



UVA CENTER FOR DIABETES TECHNOLOGY

Adaptive Behavioral Control (ABC) in a Closed-Loop System: A Randomized Crossover Clinical Trial

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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	Sue Brown, Patricio Colmegna	Sue Brown	25-Aug-2022	Original Protocol
1.1	Sue Brown	Sue Brown	08-Sep-2022	FDA modifications: • Clarified inclusion criteria (section 4.3) • Edited insulin pump training (section 5.2 & 6.1)
1.2	Mary Oliveri, Sue Brown	Sue Brown	12-Sep-2022	FDA modifications: • Staged enrollment (section 2.4) • Added inclusion criteria (section 4.3) • Insulin parameters change training (section 5.2 & 6.2.1) • Maximum insulin parameters adjustment is 10% (section 5.2.2) • Added request the participant's username and passwords (section 5.4) • Addition of visit 2a and 2b (section 6.1) • Added Data Safety Monitoring Board oversight (section 9.10)
1.3	Mary Oliveri, Sue Brown	Sue Brown	13-Sep-2022	FDA modifications: • Record number of pump parameter changes during visit 3-13 (section 6.4) • Individual stopping criteria revised from 2 SH/DKA events to 1 event (section 9.9.1) • Overall study stopping criteria revised from 3 SH/DKA events to 2 events (section 9.9.2)
1.4	Sue Brown	Sue Brown	15-Sep-2022	FDA modifications: • Aligned the WIT language throughout document
1.5	Mary Oliveri	Mary Oliveri	23-Sep-2022	Study team modification: • Purpose of Demographic survey defined (Section 4.5)
1.6	Mary Oliveri	Sue Brown	09-Oct-2022	IRB Prereview modifications: • Deleted screening procedures description from Chapter 4. • Edited randomization description (Protocol Summary & section 6.2.2) • Edited consent procedures (section 13.3.1)

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1.7	Mary Oliveri	Mary Oliveri	24-Oct-2022	IRB Prereview modifications: • Changed title of project to include 'crossover'
1.8	Mary Oliveri	Sue Brown	13-Jan-2023	Study Team modifications: • Clarified pregnancy tests (section 6.8, 7.1.3) • Clarified timing between study visits (Table 1, section 6.1, and 6.2.1) • Added additional ketone meter option (Keto-Mojo) (section 3.4) • Added optional use of study CGM for baseline CGM data (section 6.1) • Clarified CMP if requested by MD (section 7.1.1) • Edited hyperglycemic events description (section 9.2.2) • Corrected name of Hypoglycemia Fear Survey II Adults (HFSII Adults) survey (section 7.2)
1.9	Mary Oliveri	Sue Brown	20-Jun-2023	Study Team modifications • Reinserted DCCT definition "Serum ketones ≥ 3.0 mmol/L, even if there was no communication with a health care provider" (section 9.2.2).
1.10	Mary Oliveri	Sue Brown	16-Jan-2024	Study Team modification • Added commercially approved Dexcom (e.g. G6 or G7). • Removed specific names of Dexcom and Tandem cloud accounts as manufacturers are providing additional options to download data and are changing names of these accounts.

Site Principal Investigator Statement of Compliance

Protocol Title: Adaptive Biobehavioral Control (ABC) in a Closed-Loop System: A Randomized Crossover Clinical Trial

Protocol Version/Date: v 1.10/16-Jan-2024

I have read the protocol specified above. In my formal capacity as a Site Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature _____ Date: ____ / ____ / ____

Investigator's Name: _____

Site Name: University of Virginia

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ABC	Adaptive Biobehavioral Control
AID	Automated Insulin Delivery Device
ATM	Auto Titration Module
ADRR	Average Daily Risk Range
AP	Artificial Pancreas
AGP	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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMI	Glucose Management Indicator
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
PAM	Physical Adaptation Module
POC	Point-of-Care
SAP	Sensor-Augmented Insulin Pump

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QC	Quality Control
UI	User Interface
WIT	Web Information Tool
WST	Web Simulation Tool

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Adaptive Biobehavioral Control (ABC) in a Closed-Loop System: A Randomized Crossover Clinical Trial
Investigational Device	There is Investigational software known as a Web-based Information Tool (WIT), the clinical software implementation of the ABC concept, that consists of two components (software modules) collectively known as ABC: - Behavioral Adaptation Module (BAM) - Physiological Adaptation Module (PAM) that consists of an Auto Titration Module (ATM) and a Web Simulation Tool (WST). There is no investigational device
Investigational Medication	None
Objectives	This study is intended to test a Web-based Information Tool (WIT) software providing additional information regarding time in range, glucose variability, glucose management indicator (GMI), risks for hypo- and hyperglycemia, and potential changes of insulin pump parameters, to users of the Control-IQ system.
Study Design	Randomized crossover clinical trial
Number of Sites	1
Endpoint	Primary Outcome: - CGM-measured % time in range 70-180 over last 4 weeks of CLC+ABC vs 2 weeks of CLC Secondary Outcomes: - The secondary outcome of interest will be primarily CGM-based metrics using the last four weeks of the CLC+ABC, 4 weeks of CLC+BAM and the two-week CLC data to compare: CLC +ABC vs CLC +BAM and CLC+BAM vs CLC
Population	Key Inclusion Criteria: - Age 18-70, inclusive, with Type 1 Diabetes for at least one year - Current or anticipated user of t:slim X2 insulin pump with Control-IQ Technology (Closed-loop control or CLC) by randomization Key Exclusion Criteria: - Recent severe hypoglycemic event or DKA during the past one year
Sample Size	The recruitment target is to complete 72 subjects
Treatment Groups	- Group 1: CLC use (2 wk) followed by CLC + BAM (4 wk) followed by CLC +BAM and PAM (16 wk) - Group 2: CLC+BAM and PAM (16 wks) followed by CLC + BAM (4 wk) followed by CLC use (2 wk)
Participant Duration	Up to 26 weeks
Protocol Overview/Synopsis	Each group will undergo screening and collection of baseline data from their personal CLC system (Control-IQ) followed by randomization 1:1 into two groups. Both groups will have the same three interventions but will progress in the study in a different order. The three interventions are: - Use of personal CLC system for 2 weeks - Use of personal CLC system and adding a behavioral adaptation module (BAM) for 4 weeks

	• Use of personal CLC system and adding the ABC which includes three components: BAM, Auto Titration Module and WST (the last 2 also known as PAM). The BAM will consist of modules in which information only is given to participants (e.g. time in range, Glucose Management Indicator (GMI), hyper-and hypoglycemic risks, daily glycemic profiles, and variability tracker). The PAM includes auto titration of insulin pump parameters every two weeks (ATM) and is aided by a web simulation tool (WST) which can replay several ‘what if’ scenarios for the participant based on various combinations of insulin pump parameter changes.
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Table 1 Schedule of Study Visits and Procedures

Visit Name	Visit 1	Visit 2	Visit 2a & 2b	Visit 3	Visit 4-13	Visit 14
Description	Screening Visit	Device Training & Data Collection	Check-In visits for non-CIQ users	Randomization	Bi-Weekly Check-In	Final Visit
Timing	-12 weeks to 0 days of Visit 3	-4 weeks to 0 days of Visit 3	V2a within 2 +/-1 days of V2: V2b within 7 +/-3 days of V2	Day 1	Every 14 +/-5 days	Day 154±7 days (22 weeks)
Location (office visit, phone, email, text, or telecommunication visit may be used as recommended by the study team)	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				
Physical Exam (if applicable)	X					
Vital Signs (including height/weight)	X					
Historical baseline data		X				
Training on Relevant Devices or Modules		X		X		
Review CGM & pump downloads			X			
Randomization				X		
Questionnaires		X			Only at the end of each phase: Group 1: Visit 4, 6 Group 2: Visit 11, 13	X (Both Groups)
Review diabetes management and AEs	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 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 study is intended to test the Web Information Tool (WIT), the clinical software implementation of the ABC concept, which is a web-based software that provides additional information regarding time in range, glucose variability, Glucose Management Indicator (GMI), 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 out under NIH/NIDDK project UC4DK108483 “*Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed Loop (iDCL) Trial.*” The iDCL Trial became one of the most successful studies 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:

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

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.

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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 Concept: The ABC concept 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 set 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 glucose variability by CGM and/or other signals. 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).

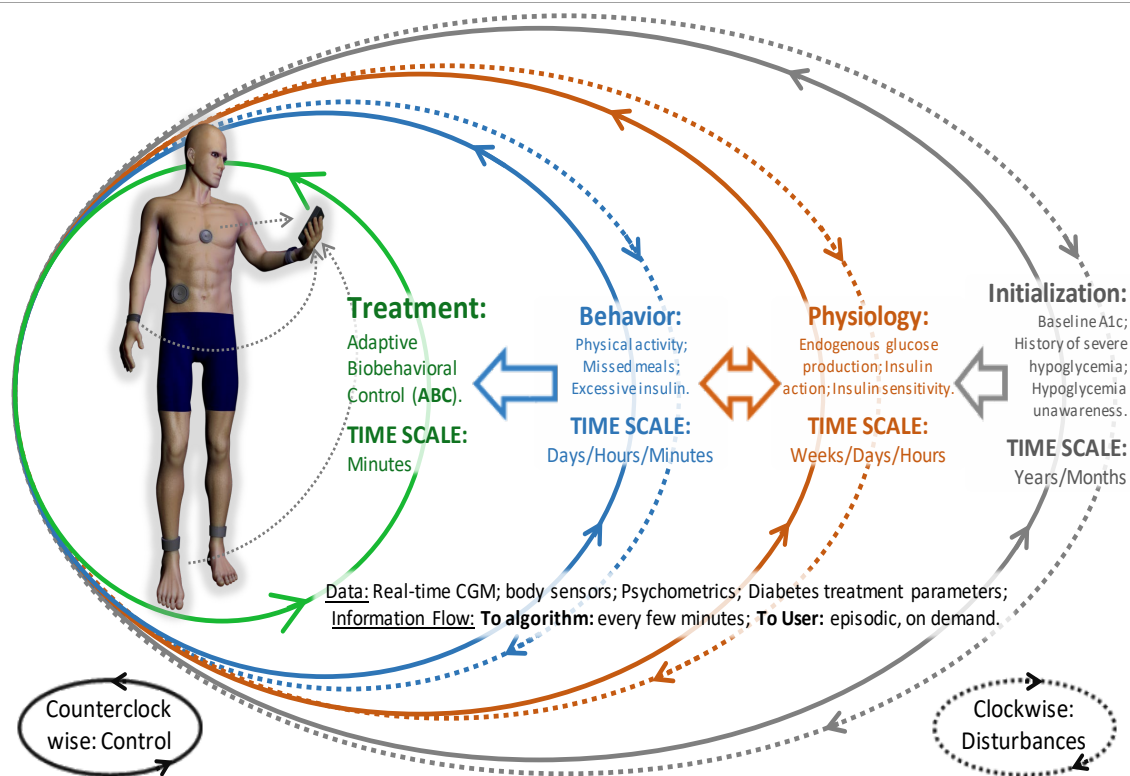


Figure 1: Main premise, signals, time scales, and control action of the recursive ABC process: initialization with routine T1D treatment parameters; behavioral and physiological perturbations monitored through CGM and other signals, and human-machine co-adaptation using pattern/risk information presented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

The overall objective of the ABC concept 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. We have already completed a 30- person pilot to test elements of WIT, the clinical software implementation of the ABC concept, and receive user feedback. Thus, we can confidently propose to 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 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*

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168 *user and will be accompanied by an option to replay treatment scenarios via computer simulation*
169 *but will not be implemented automatically.*

170 **1.2 Description of the Equipment**

171 Closed-Loop Control System: This system is used without modification.

172 **Trade/Device Name:** Control-IQ Technology

173 **Name:** Interoperable automated glycemic controller

174 System components include:

- 175 1. t:slim X2 insulin pump with Control-IQ technology, and
- 176 2. Dexcom commercially approved (e.g. G6 or G7) continuous glucose monitor (CGM).

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

179 Description of the Information Modules:

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

- 181 1. A Behavioral Adaptation Module (BAM);
- 182 2. A Physiological Adaptation Module (PAM) that consists of an Auto Titration Module
183 (ATM) and a Web Simulation Tool (WST);
- 184 3. Adaptive Biobehavioral Control (ABC): this refers to when the two components are
185 available concurrently to the user (BAM+PAM).

186 The two information modules BAM and PAM will be provided to users of the t:slim X2 with
187 Control-IQ closed-loop system in a Web-based interactive format via a website that allows for
188 unique login and can be accessed from a mobile application. These modules will provide the user
189 with potentially useful recommendations but will not interfere automatically with the functioning
190 of the CLC system. The primary purpose of this trial is safety testing and efficacy testing.

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

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The BAM uses well-established metrics of glycemic control computed daily:

Measure	Computed From
Time spent in various glucose ranges	Previous day, two weeks or one month of CGM data
Glucose Management Indicator (GMI)	14 days of CGM data
Low/High BG [Risk] Indices (LBGI/HBGI) – measures of risk for hypo- or hyperglycemia	Previous day of CGM data, or two weeks
Coefficient of variation – measures glucose variability	Previous day of CGM data

Table 2: Glycemic metrics used by the BAM

Results will be available on a daily basis. All 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.

The PAM:

1. ATM is a set of optimization algorithms designed to use the participants’ data and provide biweekly updates for their default insulin pump parameters: basal rate profile, insulin to carbohydrate ratio profile (CR), and insulin sensitivity factor profile (CF). To this end, ATM obtains a model of the user’s glucose excursions each day. Every two weeks, the module uses all the identified models over that period to evaluate multiple different combinations of the insulin pump parameters and estimate the optimal one. Recommended insulin pump parameter changes are limited to maximum of 10% of their current settings.
2. 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 data streams, summary indices, and summary graphical representation (in a format similar to an ambulatory glucose profile, Ambulatory Glucose Profile (AGP), but can also modify the recommended insulin treatment strategies, play “what-if” scenarios, and observe the predicted glycemic impact. For example, a user could observe there is still an early morning hypoglycemia tendency (from the summary graphical representation), further reduce the underlying basal rate, 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 relies on the same replay simulation technology¹¹⁻¹³ as the ATM and is supported by a transfer of data from the user devices

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219 (in the case of this study, an automated transmission of the t:slim X2 data to the Tandem
220 phone app and then to the Tandem web system, with a frequent pull triggered by our
221 AWS infrastructure of the Tandem data via a Tandem API).

Chapter 2: Study Description

2.1 Study Objective

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

The Adaptive Biobehavioral Control (ABC) concept represents the 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. This concept will be implemented on the Web Information Tool (WIT) platform/system and includes the following modules to be used alongside the AID device:

1. Behavioral Adaptation Module (BAM) – a behavioral intervention deployed in a website which can be accessed through a mobile app to assist a person’s adaptation to automated insulin delivery by information and risk assessment primarily regarding glycemic risks, and
2. Physiological Adaptation Module (PAM) that consists of:
 - An 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 every two weeks 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.
 - A 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 randomized two-arm crossover group trial in which both groups will use the AID (Control-IQ) plus WIT. The difference between the two groups will be the order of the interventions. This is illustrated in Figure 2.

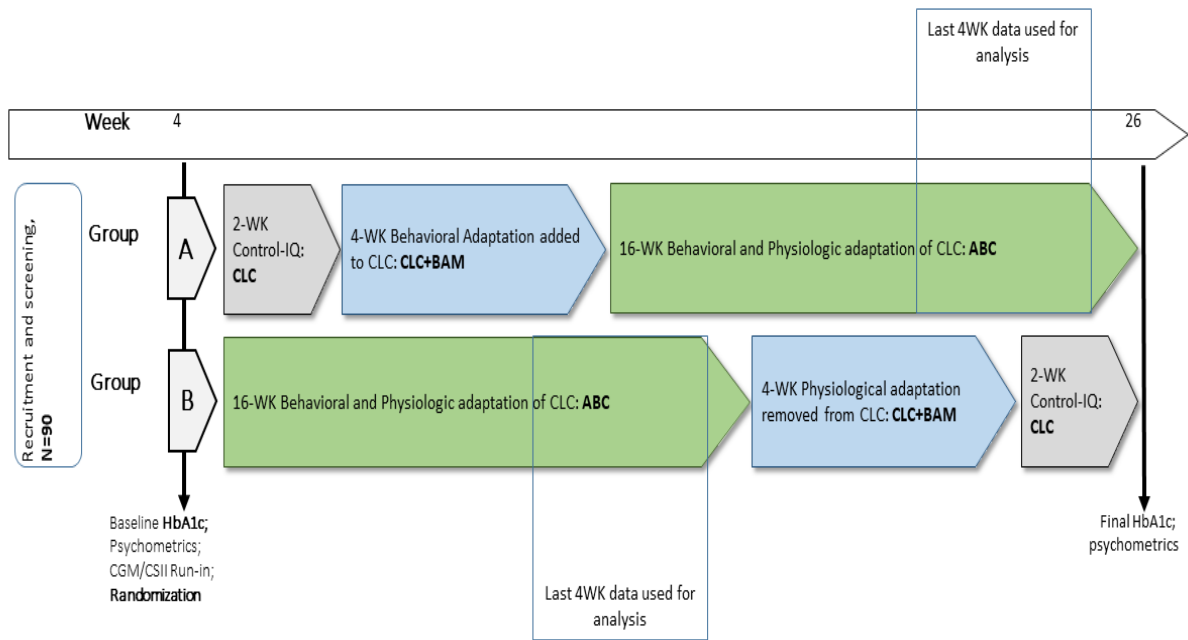


Figure 2: Study Diagram

2.3 Purpose/Objectives of Clinical Study

This study is intended to test a Web-based Information Tool (WIT) software providing additional information regarding time in range, GMI, hypo- and hyperglycemia risks, variability tracker, daily glycemic profiles, 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 72 subjects. Study duration is approximately 26 weeks. Up to 90 participants may sign the consent form.

The first 15 participants enrolled will be experienced Control-IQ users defined by 1) actively using Control-IQ at the time of the screening and 2) having had at least two months prior experience with the use of the Control-IQ device. Once these first 15 participants have completed 8 weeks of the protocol following randomization (Visit 7), a review of insulin parameters adjustment recommendations and implementation will be conducted as well as an evaluation for AEs including SAEs. The following criteria will be used: 1) verification that all changes suggested by the WIT system were within expected 10% constraints 2) no instances of AEs associated with insulin parameter changes associated with WIT. If there are no identified safety concerns by the above criteria requiring further mitigation, then additional participants could be enrolled who have at least two months experience using the t:slim X2 pump but have not enabled the CLC system Control-IQ for at least two months.

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272 The study team may continue to enroll experienced Control-IQ users without pause throughout the
273 study.

274 Screening failures and study dropout participants may be replaced.

275 **2.5 Clinical Sites**

276 The study will be performed at the University of Virginia.

277 **2.6 Primary Specific Aim**

278 The primary outcome will be CGM-measured % time in range 70-180 over last 4 weeks of
279 CLC+ABC compared to 2 weeks of CLC.

280 **2.7 Secondary Specific Aim**

281 The secondary outcome of interest will be primarily CGM-based metrics using the last four weeks
282 of the CLC+ABC, 4 weeks of CLC+BAM and the two-week CLC data to compare:

- 283 1. CLC +ABC vs CLC +BAM
284 2. CLC+BAM vs CLC

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. The participant's personal Tandem account may be used, or an anonymous, study-provided account will be used during the study.

3.2 Continuous Glucose Monitor

Participants will receive a commercially approved Dexcom CGM while using the Tandem t:slim X2 insulin pumps. This system will be used without modifications. The CGM sensor is viable for 10 days. 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 Dexcom CGM during the study. The study will provide Dexcom CGM supplies, as necessary. As previously noted, data may be obtained through commercial applications provided by the manufacturer (e.g., t:connect, Source, Clarity, Healthcare accounts, etc.)). The participant's personal account may be used, or an anonymous, study-provided account will be used during the study.

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 or Keto-Mojo meter and strips in accordance with the manufacturer's labeling. The blood glucose meter component of these devices will not be used.

3.5 Phones

Participants will be permitted to use their personal phones throughout the study. A study phone may be provided to the participant as needed. The Dexcom app and the Tandem Mobile App will be based to the participant's phone if not already installed. For iOS (Apple) phone users, the study team will need to add the unique device identifier (UDID) of the phone into the developer account.

3.6 Study Devices Accountability Procedures

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

Chapter 4: Study Screening

4.1 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 are 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.

4.2 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 an insulin pump for at least six months
4. Currently using insulin for at least six months
5. Currently using the t:slim X2 insulin pump for at least two months
6. Currently using or anticipated to be using the t:slim X2 insulin pump with Control-IQ technology at randomization (Visit 3).
7. 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
8. Access to internet and willingness to upload data during the study as needed
9. Willing to use an app on a smart phone during the study.
10. For females, not currently known to be pregnant or breastfeeding
11. 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.

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12. 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
13. Total daily insulin dose (TDD) at least 10 units per day
14. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (including metformin (biguanides), GLP-1 receptor agonists, pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas)
15. An understanding and willingness to follow the protocol and signed informed consent

4.3 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 or GLP-1 receptor agonists following screening (including 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.

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

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- 383 a. Duration of disease (number of years)
- 384 b. Current insulin pump model
- 385 c. History of CGM use
- 386 d. Current treatment
- 387 e. Severe hypoglycemia history
- 388 f. Severe hyperglycemia history
- 389 g. History of seizures
- 390 h. Loss of consciousness

391 4. Insulin Usage

- 392 Basal rates
- 393 Carbohydrate ratios
- 394 Insulin sensitivity factors
- 395 Target glucose
- 396 Average daily insulin

397 5. Surgical history

398 6. Allergies

399 7. Concomitant medications

400 8. Physical Examination – If performed remotely, a historical history and physical report
401 within 18 months of screening appointments may be used but is not required for
402 eligibility. If vitals are not available, may include self-reported weight and height.

- 403 a. Weight (may be self-reported)
- 404 b. Height (may be self-reported)
- 405 c. Blood pressure
- 406 d. Temperature
- 407 e. Heart Rate

408 9. Screening Labs

- 409 a. Hemoglobin A1c (not an eligibility criteria)
- 410 b. Urine or serum pregnancy test for all women of childbearing potential (this test can be
411 done remotely with results sent to the study team)

412 If needed based on medical history, investigators may include baseline chemistry panel, liver
413 function tests, hematocrit, and thyroid stimulating hormone (lab results within one year of
414 screening appointment may be used).

415 Up to 6 months of historical data from the participant's personal insulin pump, glucometer, or
416 continuous glucose monitor may be downloaded or recorded. Data will be obtained from the
417 participant's personal insulin pump and CGM. This data may be obtained through the commercial
418 applications provided by the manufacturer.

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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.

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.

4.4 Demographic Data Survey

The study team has expanded the demographic questionnaire to include additional questions regarding race/ethnicity and socio-economic status (SES). This is in response to the growing body of research in diabetes treatment and technology revealing significant disparities in minoritized population's representation in clinical trials and access to devices/treatments that improve diabetes outcomes. Researchers are being asked by NIH and other funding institutions to make attempts to reduce this under-representation in clinical trial representation. For this reason, 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. However, it is important to note that individuals completing demographic questionnaires are clearly instructed that responses to these items are not mandatory and will not affect their ability to participate in the study

The Demographic Data Survey will be electronically administered once eligibility has been met.

a. Gender

b. Race

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- 453 c. Ethnicity
- 454 d. Marital status
- 455 e. Level of education
- 456 f. Employment status
- 457 g. Household income
- 458 h. Health insurance status
- 459 i. Monthly insulin costs Medical History, including diabetes history

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 8 weeks.

All participants will be asked to use their personal t:slim X2 insulin pump with Control-IQ Technology and a commercially approved Dexcom CGM throughout the study period from Visit 2 through the Final Study Visit. Study supplied phones will be available upon request. The participant may elect to use their personal Dexcom CGM equipment during the trial but will request the study CGM be used whenever possible.

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 commercially approved Dexcom CGM (e.g. G6 or G7) 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 produced online training videos (e.g. <https://www.dexcom.com/training-videos>) to assist in the training session. For new CGM users, the study team will provide a comprehensive training of CGM.

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 t:slim X2 insulin pump for at least two months prior to enrollment and therefore would have obtained training on the device prior to enrollment. Participants who have previously obtained a Control-IQ pump but are not actively using it in CLC mode prior to Visit 2 may initiate Control-IQ using the study CGM following Visit 2. The Tandem training checklist will be followed for each participant who has had less than two months of CLC use of Control-IQ. All participants will receive training on how to change parameters and will demonstrate to the study team their ability to change parameters at Visit 2 (both Group A and B), Visit 3 (both Group A and B if not completed the same day as Visit 2) and Visit 6 (for Group A only). Participants will be directed to the relevant sections of the Tandem User Guide for parameter changes and will be given the Tandem Quick Reference for Parameter Changes.

All participants 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

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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.

All participants 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.

All participants 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 every two-week Auto titration adjustments during applicable study phases. 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 Auto Titration of Insulin Pump Settings

Participants will receive recommendations via the mobile app and/or email for adjustments to insulin parameters derived from the WIT every two weeks. Participants will be allowed to decide if they wish to implement those parameters adjustments as suggested or not and if they choose to do so 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.

These insulin pump setting adjustments suggested by the auto titration module every two weeks are limited to maximum of 10% of their current settings.

5.3 Training on the Investigational Applications

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

PAM (ATM and WST) training consists of:

1. Review of how to access the web-based application (e.g., on a smart phone, iPad, or computer).
2. Review of menus of the application.
3. Review of actual parameters being adjusted (e.g., basal rates, correction factors)
4. Review of frequency of parameter updates (i.e., once biweekly)

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5. Participants will be instructed to contact the study team to review parameters updates at any time if they are concerned about appropriateness of adjustments
6. Participants will be instructed to contact the study team to confirm the institution of parameter adjustments
7. Participants will be instructed how to run a simulation and interpret the results displayed on the screen

BAM training will generally consist of the following:

1. Hands-on training of information modules components and how to access the information modules and an explanation of those modules
2. Participants will be notified that GMI is for informational purposes only and not to be used for short-term changes to insulin settings

Information Modules will include:

1. Time in range and GMI
2. Hypo- and hyperglycemia risk gauge and calendar
3. Standard Ambulatory Glucose Profile (AGP) graph that displays glucose median and percentiles over the last two weeks.²⁷

Study staff will be available 24/7 to assist the participant and troubleshoot the system 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 manufacturer provided cloud servers. The chosen phone will also allow the participant to access the WIT through a mobile application installed on the phone.

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 app, the Tandem 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 cloud. The Tandem Mobile App will be downloaded to their phone in order allow the participant to stream insulin pump data to the Tandem 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 app and the Tandem 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 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. The study team may need to request the participant's username and passwords to access these accounts.

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

566 **5.5 Blood Glucose Training**

567 Participants will use their personal home glucometer.

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

571 **5.6 Blood Ketone Training**

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

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

577 Participants will be instructed to perform blood ketone testing as described in Glycemic Treatment
578 Guidelines (Appendix A-11). A home glucagon emergency kit is considered standard of care.
579 Participants who currently do not have one will be asked to obtain a prescription for the glucagon
580 emergency kit.

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

Chapter 6: Study Procedures

6.1 Baseline Data Collection (Visit 2)

After eligibility is confirmed, two weeks of historical baseline data will be obtained from the study participant. This visit may occur on the same day as the screening visit and should be completed within 8 weeks 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 baseline data collection 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 DexcomCGM while at home prior to the start of the study. If baseline data are not available from the prior two weeks, the study team will look at historical data to identify a two-week data period in which more than 75% of CGM data is available from the participants home data. If participants do not have historical data that meet baseline criteria, then participants may be given a study CGM and trained on its use during Visit 2 to collect baseline data prior to Visit 3.

At Visit 2, participants will be trained in the CGM and given training on the insulin pump, if relevant, as described in section 5.1 and 5.2. Participants will also be trained on blood glucose meter, if relevant, and the ketone meter as described in section 5.5 and 5.6.

Participants not actively using Control-IQ Technology at time of study enrollment will participate in two additional study visits – Visit 2a within 2 days (+/- 1 day) and Visit 2b within 7 days (+/-3 days) of starting use of Control-IQ Technology. During these visits, the study team will:

1. Answer any questions and inquire about any device complaints.
2. Inquire about adverse events, and whether the adverse event was related to study device use.
3. Inquire about ketone readings (a ketone meter download will not be required)
4. Review the downloaded/uploaded data to assess completeness including verifying insulin parameters if applicable.

A pregnancy test at Visit 2 will be repeated as needed if more than 30 days have passed 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.

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6.2 Randomization Visit (Visit 3)

6.2.1 Randomization Criteria

After obtaining at least 2 weeks of baseline data, participants will have a randomization visit. This visit can occur on the same day as visit 2 and should be completed up to 4 weeks from Visit 2. This visit can be conducted either in-person office visit or as a remote visit.

If visit 2 and visit 3 are completed on separate days, all participants will review training on how to change parameters and will demonstrate to the study team their ability to change parameters.

6.2.2 Participants

Participants will be randomized 1:1 to either:

- Group 1:** Control-IQ for 2 weeks followed by Control-IQ+ BAM for 4 weeks followed by Control-IQ+ BAM and PAM for 16 weeks
- Group 2:** Control-IQ+ BAM and PAM for 16 weeks followed by Control-IQ+ BAM for 4 weeks followed by Control-IQ for 2 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 2.1.

6.4 Check-In Visits (Visit 4-13)

These visits will occur either as in-person office visits or remote visits. These visits will occur every two weeks (+/- 5 days). 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 Tandem mobile app or Dexcom mobile app). During these visits, the study team will:

- Answer any questions and inquire about any device complaints.
- Inquire about 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 including verifying insulin parameters with the participant if applicable.
- Record number of pump parameter changes made by the participant since the last check-in visit.
- At the end of each study phase: questionnaires will be completed and any new medications or updates to medical conditions will be assessed.

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6.5 Participant Study Compliance

The study team may contact the study participant as needed to ensure study compliance. Participants will have BAM updates daily and will be asked to check the BAM module on a daily basis during the relevant phase. Participants will be PAM and will have access to that system whenever they wish to interact with it but will be asked to evaluate the parameter suggestions every two weeks.

6.6 Study System Issues

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

The AID system will be 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 14)

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

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

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. Participants may continue to use study related CGM devices already in use at the end of the study per investigator discretion and will be asked to return unused devices.

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:

1. Adverse events

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678 2. Confirm HbA1c completed

679 3. Equipment returned in person or via Federal Express

680 **6.10 Early Withdraw**

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

Chapter 7: Testing Procedures

7.1 Laboratory / Point of Care Testing

7.1.1 HbA1c

1. 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.
2. HbA1c level may be measured by study team using the DCA2000, a comparable point of care device, at time of screening
3. Labs may be obtained at a local laboratory convenient to the participant.

7.1.2 Comprehensive Metabolic Panel/TSH/Hematocrit

1. A blood sample may be obtained at screening to assess kidney and liver functioning, thyroid function or hematocrit if requested by study physician/clinician.
2. Labs may be obtained at the University of Virginia laboratory or 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 and visit 2 (if more than 30 days from date of last study pregnancy test) and any time pregnancy is suspected. Test must be negative to participate in the study. Pregnancy occurring during the study will be recorded.

7.2 Questionnaires

Psychometric questionnaires will be completed at baseline and after completion of each treatment modality (4 time periods). Participants will complete established psychometric scales assessing key diabetes-related quality of life constructs.

1. Diabetes Distress Scale
2. Pittsburgh Sleep Quality Index
3. Hypoglycemia Fear Survey II (HFS-II) in Adults
4. Hyperglycemia Avoidance Scale
5. Technology Acceptance Survey
6. Clarke's Hypoglycemia Awareness scale

7.2.1 Questionnaire Schedule

1. **Group A:** Baseline, post 2 weeks, post 4 weeks, post 16 weeks (study end)
2. **Group B:** Baseline, post 16 weeks, post 4 weeks, post 2 weeks (study end)

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 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.

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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, glucose and ketone meters 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 modules in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4) rapid reversal of hypoglycemia and

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783 hyperglycemia can be achieved, it is the assessment of the investigators that this protocol falls
784 under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of the
785 investigators that this study also presents prospects of direct benefit to the participants and general
786 benefit to others with diabetes.

787 **8.2 General Considerations**

788 The study is being conducted in compliance with the policies described in the study policies
789 document, with the ethical principles that have their origin in the Declaration of Helsinki, with the
790 protocol described herein, and with the standards of Good Clinical Practice (GCP).

791 Whenever possible, data will be directly collected in electronic case report forms, which will be
792 considered the source data.

793 The protocol is considered a significant risk device study, due to the fact that investigational
794 modules of BAM and ATM / WST are experimental. Therefore, an investigational device
795 exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the
796 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:

1. results in death.
2. 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).
3. requires inpatient hospitalization or prolongation of existing hospitalization.
4. results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (life threatening).
5. is a congenital anomaly or birth defect.
6. 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

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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:

1. a serious adverse event as defined in section 9.1.2
2. an adverse device effect as defined in section 9.1.4, unless excluded from reporting in section 9.7
3. an adverse event as defined in section 9.1.4 occurring in association with a study procedure
4. an adverse event as defined in section 9.1.1 which leads to discontinuation of a study device for 2 or more hours
5. hypoglycemia meeting the definition of severe hypoglycemia as defined in section 9.2.1
6. 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
7. 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:

1. the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions;
2. 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;
3. 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:

1. Evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis

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2. Blood ketone level ≥ 1.5 mmol/L and communication occurred with a health care provider at the time of the event
3. Blood ketone level ≥ 3.0 mmol/L, even if there was no communication with a health care provider
4. The event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below:

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 ; and
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:

1. 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.
2. 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.

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.

1. MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.

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2. 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.
3. 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:

1. RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
2. RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
3. 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.
4. NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
5. An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
6. 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.
7. UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

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

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation within 2 weeks. If the adverse event has not been resolved, additional follow-up will

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

1. Component disconnections
2. CGM sensors lasting fewer than the number of days expected per CGM labeling
3. CGM tape adherence issues
4. Pump infusion set occlusion not leading to ketosis
5. Battery lifespan deficiency due to inadequate charging or extensive wireless communication
6. Intermittent device component disconnections/communication failures not leading to system replacement
7. Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
8. 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

1. UADEs must be reported within 10 working days to the FDA after the sponsor first receives notice of the adverse effect.
2. 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.
3. The IDE Sponsor will investigate the UADE and if indicated, report the results of the investigation to the IRB, FDA, and DSMB within 10 working days of the study team becoming aware of the UADE per 21CFR 812.46(b) (2).
4. The FDA and DSMB will determine if the UADE presents an unreasonable risk to participants. If so, the Study PI 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 makes this determination and no later than 15 working days after first receipt notice of the UADE.
5. 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.

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9.9 Stopping Criteria

9.9.1 Participant Discontinuation

Rules for discontinuing study device use are described below.

1. 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
2. The participant requests that the treatment be stopped
3. One distinct episode of DKA events that is related/likely related to the study device
4. One distinct severe hypoglycemia event that is related/likely related to the study device 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 two severe hypoglycemia events or two 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.

9.10 Independent Safety Oversight

A Data and Safety Monitoring Board (DSMB) will review compiled safety data at periodic intervals. In addition, the DSMB will review all DKA and severe hypoglycemia irrespective of relatedness to study device use, and all serious events (including UADEs) related to study device use at the time of occurrence. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding DSMB review will be documented in a separate DSMB document.

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1007 **9.11 Definition of a Data Breach**

1008 A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition,
1009 access, or use of protected health information (PHI) that compromises the security or privacy of
1010 such information.

1011 **Chapter 10: Miscellaneous Considerations**

1012 **10.1 Prohibited Medications, Treatments, and Procedures**

1013 Participants using non-approved insulins at the time of enrollment will be asked to contact their
1014 personal physician to change their prescribed personal insulin to a rapid-acting insulin approved
1015 for use in the t:slim X2 pump (e.g., lispro or aspart) for the duration of the trial.

1016 The devices (insulin pump, CGM) must be removed before Magnetic Resonance Imaging (MRI),
1017 Computed Tomography (CT) or diathermy treatment. Participants may continue in the trial after
1018 temporarily discontinuing use if requiring one of the treatments above.

1019 **10.2 Participant Withdrawal**

1020 Participation in the study is voluntary. Participant may withdraw at any time. For participants who
1021 do withdraw from the study, the study team will determine if their data will be used in analysis.

1022 **10.3 Confidentiality**

1023 For security and confidentiality purposes, subjects will be assigned an identifier that will be used
1024 instead of their name. Protected health information gathered for this study may be shared with the
1025 third-party collaborators. De-identified subject information may also be provided to collaborators
1026 involved in the study after the appropriate research agreement has been executed.

Chapter 11: Statistical Consideration

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 two groups with the same interventions in different order. The randomization list will use a sequence of computer-generated pseudorandom Bernoulli trials. The last 4 weeks of CLC+ABC, the 4 weeks of CLC+BAM and the 2 weeks of CLC alone will be used for analysis of CGM-based metrics of glycemic control.

11.2 Sample Size

We intend to recruit up to 90 users of Control-IQ. Sample Size Determination is based on the effect observed for the primary outcome (CGM-measured TIR 70-180 mg/dL) in our prior studies, specifically TIR differences associated with technology upgrade and HbA_{1c} stratification. We conservatively estimate that the effect size of ABC vs. CLC, in a crossover design with two groups and two repeated measures, will be $f \geq 0.2$. Power calculations assuming 2-sided type 1 error of 0.05, 90% power, correlation of 0.5 between the repeated measures, and attrition of 20% yield a sample size of **N=90** subjects to be randomized, with **N=72** subjects completing the study. This sample size was computed using the G*Power 3 software.²⁵ The effect size assumptions are intentionally conservative to account for uncertainties that are inherent when new technology is introduced, and to further reinforce the hierarchical comparisons described below.

11.3 Outcome Measures

11.3.1 Primary Efficacy Endpoint

CGM-measured % time in range 70-180 over last 4 weeks of CLC+ABC vs 2 weeks of CLC.

11.3.2 Statistical Hypotheses:

The primary outcome for this study is CGM-measured % in range 70-180 mg/dL over the last 4-week periods on CLC+ABC vs 2 weeks of the current CLC system. The intervention will be considered effective if the CLC+ABC is superior to the CLC alone in a crossover design using a statistical significance of $\alpha=0.05$.

The null/alternative hypotheses are:

Null Hypothesis: There is no difference in mean CGM-measured TIR 70-180 mg/dL between CLC+ABC and CLC;

Alternative Hypothesis: The mean CGM-measured TIR 70-180 mg/dL is different for CLC+ABC and CLC.

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11.3.3 Secondary Outcomes

To preserve the overall type 1 error for selected key secondary endpoints, a hierarchical testing procedure will be used. If the primary analysis for time in range described above results in a statistically significant result ($p < 0.05$), then testing (similar to the model for the primary outcome) will proceed to the next outcome metric in the following order:

1. CGM-measured % in range 70-180 mg/dL (primary outcome);
2. CGM-measured % above 180 mg/dL during the day;
3. CGM-measured % below 70 mg/dL during the day;
4. CGM-measured mean glucose, and
5. CGM-measured coefficient of variation during the day.

This process continues iteratively moving to the next variable down on the list until a non-significant result ($p \geq 0.05$) is observed, or all variables have been tested. If a non-significant result is encountered, then formal statistical hypothesis testing is terminated and any variables below on the list are not formally tested and analysis of these variables become exploratory.

Other Secondary Endpoints: The following endpoints are considered exploratory including questionnaire data.

1. TIR 70-140 mg/dL and TIR < 60 mg/dL;
2. LBG1 and HBGI¹⁰;
3. TIR > 250 mg/dL and TIR > 300 mg/dL;
4. HbA1c at end of study;
5. Diabetes Distress Scale;
6. Pittsburgh Sleep Quality Index;
7. Fear of Hypoglycemia Survey;
8. Hyperglycemia Avoidance Scale;
9. Technology Acceptance Survey;
10. Clarke's Hypoglycemia Awareness scale.

Questionnaires: All questionnaires will be administered online, and subjects can skip specific questionnaires or items within a questionnaire. All questionnaires will be scored according to the instructions given in the manual. In case no manual exists for a given questionnaire or the manual does not provide guidance on how to handle missing, then the following criteria will be applied. At least 75% of the questions must be completed to be included in the analysis. This 75% rule will be applied separately for the total score and each subscale so it is possible the sample size will be different for some subscales. The score used for analysis will be based on the average among the questions that were answered and then scaled accordingly.

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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:

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

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:

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

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

11.7 Analytical Approach

Primary and Secondary Analyses: The study design includes repeated measures on all outcomes; 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 “Group” as a fixed factor. The models will adjust for age, prior CGM use and pump use 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). A mixed model is also more flexible and will allow us to address additional questions, such as introducing time between sessions as a continuous variable.^{26,27}

The general principles that will be followed during analysis are:

1. The analysis will follow an Intention-to-treat (ITT) approach.
2. All randomized participants will be included in the primary and secondary analyses of CGM metrics.
3. 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.
4. 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; however, the differences between treatment modalities are expected to follow a normal distribution.
5. Per Protocol analyses will be conducted excluding periods of time when the system was not in use, e.g., periods of system downtime due to the necessity to fix software problems. This type of forced discontinuations of system use have occurred in previous studies and were handled the same way.

Sensitivity Analysis: The primary and secondary hierarchical analyses will include adjustment for pre-specified covariates. Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated by additionally including factors potentially associated with the outcome for which there is an imbalance between groups (assessed based on clinical judgement reviewing the distributions in the two treatment arms, not on a p-value).

Missing Data: All subjects will be included in primary analyses and any missing post-randomization data will be handled using direct likelihood. It is also worth emphasizing that any statistical method for handling missing data makes a number of untestable assumptions. The goal will be to minimize the amount of missing data in this study so that results and conclusions will not be sensitive to which statistical method is used. To that end, sensitivity analyses will be performed to explore whether results are similar for primary and secondary hierarchical analysis

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- 1163 when using different methods. The following methods will be applied: (i) Direct likelihood; (ii)
1164 Rubin's multiple imputation, and (iii) Available cases only.
- 1165 Summary statistics (mean $\pm$ SD or median (quartiles)) will be reported for all CGM-based metrics.

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.

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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 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 participant will sign the informed consent document prior to any procedures being done specifically for the study. 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. The study team will follow the FDA part 11 compliant process of verification of reviewing two forms of identification if signing electronically off site. A HIPAA compliant video conferencing tool will be utilized during the consenting process of the telecommunication screening visit to facilitate review of the participant's identification. 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.

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13.3.2 Participant and Data Confidentiality

1224
1225 The study monitor, representatives of the IRB or device company supplying study product may
1226 inspect all documents and records required to be maintained by the investigator, including but not
1227 limited to, medical records (office, clinic, or hospital) for the participants in this study.

1228 The study participant's contact information will be securely stored at the clinical site for internal
1229 use during the study. At the end of the study, all records will continue to be kept in a secure
1230 location for as long a period as dictated by local IRB and Institutional regulations.

1231 Study participant research data, which is for purposes of statistical analysis and scientific reporting,
1232 will be transmitted to and stored at the University of Virginia Center for Diabetes Technology.
1233 The study data entry and study management systems used by research staff will be secured and
1234 password protected. At the end of the study, all study databases may be de-identified and archived
1235 at the University of Virginia Center for Diabetes Technology.

Chapter 14: References

1. Kovatchev BP, Anderson SM, Raghinaru D, et al, for the iDCL Trial Research Group. Randomized Controlled Trial of Mobile Closed-Loop Control. *Diabetes Care*. 2020; 43:607-615. PMID: 31937608
2. 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.
3. 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.
4. Kovatchev BP, Cobelli C. Glucose variability: timing, risk analysis, and relationship to hypoglycemia in diabetes. *Diabetes Care*. 2016; 39: 502-510. PMCID: PMC4806774
5. Ching Ng W-K, Ching MK W. *Markov Chains*. Springer-Verlag; 2006.
6. Kovatchev BP. *Decision Support System for Patients with Diabetes: Concept, Goals, and Feasibility*. Advanced Technologies and Treatments for Diabetes (ATTD), Berlin, Germany, 2019.
7. Kovatchev BP. *Building a Virtual Image of a Patient – the VIP Approach to Precision Medicine for Diabetes*. Advanced Technologies and Treatments for Diabetes (ATTD), Berlin, Germany, 2019
8. Kovatchev BP, Mendosa P, Anderson SM, Hawley JS, Ritterband LM, Gonder-Frederick L. Effect of automated bio-behavioral feedback on the control of type 1 diabetes. *Diabetes Care*. 2011; 34: 302-307. PMCID: PMC3024338
9. Fabris C, Heinemann L, Beck RW, Cobelli C, Kovatchev B. Estimation of Hemoglobin A1c From Continuous Glucose Monitoring Data in Individuals with Type 1 Diabetes: Is Time in Range All We Need? *Diabetes Technol Ther*. 2020 doi: 10.1089/dia.2020.0236
10. Kovatchev BP. Metrics for glycaemic control: from HbA1c to continuous glucose monitoring. *Nature Reviews Endocrinology*. 2017; 13: 425-436. PMID: 28304392
11. Patek SD, Lv D, Ortiz EA, Hughes-Karvetski C, Kulkarni S, Zhang Q, Breton MD. Empirical representation of blood glucose variability in a compartmental model. In *Prediction Methods for Blood Glucose Concentration 2016* (pp. 133-157). Springer, Cham.
12. Colmegna P, Wang K, Garcia-Tirado J, Breton MD. Mapping data to virtual patients in type 1 diabetes. *Control Engineering Practice*. 2020 Oct 1;103:104605.
13. Hughes J, Gautier T, Colmegna P, Fabris C, Breton MD, Replay Simulations with Personalized Metabolic Model for Treatment Design and Evaluation in Type 1 Diabetes. *J Diabetes Sci Technol*. 2021 Nov;15(6):1326-1336. PMID: 33218280.
14. Brown S, Raghinaru D, Emory E, and Kovatchev BP. First Look at Control-IQ: A New-Generation Automated Insulin Delivery System. *Diabetes Care* 2018; 41:2634-2636, PMID: 30305346

CLINICAL PROTOCOL

- 1274 15. Kovatchev BP, Kollar L, Anderson SM, Barnett C, Breton MD, Carr K, Gildersleeve R, Oliveri
1275 MC, Wakeman CA, Brown SA. Evening and overnight closed-loop control versus 24/7
1276 continuous closed-loop control for type 1 diabetes: a randomized crossover trial. *Lancet Digital*
1277 *Health* 2020; 2: e64-e73; PMID: 32864597.
- 1278 16. Ekhlaspour L, Forlenza GP, Chernavvsky D, Maahs DM, Wadwa RP, DeBoer MD, Messer
1279 LH, Town M, Pinnata J, Kruse G, Kovatchev BP, Buckingham BA, Breton MD. Closed Loop
1280 Control in Adolescents and Children During Winter Sports: Use of the Tandem Control-IQ AP
1281 System. *Pediatr Diabetes* 2019; 20(6):759-768. PMID: 31099946.
- 1282 17. Polonsky WH, Fisher L, Earles J, Dudl RJ, Lees J, Mullan J, Jackson RA. Assessing
1283 Psychosocial Distress in Diabetes: Development of the Diabetes Distress Scale. *Diabetes Care*
1284 2005; 28:626-631. PMID: 15735199157.
- 1285 18. Fisher L, Hessler DM, Polonsky WH, Mullan J. When Is Diabetes Distress Clinically
1286 Meaningful? Establishing cut points for the Diabetes Distress Scale. *Diabetes Care* 2012;
1287 35:259–264. PMID: 22228744
- 1288 19. Buysse, DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality
1289 Index (PSQI): A new instrument for psychiatric research and practice. *Psychiatry Research*
1290 1989; 28:193-213. PMID: 2748771.
- 1291 20. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia:
1292 quantification, validation, and utilization. *Diabetes Care*. 1987; 10: 617-21. PMID:
1293 3677982155.
- 1294 21. Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the
1295 hypoglycemia fear survey-II for adults with type 1 diabetes. *Diabetes Care*. 2011; 34(4): 801-
1296 806. PMID: 21346182.
- 1297 22. Singh H, Gonder-Frederick L, Schmidt K, Ford D, Vajda KA, Hawley J, Cox DJ.
1298 Assessing hyperglycemia avoidance in people with type 1 diabetes. *Diabetes Management*.
1299 2014; 4: 263–271. doi: 10.2217/DMT.14.3180.
- 1300 23. Weissberg-Benchell J, Hessler D, Polonsky WH, and Fisher L. Psychosocial impact of the
1301 bionic pancreas during summer camp. *J Diabetes Sci Technol* 2016; 10:840–844. PMID:
1302 26993252182.
- 1303 24. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D., Polonsky W. Reduced
1304 awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic
1305 frequency and associated symptoms. *Diabetes Care*. 1995; 18: 517-22. PMID: 7497862
- 1306 25. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis
1307 program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;
1308 39:175-191. PMID: 17695343.
- 1309 26. West BT. Analyzing longitudinal data with the linear mixed models procedure in SPSS.
1310 *Evaluation & the Health Professions*. 2009; 32: 207-228. PMID: 19679634.

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-
- 1311 27. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures
1312 data and its reflection in papers published in the Archives of General Psychiatry. Arch Gen
1313 Psychiatry. 2004; 61: 310-7, PMID: 14993119.
- 1314 28. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA,
1315 Cefalu WT, Close KL, Cobelli C, Dassau E, DeVries JH, Donaghue KC, Dovc K, Doyle FJ
1316 3rd, Garg S, Grunberger G, Heller S, Heinemann L, Hirsch IB, Hovorka R, Jia W, Kordonouri
1317 O, Kovatchev B, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy HR, Nimri
1318 R, Nørgaard K, Parkin CG, Renard E, Rodbard D, Saboo B, Schatz D, Stoner K, Urakami T,
1319 Weinzimer SA, Phillip M. Clinical Targets for Continuous Glucose Monitoring Data
1320 Interpretation: Recommendations From the International Consensus on Time in Range.
1321 Diabetes Care. 2019 Aug;42(8):1593-1603. doi: 10.2337/dci19-0028. Epub 2019 Jun 8. PMID:
1322 31177185.