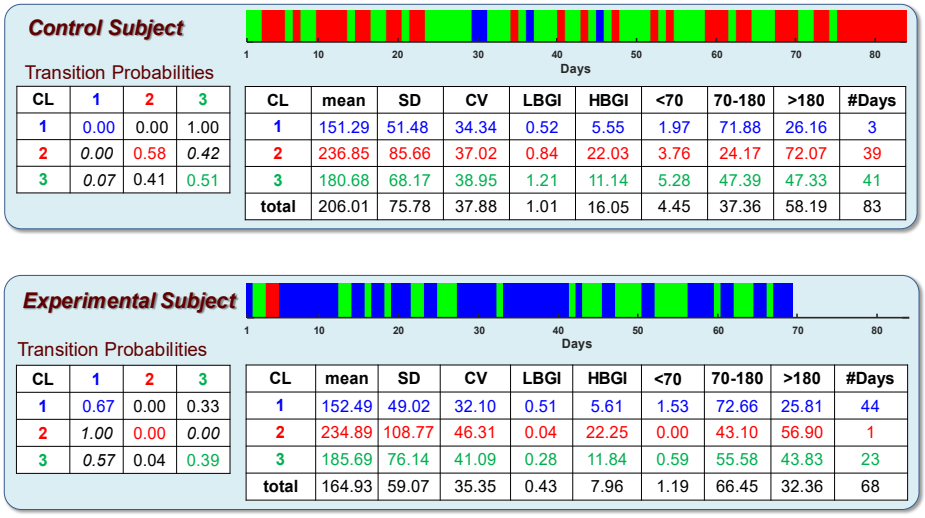
Figure 1: Main premise, signals, time scales, and control action of the recursive ABC process: initialization with routine T1D treatment parameters; behavioral and physiological perturbations monitored through CGM and other signals, and human-machine co-adaptation using pattern/risk information presented to the user and to the control algorithm. Clockwise cycles indicate system disturbances; Counterclockwise cycles indicate adaptation.

Monitoring the ABC Process: Observed in time, the compounded effect of the recurrent processes presented in Figure 1 is a stochastic process of glycemic variation[5] governed by transition probabilities from one CGM daily profile to the next. We introduced this concept in February 2019, in two consecutive presentations at the international ATTD conference, focusing on its applications to patient decision support[6] and adaptation of automated control built upon a virtual image of the patient (VIP).[7] These two applications will be used in the proposed study to enable: (i) behavioral co-adaptation through pattern/risk information provided to the user and intended to provoke thoughts and prompt, but not suggest or require, adaptive behavioral reaction, and (ii) adaptation of the insulin pump parameters used by control algorithm, which will be proposed to the user, but not implemented automatically in this pilot phase of research.

Pattern Recognition, Clustering, and Classification: *At the core of the ABC technology is an innovative method for pattern-based therapy optimization. In this approach, the collection of all possible daily patterns, i.e. the state space of the ABC process, is defined by machine-learning classification of CGM profiles into clusters derived from our library of over 50,000 CGM daily profiles accumulated in our studies.* To illustrate how this works, we use data from the International Diabetes Closed-Loop (iDCL) Trial Protocol 1, NCT02985866. This study yielded ~9,000 CGM daily profiles, which allowed performing the following steps: (1) CGM daily profiles are classified into identifiable clusters; (2) Over time, each person transitions through a sequence of clusters, which are approximated by a stochastic Markov chain identified by an individual transition probability matrix; (3) Treatment adaptation is then assisted by presenting pattern/risk predictions to the patient and to the control algorithm, aiming to maximize the probabilities of favorable daily transitions. For illustrative purposes, Figure 2 shows results for a 3-cluster solution. Clusters are color coded according to their clinical interpretation: Cluster 1: Tight Control/Intensive Treatment; Cluster 2: Hyperglycemic exposure; Cluster 3: Intermediate/ Average Control.

Each cluster is associated with a specific level of glucose control, and over time each person transitions through a sequence of clusters, each describing this person's glycemic control for one day.

The color-coded profiles in Figure 2 present the daily stochastic transitions of two participants in the iDCL Protocol 1 using sensor-augmented pump (SAP) and CLC, respectively. Underneath, we present a set of glycemic control metrics that reflect the state of each person when s/he was in each one of the three clusters. By cluster design, despite the marked differences in the overall control of these subjects, their glycemic characteristics are very similar when they are in the same cluster. For example, both had mean glucose of 151-152mg/dL when in a blue



Control Subject

Transition Probabilities

CL	1	2	3
1	0.00	0.00	1.00
2	*0.00*	0.58	*0.42*
3	*0.07*	0.41	0.51

CL	mean	SD	CV	LBGI	HBGI	<70	70-180	>180	#Days
1	151.29	51.48	34.34	0.52	5.55	1.97	71.88	26.16	3
2	236.85	85.66	37.02	0.84	22.03	3.76	24.17	72.07	39
3	180.68	68.17	38.95	1.21	11.14	5.28	47.39	47.33	41
total	206.01	75.78	37.88	1.01	16.05	4.45	37.36	58.19	83

Experimental Subject

Transition Probabilities

CL	1	2	3
1	0.67	0.00	0.33
2	*1.00*	0.00	*0.00*
3	*0.57*	0.04	0.39

CL	mean	SD	CV	LBGI	HBGI	<70	70-180	>180	#Days
1	152.49	49.02	32.10	0.51	5.61	1.53	72.66	25.81	44
2	234.89	108.77	46.31	0.04	22.25	0.00	43.10	56.90	1
3	185.69	76.14	41.09	0.28	11.84	0.59	55.58	43.83	23
total	164.93	59.07	35.35	0.43	7.96	1.19	66.45	32.36	68

Figure 2: Daily transitions, cluster assignment, and transition probability for two representative participants in iDCL Protocol 1.

cluster for the day, or 237-235mg/dL when in a red cluster. *The major difference between these two study participants is the time they spent in each cluster type, e.g., 44 days in the blue cluster for the CLC Subject and only 3 days for the SAP Subject* (Figure 2). Further, each person's stochastic transitions from one day to the next are approximated by a Markov chain[5] governed by individual transition probability matrices presented in Figure 2. For example, the probability is *zero* for the control subject to remain in tight control for two consecutive days (blue-to-blue), while this probability is *67%* for the Experimental Subject. *We therefore conclude that: (i) A library of clinically-relevant clusters describes the possible one-day glycemic profiles for each person; (ii) When in the same cluster, the glycemic metrics for different people are similar; (iii) However, each person transitions through a different sequence of daily profiles, governed by individual transition probability matrices; (iv) This allows each person's ABC process to be encoded in a Markov chain of consecutive daily profiles; (v) This encoding results in estimates of the probabilities for upcoming events, i.e. the chances from transition to a particular cluster tomorrow, which informs a person's treatment decisions and the control algorithm's adaptation.*

With this conceptual description in mind, the overall objective of the ABC strategy is to enable a new generation of artificial pancreas technologies which will: (i) Provide information to the user to inform user's adaptation to the CLC system, and (ii) Adapt automatically the action of the control algorithm to follow daily changes in physiology and behavior. To the best of our knowledge, such bi-directional *human-machine co-adaptation* has not been attempted before, partially due to underestimation of the behavioral challenges related to CLC use, and partially due to the relative immaturity of CLC systems, which until recently could not sustain long-term use without facing significant technical problems or requiring extensive user involvement.

In this IDE application, we make the case that we are now equipped with well-established CLC technology (Control-IQ, Tandem Diabetes Care), with which we have very extensive experience. We will rely on our extensive track record of behavioral interventions concerning technology,[8] and on one of the largest CLC databases collected to date. Thus, we can confidently propose to pilot test and evaluate the ability of an adaptive CLC system to optimize metabolic control in the context of behavioral management and response to such technology. *In this first pilot study, the feedback to the patient will be limited to information about relevant glycemic parameters and risks. No prescription will be given for behavioral changes or adaptation. Similarly, adjustment of the control parameters, will be proposed to the user and will be accompanied by an option to replay treatment scenarios via computer simulation, but will not be implemented automatically*.

1.2 Description of the Equipment

Closed-Loop Control System:

Trade/Device Name: Control-IQ Technology

Regulation Name: Interoperable automated glycemic controller
System components include:

- t:slim X2 insulin pump with Control-IQ technology, and
- Dexcom G6 continuous glucose monitor (CGM).

The CLC system and its components are approved by the FDA for clinical use in children and adults ages 6 years old or older.

1.3 Description of the Information Modules

The WIT is the clinical implementation of the ABC concept, which includes:

- A Behavioral Adaptation Module (BAM);
- An Auto Titration Module (ATM), and
- A Web Simulation Tool (WST).

The three information modules BAM, ATM, and WST will be provided to users of the t:slim X2 with Control-IQ closed-loop system in a Web-based interactive format via a website that allows for unique login. These modules will provide the user with potentially useful recommendations, but will not interfere automatically with the functioning of the CLC system. The primary purpose of this pilot trial is safety testing and receiving feedback from the participants regarding module functionality and user interface.

Briefly, the WIT presents daily updates by the BAM first, and allows the user to navigate to other modules. Details for all algorithm modules are provided in Appendix A-2.

BAM uses the concept described in the Introduction under “Monitoring the ABC Process” and well-established metrics of glycemic control computed daily:

Measure	Computed From
Estimated A1c	14 days of CGM data plus lab HbA_{1c} calibration[10]
Low/High BG [Risk] Indices (LBGI/HBGI) – measures of risk for hypo- or hyperglycemia	Previous day of CGM data[8]
Average Daily Risk Range (ADRR) – a measure of glucose variability	Computed as the average of the HRRs (Hourly Risk Range) for the previous day[8]
Forecast-today	8 days of CGM data, plus today's readings by 6AM

Table 2: Glycemic metrics used by the BAM

Results will be presented every morning, e.g. at 7AM. All Variability and Risk metrics are mapped to the interval [0-11] as follows: 0 is mapped to 0; 99th percentile of the metric is mapped to 11.

ATM is a set of optimization algorithms designed to use the participants' data and provide weekly updates for their default insulin pump parameters: basal rate profile, insulin to carbohydrates ratios profile (CR), and insulin sensitivity factors profile (CF). The module is derived from the optimization already used in G200122 and is largely identical but for one key element: the CR and CF profiles are not using fixed timestamps (e.g. 3am-11am and 11am-3am), but automatically determined in concert with the basal profile so as to ensure no more than 12 segments for the combinations of the daily profiles. As the timing of each CR/CF profile segments is not fixed, the algorithm has been modified to use all historical boluses for each profile segments (vs using only boluses that fell in the segment specific time interval) with appropriate weighing (a historical bolus at 1pm has a much larger influence on a noon-3pm segment than a historical 11pm bolus).

WST is a simulation infrastructure that allows individuals to interact with their data in a novel way: each user can not only see their historical CGM/insulin/meal data streams, summary indices, and summary graphical representation (in a format similar to an ambulatory glucose profile, AGP), but can also modify their insulin treatment strategies, play "what-if" scenarios, and observe the predicted glycemic impact. For example, a user could observe an early morning hypoglycemia tendency (from the summary graphical representation), reduce the underlying basal rate (say 3am-6am) by 10%, and see if such change would have limited the hypoglycemic exposure and/or increase late morning hyperglycemia. Therefore, WST can be considered an advanced education tool for people with T1D to leverage their own data and experience and gain insight in possible behavioral/therapeutic changes they may want to consider with their care team. This module is based on our replay simulation technology[11-13] and is supported by a transfer of data from the user devices (in the case of this study, an automated transmission of

the t:slim X2 data to the Tandem phone app and then to the t:connect web system, with a frequent (every 6h) pull triggered by our AWS infrastructure of the t:connect data via a Tandem API) (Application Programming Interface).

Chapter 2: Study Description

2.1 Study Objective

The purpose of this pilot study is to test the safety and feasibility of using two or three research modules in conjunction with an approved automated insulin delivery device (AID) (t:slim X2 insulin pump with Control-IQ technology, Tandem Diabetes Care).

This concept is implemented in the Adaptive Biobehavioral Control (ABC) system – ABC will use human-machine co-adaptation of CLC, recognizing both the necessity for the control algorithm to adapt to changes in human physiology, and the necessity for the person to adapt to CLC action. ABC will be implemented on the Web Information Tool (WIT) platform/system and includes the following modules to be used alongside the automated insulin delivery device:

- Behavioral Adaptation Module (BAM) – a behavioral intervention deployed in a mobile app to assist a person's adaptation to automated insulin delivery by information and risk assessment primarily regarding glycemic risks, and
- Auto Titration Module (ATM) — a web-based tool with an automated procedure to track risk status and changes in the participant's metabolic profile. This module will present updated insulin control parameters (e.g. basal rate, carb ratio, correction factor) to the user once a week using a web-based format accessible to the participant. These adjusted parameters are not able to directly update the pump automatically, so the participant will then need to manually enter the suggested changes directly onto their insulin pump.
- Web-based Simulation Tool (WST) --a web-based education tool for participants to interact with their data to visualize and replay various scenarios to understand the impact of insulin parameter changes.

2.2 Study Design

This is a safety and feasibility study with a randomized two-arm parallel group trial in which both groups will use the AID (Control-IQ) plus ATM and WST. The difference between the two groups will be the behavioral module. One group will be randomized to add BAM and one group will not use BAM. This is illustrated in Figure 2:

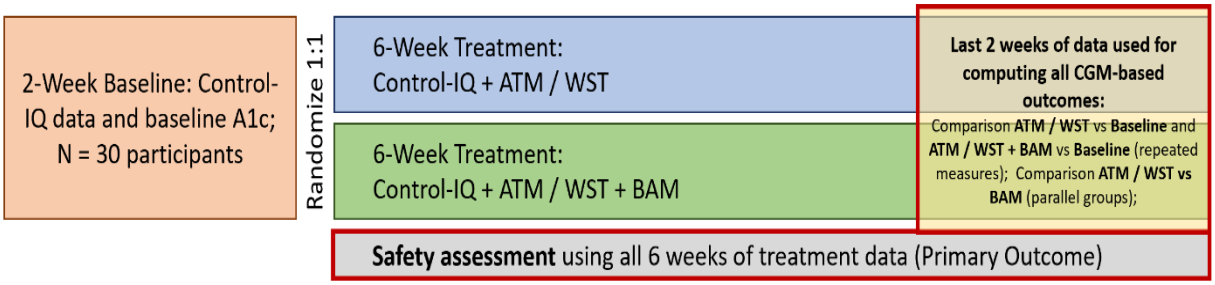


Figure 3: Study Diagram

2.3 Purpose/Objectives of Clinical Study

This pilot study is intended to test a Web-based Information Tool (WIT) software providing additional information regarding glucose variability, estimated A1c, risks for hypo- and hyperglycemia, and potential changes of insulin pump parameters, to users of the Control-IQ system.

2.4 Study Participants

Enrollment in the study will proceed with the goal of completing approximately 30 subjects. Study duration is between 8-10 weeks.

Up to 45 participants may sign the consent form.

2.5 Clinical Sites

The study will be performed at the University of Virginia.

2.6 Primary Specific Aim

The primary outcome will be a safety assessment using all 6 weeks of treatment data in terms of incidence of DKA or severe hypoglycemia.

2.7 Secondary Specific Aim

The secondary outcome of interest will be primarily CGM-based metrics using the last two weeks of the treatment data and the two-week baseline to compare:

- ATM / WST vs. Baseline
- ATM / WST + BAM vs. Baseline
- Group 1 vs. Group 2: ATM / WST vs. ATM / WST + BAM.

Chapter 3: Study Devices

3.1 Insulin Pump

Participants will use their personal FDA-approved Tandem t:slim X2 with Control-IQ Technology which will be used without modifications.

3.2 Continuous Glucose Monitor

Participants will be provided a study provided CGM that includes Dexcom G6 transmitter and sensors while using the Tandem t:slim X2 insulin pumps. The CGM sensor is viable for 10 days. All participants will be provided a Dexcom G6 system by the study team as needed. This system will be used without modifications. The CGM device will be calibrated, if needed, using the glucometer in accordance with the manufacturer's labeling. The participant may elect to continue use of their personal CGM during the study. The study will provide CGM supplies, as necessary. As a previously noted, data may be obtained through the commercial applications (e.g. t:connect and Dexcom G6).

3.3 Blood Glucose Meter and Strips

Blood glucose levels will be measured using the participant's personal glucometer.

3.4 Ketone Meter and Strips

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

3.5 Study Devices Accountability Procedures

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

Chapter 4: Study Screening

4.1 Participant Recruitment and Enrollment

Enrollment in the study will proceed with the goal of completing approximately 30 subjects.

Up to 45 participants may sign the consent form.

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

4.2 Informed Consent and Authorization Procedures

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

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

Consenting procedures and documentation is defined in section 13.3.

Telecommunicated study visits may take the place of all in-person study visits as deemed feasible by the study team.

4.3 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by licensed study personnel or using a historical exam within 12 months if the visit is done remotely, and pregnancy testing (if applicable) to screen for exclusionary medical conditions.

Once all results of the screening evaluations are available, a decision will be made to determine the participant's eligibility for the study, or if one or more parts of the screening will have to be repeated. These may be repeated at the discretion of the Principal Investigator

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

4.4 Participant Inclusion Criteria

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

1. Age ≥18.0 and ≤70 years old at time of consent
2. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year
3. Currently using insulin pump for at least six months
4. Currently using insulin for at least six months
5. Currently using or anticipated to be using the t:slim X2 insulin pump with Control-IQ technology at the start of the run-in phase (Visit 1).
6. Using or willing to use insulin parameters such as carbohydrate ratio and correction factors consistently on their pump in order to dose insulin for meals or corrections
7. Access to internet and willingness to upload data during the study as needed
8. Willing to use an app on a smart phone during the study.
9. For females, not currently known to be pregnant or breastfeeding
10. If female, sexually active, and of childbearing potential, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of childbearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
11. Willingness to use only insulin analogs approved for use in the t:slim X2 pump such as lispro (Humalog) or as part (Novolog) and not use ultra-rapid acting insulin analogs (e.g. FiAsp) during the study
12. Total daily insulin dose (TDD) at least 10 units per day
13. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (including metformin, GLP-1 agonists, pramlintide, DPP-4 inhibitors, biguanides, and sulfonylureas)
14. An understanding and willingness to follow the protocol and signed informed consent

4.5 Participant Exclusion Criteria

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

1. Concurrent use of any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas)

2. A condition, which in the opinion of the investigator or designee, would put the participant at risk or interfere with the completion of the protocol.
3. History of diabetic ketoacidosis (DKA) in the 12 months prior to enrollment
4. Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment
5. Currently being treated for a seizure disorder
6. Hemophilia or any other bleeding disorder
7. Planned surgery during study duration
8. Participation in another pharmaceutical or device trial at the time of enrollment or during the study
9. Having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (e.g. study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial.

4.6 Screening Procedures

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

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

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:

- Inclusion and exclusion criteria assessed
- Demographics (date of birth, gender, race and ethnicity, and socioeconomic indicators)
- Contact information
- Diabetes history including severe hypoglycemia history
- Medical history
- Concomitant Medications
- Physical examination to include (a physical exam report within last 52 weeks may be substituted):
- Weight, height (may be self-reported)
- Vital signs including measurement of blood pressure and pulse (may use medical record within 6 months or self-report)
- Urine or serum pregnancy test for all females of child-bearing potential (this test can be done remotely with results sent to the study team)
- HbA1c level measured using the DCA Vantage or similar point of care device or local lab

- 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)
- Diabetes Management Information: We will record the participant's average total daily insulin use, carbohydrate ratio, correction factor (insulin sensitivity factor), and insulin infusion basal rate profile. 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 and CGM. This data may be obtained through the commercial applications (e.g. t:connect and Dexcom G6).
- If participants are on-site, the participant's glucometer may be uploaded to ensure that the participant can successfully upload the equipment.
- 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.

Participants travelling from a distance or participants wishing to be pre-screened for eligibility may elect to have the consent read and explained by study staff by phone. Once all questions have been answered, the signed consent will be sent to study personnel and the participant may then have pre-screening with labs performed locally (e.g. LabCorp) prior to Visit 1.

The study physician or physician designee will have the discretion to repeat screening tests. The repeat screening tests may be conducted locally (e.g. LabCorp). 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.

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 at a later date if their clinical situation changes as determined by the study physician.

Chapter 5: Study Equipment Training

Equipment training relevant to the study visit may begin immediately after screening eligibility has been met or may be deferred for a maximum of 30 days.

All participants will be asked to use their personal t:slim X2 insulin pump with Control-IQ Technology and study Dexcom G6 CGM throughout the study period from Run-In Visit through the Final Study Visit. Study supplied phones will be available upon request.

Study contact information will be provided to the participant. The study team will be available by phone as needed throughout the study duration.

All study training may be performed as an office visit, or via telecommunication.

5.1 CGM Training

A Dexcom G6 CGM will be provided to all participants at the training session. The participants may choose to use their personal CGM equipment or will be provided with study CGM equipment. Participants will be instructed to use the study CGM on a daily basis. If the participant has prior use of the CGM, re-training will be specific to the individual. The study team may elect to have less frequent CGM users watch the Dexcom online training videos (https://www.dexcom.com/training-videos) to assist in the training session.

The participants will be asked to perform fingerstick blood glucose measurements (if needed) in accordance with the labeling of the CGM device.

5.2 Insulin Pump Training

Participants are current users of Control-IQ and therefore do not require training on the pump. The participant will be instructed on how to use the system if insulin is delivered by any means other than the Control-IQ pump (e.g. injection of subcutaneous insulin via syringe in the event of infusion site failure). If insulin is delivered by any means other than the study pump, the participant will be instructed to turn off Control-IQ for approximately four hours.

The participant will be provided with contact information and will be asked to call the study clinical staff during periods of illness with an elevated temperature >101.5 degrees Fahrenheit (38.6 degrees Celsius), periods of significant illness, or during periods of use of medications such as epinephrine for the emergency treatment of a severe allergic reaction or asthma attack in addition to use of oral or injectable glucocorticoids to determine if automated insulin delivery should be temporarily discontinued.

The participant will be provided Glycemic Treatment Guidelines (Appendix A-11) to use at home.

5.2.1 Optimization of Insulin Pump Settings

Throughout the study, study clinicians will refrain from adjusting insulin pump settings beyond the once-weekly Auto-titration adjustments. However, data-driven optimization of pump settings can occur at any time during the study for safety reasons, particularly if the participant contacts the study team due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

5.2.2 Autotitration of Insulin Pump Settings

Participants will receive recommendations via email for adjustments to insulin parameters derived from the WIT once a week. Participants will be asked to implement those parameters as suggested and will manually change the settings on their personal pump. Participants may contact the study clinicians to discuss concerns they may have with the suggested settings. The study clinician will then evaluate and may alter the implementation of some or all of the parameters if deemed a significant safety concern.

5.3 Training on the Investigational Applications

All participants in both groups will be trained on the WIT application.

Autotitration / WST training consists of:

- Review of how to access the web-based application (e.g. on a smart phone, iPAD or computer).
- Review of menus of the application.
- Review of actual parameters being adjusted (e.g. basal rates, correction factors)
- Review of frequency of parameter updates (i.e. once weekly)
- Participants will be instructed to contact the study team to review parameters updates at any time if they are concerned about appropriateness of adjustments
- Participants will be instructed to contact the study team to confirm the institution of parameter adjustments
- Participants will be instructed to how to run a simulation and interrupt the results displayed on the screen

Participants who are randomized to Group 2 will also receive BAM training and will generally consist of the following:

- Review of how to access the BAM application components and troubleshooting.
- Hands-on training of identification of information modules components and how to access the information modules and an explanation of those modules

- Hands-on training of how to access prescriptive modules on demand and an explanation of those modules
- Participants will be notified that eA1c is for informational purposes only and not to be used for short-term changes to insulin settings

Information Modules will include:

i. *Hypoglycemia Risk Indicator* based on pattern recognition and risk assessment;
ii. Daily glycemic profile forecast;
iii. *Estimated A1c* (*eA1c*) which will assist with tracking average glycemia and goal setting, and
iv. *Variability tracker* highlighting glycemic patterns related to behavioral challenges such as meals and exercise.

Study staff will be available 24/7 to assist the participant and troubleshoot the BAM and auto-titration modules.

5.4 Ancillary Device Training

Participants will have the option to receive a study-owned smartphone or to use their personal smartphone in order to collect the data from the CGM and insulin pump devices and stream it to respective cloud servers. The chosen phone will also allow the participant to access the WIT application.

If participants choose the study-owned smartphone option, they will be provided a study phone with a data plan, an anonymous email account, the Dexcom G6 app, the Tandem t:connect Mobile App, and access to the WIT system for the duration of the study. The Dexcom app will allow the participant to monitor the CGM values and alerts in real-time and stream CGM data to the Dexcom Clarity cloud. The Tandem t:connect Mobile App will be downloaded to their phone in order allow the participant to stream insulin pump data to the Tandem t:connect cloud. Study staff will register a subject account and login so that the subject can access the WIT system via the smartphone.

If the participant elects to use a personal smartphone, the Dexcom G6 app and the Tandem t:connect Mobile App will be downloaded to their phones if they are not already installed.

In both cases, the participant will have the option of using their personal Dexcom and their personal Tandem t:connect accounts or anonymous, study-provided accounts. Participants who do not wish to use their personal accounts, or do not have personal accounts and do not wish to create one, will be provided an anonymous account created by study staff.

Participants who elect to use a study phone will be trained on the basic functioning of the phone (e.g. charging, password entry, accessing apps). All participants will be asked to verify successful installation of apps (where applicable) and account access.

5.5 Blood Glucose Training

Participants will use their personal home glucometer.

The study team may inquire about glucometer readings if the study visits are performed remotely. If visits are done in person, the glucometer may be uploaded. Participants will be reminded to use the same blood glucose meter for all fingerstick BGs during the study.

5.6 Blood Ketone Training

Participants will be provided with a study blood ketone meter and test strips to be used at home per manufacturer guidelines.

All study blood ketone meters will be QC tested by study staff with at least two different concentrations of control solution, if available. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling.

Participants will be instructed to perform blood ketone testing as described in Glycemic Treatment Guidelines (see Participant Manual). A home glucagon emergency kit is considered standard of care. Participants who currently do not have one will be asked to obtain a prescription for the glucagon emergency kit.

The study team may inquire about ketone readings if the study visits are performed remotely. If visits are done in person, the glucometer may be uploaded.

Chapter 6: Study Procedures

6.1 Run-In Phase (Visit 2)

After eligibility is confirmed, participants will undergo a run-in phase. This visit may occur on the same day as the screening visit and should be completed within 30 days once screening elements are completed and eligibility determined. This visit may occur as an in-person office visit or via telecommunication. For visits occurring remotely, these relevant devices will be shipped to the participant.

The purpose of the run-in phase is to obtain about 14 days of baseline data while the participant is following their usual care with their personal t:slim X2 study pump and Dexcom G6 CGM. The study team may elect to allow the participant to repeat the run-in phase as needed.

At Visit 2, participants will be trained on the CGM and insulin pump, if relevant, as described in section 5.1 and 4.2. Participants will also be trained on blood glucose meter if relevant and the ketone meter as described in section 5.5 and 4.6.

A pregnancy test will be repeated as needed if more than 30 days has elapsed since the prior pregnancy test.

Study clinicians may optimize insulin pump settings if needed during this visit. Participants will be allowed to make insulin dosing decisions per their usual care but will be asked to avoid changing insulin pump settings during the two-week run-in.

6.2 Randomization Visit (Visit 3)

6.2.1 Randomization Criteria

After the completion of at least 2 weeks of run-in data, participants will have a randomization visit. This visit can occur between 14-28 days from Visit 2. This visit can be conducted either in-person office visit or as a remote visit.

Screening failures and study dropout participants may be replaced.

This visit may be performed as an office visit, or via telecommunication.

6.2.2 Participants

Participants will be randomized 1:1 to either:

- Group 1: Use of AID and ATM / WST for 6 weeks

- Group 2: Use of AID, ATM / WST, and BAM for 6 weeks

The randomization scheme will be completed prior to the first study participant and will be done by a study team member who is not involved with enrollment.

6.3 Optimization of Insulin Pump Settings

Insulin pump optimization will occur during the study as described in Section 4.2.1.

6.4 Check-In Visits (Visit 4-8)

These visits will occur either as in-person office visits or remote visits. These visits will occur weekly (+/- 3 day). Prior to each phone visit, participants will be asked to download any relevant devices if applicable (i.e. not using a shared web-based app for data such as the t:connect mobile app or G6 mobile app). During these visits, the study team will:

- Answer any questions and inquire about any device complaints.
- Inquire about new medications, updates to medical conditions, adverse events, and whether the adverse event was related to study device use.
- Inquire about ketone readings (a ketone meter download will not be required)
- Review the downloaded/uploaded data to assess completeness.

6.5 Participant Study Compliance

The study team may contact the study participant as needed to ensure study compliance.

Group 1 will be asked to have a minimum of weekly interaction to review and implement weekly parameter settings.

Group 2 will be asked to have a minimum of weekly interaction to review and implement weekly parameter settings. Participants engaging in the BAM module will be asked to have daily contact with that module.

The study team will determine if non-compliance should result in additional study weeks or discontinuation from the study.

6.6 Study System Issues

The study team will be available to troubleshoot with the investigational WIT, BAM, and ATM / WST.

The AID system will used per approved use without modification.

6.7 Repeating Visits & 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.

6.8 Final Visit (Visit 9)

The following procedures will be performed in both groups at the final study visit:

- Adverse events, adverse device effects, and device issues
- All devices will be downloaded (i.e. insulin pump, CGM, glucometer, ketone meter)
- Study team or participant may download the study equipment
- Questionnaires will be completed electronically when possible
- Blood will be drawn for HbA1c (which can be done on-site or locally)
- Pregnancy test (if applicable)
- Equipment may be returned in person or via Federal Express

Study participants will be instructed on how to transition back to the home insulin regimen. Subjects will be informed that there may be a risk of severe hypoglycemia and/or severe hyperglycemia during the transition back to the subject's usual home insulin parameters. The study physician will be available for consultation during this transition period.

All study devices will be returned except the study glucometers or ketone meters may be retained by the study participant after download is completed.

6.9 Post-Study Check-In Visit

Approximately 48 hours after the participant completes the home use of the equipment portion of the study, the study team will contact the participant via phone/email/text to assess:

- Adverse events
- Confirm HbA1c completed
- Equipment returned in person or via Federal Express

6.10 Early Withdraw

Participants who withdraw from the study will be asked to complete the Final and Post Study Check-In Visit requirements.

Chapter 7: Testing Procedures

7.1 Laboratory / Point of Care Testing

7.1.1 HbA1c

- A blood sample will be obtained at screening to obtain a baseline hemoglobin A1c level. Blood test obtained within 2 weeks prior to enrollment may be used.
- HbA1c level may be measured by study team using the DCA2000, a comparable point of care device, at time of screening
- Labs may be obtained at a local laboratory convenient to the participant.

7.1.2 Comprehensive Metabolic Panel/TSH/Hematocrit

- A blood sample may be obtained at screening to assess kidney and liver functioning, thyroid function or hematocrit.
- Labs may be obtained at a local laboratory convenient to the participant.

7.1.3 Pregnancy Test

- A serum or urine pregnancy test will be required for women of childbearing potential at the screening visit, prior to each study equipment training session and at the end of the study. Test must be negative to participate in the study.

7.2 Questionnaires

Questionnaires are completed as noted below for all participants.

7.2.1 Questionnaire Schedule

Screening:

- ABC Pilot Study Baseline: This questionnaire has 5 open-ended questions for baseline assessment of expectations for the investigational system.

  Administration time is approximately 5 minutes.

- INSPIRE Survey: The INSPIRE (Insulin Delivery Systems: Perceptions, Ideas, Reflections and Expectations) survey was developed to assess various aspects of a user's experience regarding automated insulin delivery. The surveys include various topics important to patients with type 1 diabetes based upon >200 hours of qualitative interviews and focus groups. The adult survey includes 31 items. Response options for all surveys include a 5-point Likert scale from strongly agree to strongly disagree, along with an N/A option.

Administration time is approximately 5 minutes.

Final Visit:

- ABC Pilot Study Follow-up: This questionnaire has 5 open-ended questions for post-study assessment of experience with investigational system that are similar to the baseline questionnaire.

  Administration time is approximately 5 minutes.

- INSPIRE Survey: Similar survey administered at Screening Visit.

  Administration time is approximately 5 minutes.

Chapter 8: Risks Associated with Clinical Trial

8.1 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.

8.1.1 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.

8.1.2 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.

8.1.3 Subcutaneous Catheter Risks (CGM)

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

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

8.1.4 Risks of Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating,

jitteriness, and not feeling well. 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.

8.1.5 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.

8.1.6 Hb1Ac Risk

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

8.1.7 Other Risks

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

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

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

8.1.8 Known Potential Benefits

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

8.1.9 Risk Assessment

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

8.2 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 investigational modules of BAM and ATM / WST are experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

Chapter 9: Adverse Events, Device Issues, and Stopping Rules

9.1 Definitions

9.1.1 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 9.2) for reportable adverse events for this protocol).

9.1.2 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).

9.1.3 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)).

9.1.4 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.

9.1.5 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).

9.2 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 9.1.2
- an adverse device effect as defined in section 9.1.4, unless excluded from reporting in section 9.7
- an adverse event as defined in section 9.1.4 occurring in association with a study procedure
- an ae as defined in section 9.1.1 which leads to discontinuation of a study device for 2 or more hours
- hypoglycemia meeting the definition of severe hypoglycemia as defined in section 9.2.1
- diabetic ketoacidosis (DKA) as defined in section 9.2.2 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.

9.2.1 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.

9.2.2 Hyperglycemia Events/Diabetes Ketoacidosis

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

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

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

- symptoms such as polyuria, polydipsia, nausea, or vomiting;
- serum ketones ≥1.5 mmol/l or large/moderate urine ketones;
- treatment provided in a health care facility
- all reportable Adverse Events—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—will be reported on an adverse event form online.

9.3 Relationship of Adverse Event to Study Device

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

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

- There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the

adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

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

9.4 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.

9.5 Coding of Adverse Events

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

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.

9.6 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 had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the

time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.

- NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
- An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
- The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

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

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

9.7 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 reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than the number of days expected per CGM labeling
- CGM tape adherence issues
- Pump infusion set occlusion not leading to ketosis
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication

- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement or pump infusion set placement that do not meet criteria for AE reporting

9.8 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 and FDA, within 10 working days of the study team becoming aware of the UADE per 21CFR 812.46(b) (2).
- 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.

9.9 Stopping Criteria

9.9.1 Participant Discontinuation

Rules for discontinuing study device use are described below.

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- Two distinct episodes of DKA
- Two distinct severe hypoglycemia events as defined in section 9.2.1.

9.9.2 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 9.2), use of the study device system will be suspended while the problem is diagnosed.

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

The study must also stop if there are three severe hypoglycemia events or three DKA events. After further medical/safety review of the events, the study may resume if the events are determined to be unrelated to an unanticipated system malfunction.

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 10: Miscellaneous Considerations

10.1 Prohibited Medications, Treatments, and Procedures

Participants using non-approved insulins at the time of enrollment will be asked to contact their personal physician to change their prescribed personal insulin to a rapid-acting insulin approved for use in the t:slim X2 pump (e.g. lispro or aspart) for the duration of the trial.

The devices (insulin pump, 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.

10.2 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.

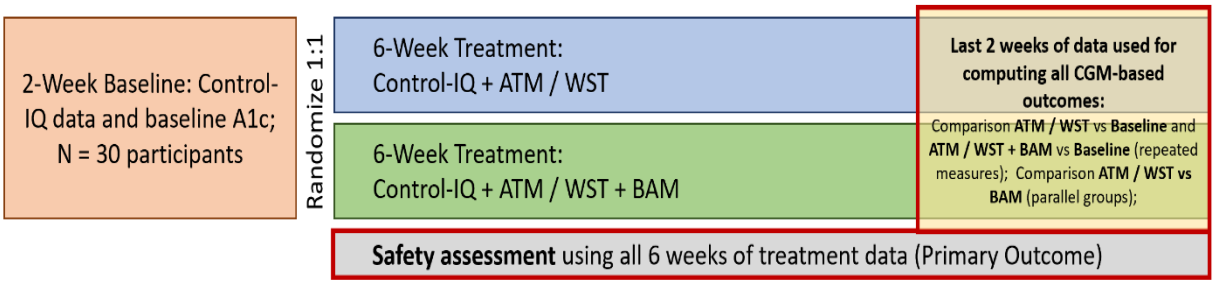
10.3 Confidentiality

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

Chapter 11: Statistical Consideration

The intent of this pilot-feasibility study is to introduce and initially test elements of two modules to be included in a future Adaptive Biobehavioral Control (ABC) system: (1) A Behavioral Adaptation Module (BAM) and (2) An Auto Titration Module (ATM) and a Web Simulation Model (WST). BAM and ATM / WST will be provided to users of the t:slim X2 with Control-IQ closed-loop system. The only purpose of this trial is safety testing and receiving feedback from the participants regarding system functionality and user interface.

11.1 Design and Randomization



The study will recruit current users of the Control-IQ system. Following a 2-week baseline using Control-IQ only, the participants will be randomized 1:1 to Control-IQ + ATM / WST vs Control IQ + ATM / WST + BAM and will be followed for 6 weeks. The randomization list will use a sequence of computer-generated pseudorandom Bernoulli trials. The 6 weeks of active trial will be used for assessment of the safety and usability of ATM / WST and BAM. The baseline data and the last 2 weeks of the active trial will be used for secondary comparisons of CGM-based metrics of glycemic control.

11.2 Sample Size

We intend to recruit up to 45 users of Control-IQ, with the objective to randomize N=30 subjects. The number of participants is a convenience sample not based on statistical principles. This sample will provide ~180 weeks of data for the assessment of the safety and utility of the ATM and up to 90 weeks for assessment of the safety and utility of the BAM.

11.3 Outcome Measures

11.3.1 Primary Efficacy Endpoint

Safety assessment of ATM / WST and BAM.

11.3.2 Secondary Outcome

CGM-based metrics and user experience (UX) questionnaires, including:

- Percentage of readings in the target ranges of 70-180 and 70-140 mg/dl;
- Mean glucose;
- Glucose variability measured by standard deviation and coefficient of variation;
- Percentage of readings <70, 60, and 54 mg/dl;
- Low blood glucose index (LBGI)[10]
- Percentage of readings >180, 250, and 300 mg/dl;
- High blood glucose index (HBGI)[10]
- ABC Pilot Pre and Post Study Questionnaire
- INSPIRE

11.4 Safety Analyses

All randomized participants will be included in these analyses and the circumstances of all reportable cases of the following will be summarized and tabulated by treatment group:

- Severe hypoglycemia;
- Diabetic ketoacidosis (DKA);
- Ketone events defined as a calendar day with ketone level >1.0 mmol/L;
- Serious adverse events (SAE) with a possible or greater relationship to a study device (including anticipated and unanticipated adverse device effects);
- Other serious adverse events not related to a study device, and
- Adverse device effects (ADE) that do not meet criteria for SAE.

Criteria for Success have been discussed with FDA during the submission of our previous pilot study (IDE G170255, "A Pilot Test of t:slim X2 with Control-IQ Technology"), which was used to introduce Control-IQ and enable a subsequent pivotal trial. These criteria included system safety checks and CGM-based performance criteria consistent with the recommendations of the International Consensus on Time-in-Range. Because these criteria are well established, we will keep them to gauge the success of the pilot evaluation of the new modules ATM / WST and BAM:

- No critical ATM / WST or BAM errors;
- No SAE or ADE related to the use of ATM / WST or BAM;
- Percent time in the range 70-180 mg/dL: mean 71% ±11;
- Percent time <70 mg/dL: median <5%.
- Percent time >250 mg/dL: median <10%.

11.5 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, and will include:

- Demographics (e.g. age, duration of diabetes, and other);
- Baseline HbA1c, and
- CGM-based metrics from the 2-week baseline use of Control-IQ:
    - Percentage of readings in the target ranges of 70-180 and 70-140 mg/dl;
    - Mean glucose;
    - Glucose variability measured by standard deviation and coefficient of variation;
    - Percentage of readings <70, 60, and 54 mg/dl;
    - Low blood glucose index (LBGI) ;[10]
    - Percentage of readings >180, 250, and 300 mg/dl;
    - High blood glucose index (HBGI).[10]

11.6 Device Issues

The following tabulations and analyses will be performed by treatment group to assess device issues:

- Device malfunctions requiring study team contact and other reported device issues
- Sensor performance metrics (difference, absolute relative difference, and International Organization for Standardization criteria) – if applicable, by sensor version.
- % time CGM data available - overall and by month
- % time in different operational modes per week - overall and by month

11.7 Analysis of Secondary CGM-based Outcomes

The study design includes repeated measures (baseline vs last 2 weeks of study) on all secondary CGM and UX outcomes (Figure 1); thus, we will use a linear mixed-effect model that corresponds well to this structure[5,6] (e.g. Linear Mixed Models in SPSS.[7]), with “Subject” as a random factor and “Group” as a fixed factor. The models will adjust for age and HbA1c as fixed effects. We should note that similar results may be generated by repeated measures ANOVA, but mixed models handle missing data better (e.g. ANOVA only uses listwise deletion, which could reduce power and introduce bias towards study completers).[8,9]

The general principles that will be followed during analysis are:

- The analysis will follow an Intention-to-treat (ITT) approach;

- All randomized participants will be included in the primary safety analysis and in the secondary analyses of CGM metrics.
- All covariates obtained on a continuous scale will be entered into the models as continuous variables, unless it is determined that a variable does not have a linear relationship with the outcome. In such a case, categorization and/or transformation will be explored. All p-values will be two-sided.
- Standard residual diagnostics will be performed for all analyses. If values are highly skewed, then an alternate transformation or nonparametric methods will be used. Previous experience suggests that no transformation or nonparametric analyses will be necessary for TIR 70-180 mg/dL, TIR above 180 mg/dL, mean glucose, or HbA_{1c}.Other outcomes, such as TIR below 70 mg/dL are typically skewed.

Chapter 12: Data Collection and Monitoring

12.1 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.

12.2 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.

12.3 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 13: Ethics/Protection of Human Participants

13.1 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.

13.2 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.

13.3 Informed Consent Process

13.3.1 Consent Procedures and Documentation

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

The participant will sign the informed consent document prior to any procedures being done specifically for the study. A copy of the informed consent document will be given to the participant for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.3.2 Participant and Data Confidentiality

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

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

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

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