The International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of the Artificial Pancreas

A Pivotal Study of t:slim X2 with Control-IQ Technology

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AP	Artificial Pancreas
BG	Blood Glucose
BT/BTLE	Bluetooth, Bluetooth low energy
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CLC	Closed-Loop Control
CSII	Continuous Subcutaneous Insulin Injection
CTR	Control-to-Range
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
EC	European Commission
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
ID	Identification
iDCL	International Diabetes Closed Loop
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IQR	Interquartile Range
JDRF	Juvenile Diabetes Research Foundation
NIH	National Institutes of Health
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
RBM	Risk-Based Monitoring
SAP	Sensor-Augmented Pump
SD	Standard Deviation
TDD	Total Daily Dose
UI	User Interface
UVA	University of Virginia

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Signature Page

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Protocol Identifying Number: DCLP3

IND/IDE Sponsor: University of Virginia

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JCHR Principal Investigator	
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Signature / Date	John Lum I am approving this document 2018-12-17 08:31-05:00
Protocol Chair/Director	
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Signature / Date	Sue Brown Digitally signed by Sue Brown Date: 2018.12.17 11:31:22 -05'00'

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: **The International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of the Artificial Pancreas - A Pivotal Study of t:slim X2 with Control-IQ Technology**

Protocol Version/Date: v10.0/5 NOV 2018

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 and providing the Jaeb Center for Health Research, which serves as the Coordinating Center for the protocol, with complete and timely information, as outlined in the protocol. 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: _____ / _____ / _____
dd mmm yyyy

Investigator's Name: _____

Site Name/Number: _____

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	The International Diabetes Closed Loop (iDCL) Trial: Pivotal Trial of t:slim X2 with Control-IQ Technology
Précis	A randomized controlled trial of 6 month at home closed loop system vs. sensor-augmented pump.
Investigational Device	t:slim X2 with Control-IQ and Dexcom G6 system
Objectives	The objective of the study is to assess efficacy and safety of a closed loop system (t:slim X2 with Control-IQ Technology) in a large randomized controlled trial.
Study Design	Randomized Clinical Trial with 2:1 randomization to intervention with the closed loop system vs. sensor-augmented pump for 6 months. See Figure 1.
Number of Sites	Seven US clinical sites
Endpoint	The primary outcome is time in target range 70-180 mg/dL measured by CGM in CLC group vs. SAP group at 6 months
Population	**Key Inclusion Criteria** • Type 1 Diabetes • Ages 14 and older **Key Exclusion Criteria** • Use of any non-insulin glucose-lowering agents except metformin
Sample Size	Up to seven clinical sites in the United States may enroll up to 225 total participants with the goal of randomizing 168 participants such that at least 150 participants complete the 6-month randomized trial.
Treatment Groups	Randomized Trial • Intervention Group: t:slim X2 with Control-IQ Technology and Study CGM. • Control Group: Sensor-augmented pump (SAP) with no automated insulin delivery, and study CGM
Participant Duration	6-8 months
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. Eligible participants not currently using an insulin pump and Dexcom G4, G5, or G6 CGM with minimum data requirements will initiate a run-in phase of 2 to 8 weeks that will be customized based on whether the participant is already a pump or CGM user. Participants who skip or successfully complete the run-in will be randomly assigned 2:1 to the use of closed-loop control (CLC group) using t:slim X2 with Control-IQ Technology vs SAP for 6 months.

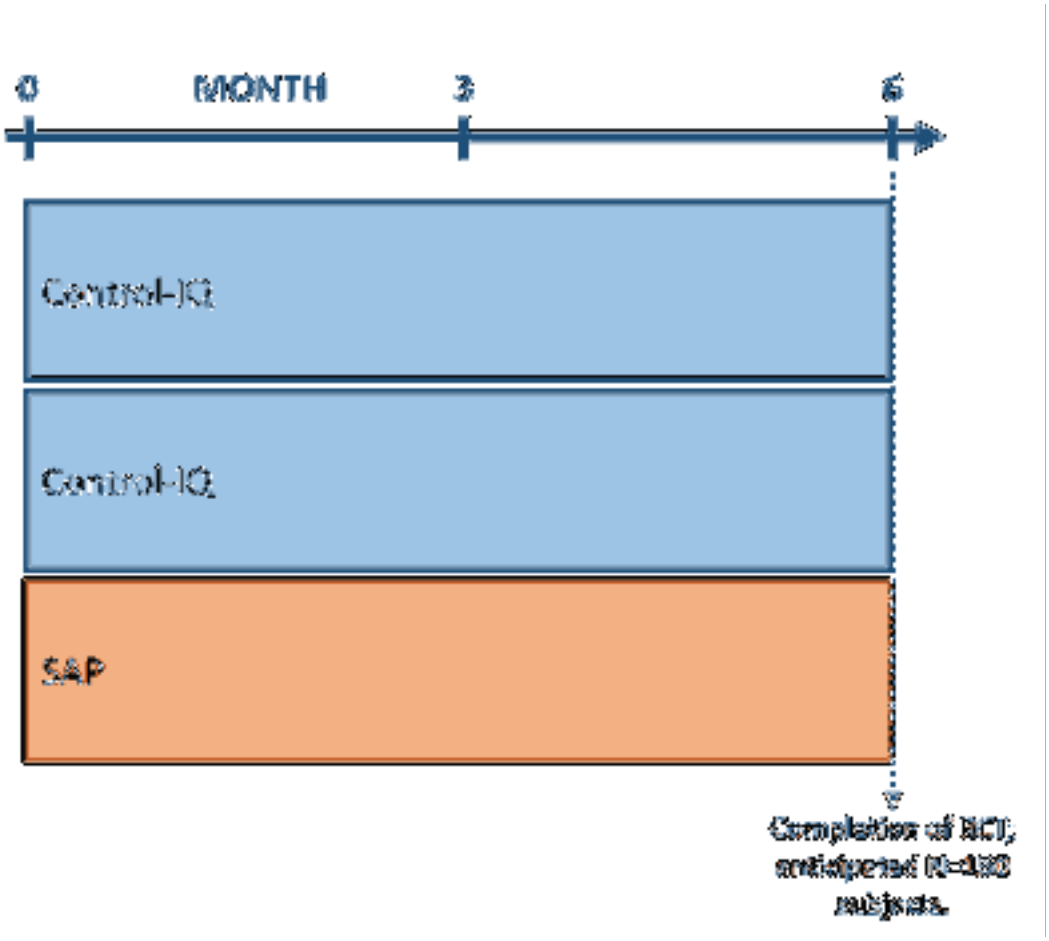

Figure 1: Study Design: Participants Randomized 2:1 Control-IQ vs. SAP

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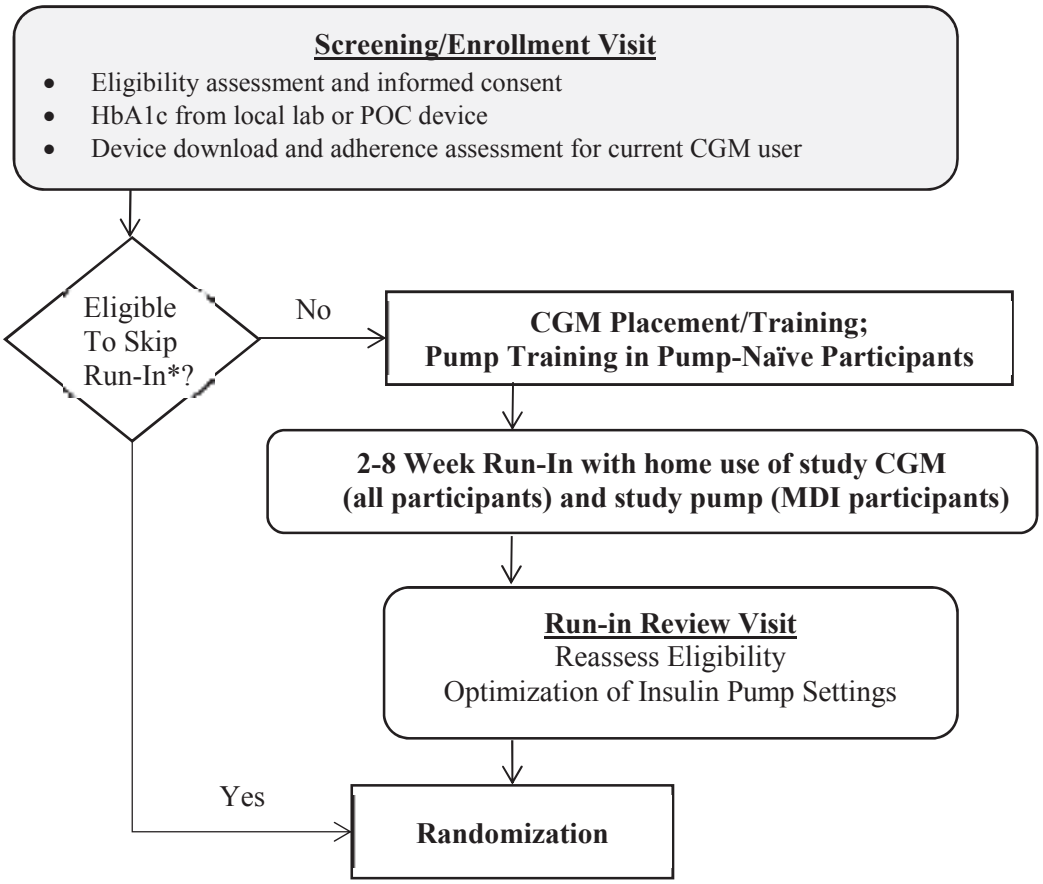
SCHEMATIC OF STUDY DESIGN



*Current use of insulin pump and Dexcom G4, G5, or G6 CGM with readings captured on at least 11 out of the previous 14 days

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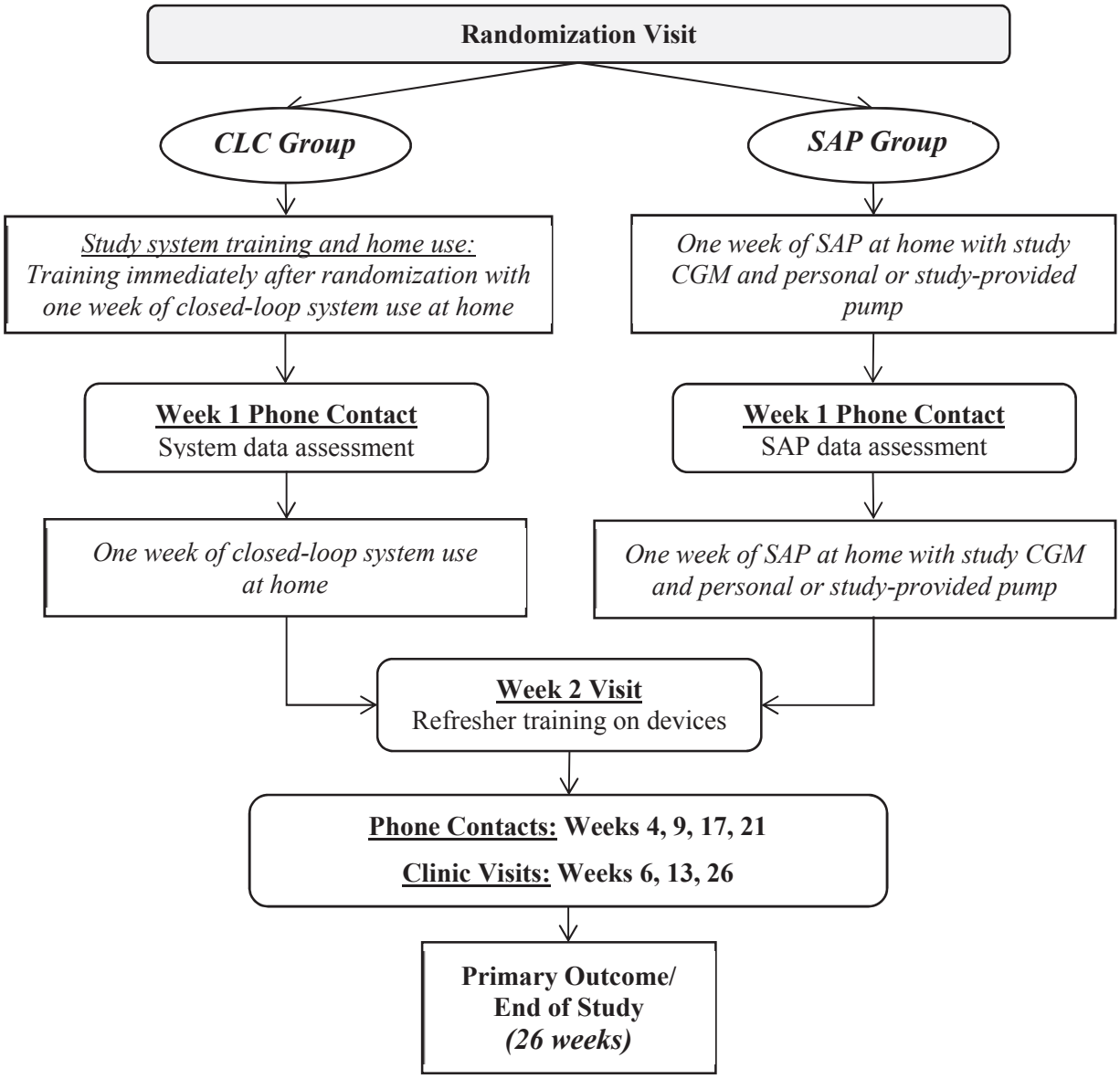
204 **Figure 2: Schematic of Study Design (Pre-Randomization)**



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206 **Figure 3. Schematic of Study Design (Post-Randomization)**

207 **Table 1. Schedule of Study Visits and Procedures**

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	Pre	Pre	0	1w	2w	4w	6w	9w	13w	17w	21w	26w
Visit (V) or Phone (P)	V	V	V	P	V	P	V	P	V	P	P	V
Comment	Screen/ Enroll	Run-in	Rand									
Eligibility Assessment	X	X	X									
HbA1c (DCA Vantage or similar point of care device, or local lab)	X		X						X			X
HbA1c (Central lab)			X						X			X
C-peptide (Central lab) and blood glucose assessment			X									
Pregnancy test (females of child-bearing potential)	X		X						X			
Device Data download(s)	X	X	X	X	X	X	X	X	X	X	X	X
Review diabetes management and AEs		X	X	X	X	X	X	X	X	X	X	X
Questionnaires as defined in section 7.2			X						X			X

Chapter 1: Background Information

1.1 Introduction

The Tandem X2 insulin pump with Control-IQ Technology is a third-generation closed-loop control (CLC) system retaining the same control algorithm that was initially tested by UVA's DiAs system and then implemented in the inControl system. DiAs is described in 13 IDEs (see IDEs 1-12 and 14 in the list below) and inControl is described in IDEs G160097, G160181, G150240, G140169/S010. For complete algorithmic and clinical background, we refer to these IDEs and to a number of scientific publications that describe glycemic control outcomes and clinical impressions from the use of these systems (see list of 25 peer-reviewed papers and scientific presentations under Bibliography). Overall, this control algorithm has been implemented in two mobile platforms (DiAs and inControl) and has been tested in 30 clinical trials by 450 adults and children with type 1 diabetes for over 280,000 hours of use to date in the U.S. and overseas.

As described in the Background, this project is a result from a sequence of clinical trials that have tested extensively the control system and in several centers in the U.S. and overseas. The following 18 IDEs reflect this progress:

1. IDE #G110095: Feasibility study of closed loop control in type 1 diabetes using heart rate monitoring as an exercise marker, approved 10/08/2011;
2. IDE #G120032: Early feasibility (pilot) study of outpatient control-to-range; 3/2/2012;
3. IDE #G120210: Early feasibility study 2 of outpatient control-to-range; 10/12/2012;
4. IDE #G130118: DiAs control-to-range nocturnal closed-loop camp study; 6/19/2013;
5. IDE #G130121: Optimizing closed-loop control of type 1 diabetes mellitus in adolescents; 6/19/2013;
6. IDE# G130142: Closed loop control in adolescents using heart rate as exercise indicator; 7/16/13;
7. IDE #G130143: Early feasibility study of adaptive advisory/automated (AAA) control of type 1 diabetes; 7/19/2013;
8. IDE #G140066: Full day and night closed-loop with DiAs platform; 5/9/14.
9. IDE #G140068: Unified Safety System (USS) Virginia Closed Loop versus sensor augmented pump therapy overnight in type 1 diabetes; 5/14/2014;
10. IDE #G140089: Outpatient control-to-range: Safety and efficacy with day-and-night in-home use; 6/6/2014;
11. IDE #G140169: Unified Safety System (USS) Virginia Closed-Loop versus Sensor Augmented Pump (SAP) therapy for hypoglycemia reduction in type 1 diabetes; 10/3/2014.
12. IDE #G150221: Reducing risks and improving glucose control during extended exercise in youth with T1DM: The AP Ski Camp; 11/09/2015;
13. IDE #G150240: Project Nightlight: Efficacy and system acceptance of dinner/night vs. 24 hr closed loop control; 11/12/2015;

14. IDE #G160047: Closed-loop in young children 5-8 years old using DiAs platform; 03/29/2016;
15. IDE #G160097: Clinical Acceptance of the Artificial Pancreas: the International Diabetes Closed-Loop (iDCL) Trial/Research Site Training Protocol; 06/03/16.
16. IDE#G160181: PROTOCOL 1 for "Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed Loop (iDCL) Trial; 09/21/16
17. IDE#G170255: Protocol 3 for "Pilot Trial of t:slim X2 with Control-IQ Technology";11/16/17 and IDE#G170255/S001 Protocol 3 for "Training Study of t:slim X2 with Control-IQ Technology"; 11/16/17
18. IDE#G170267: "Real-Time Monitoring and Glucose Control During Winter-Sport Exercise in Youth with Type 1 Diabetes: The AP Ski Camp Continued"; 11/21/17

We further reference pre-submission Q170885 and our discussion with FDA on July 18, 2017 regarding the structure of studies intended to test inControl implemented on t:slim X2. Based on the input provided by the Agency, we initially defined a series of three studies leading to a future pivotal trial of this system (36-48 hr Pilot Study, 2 week at home Training Study, followed by the Pivotal Trial). Since the time of the initial discussion, we have concluded a successful Pilot of 5 Adult (December 2017) and a Ski Camp with 12 Teenagers (January 2018) on the System. We have also received approval for the use of this system in a long-term home study (Project Nightlight/G#150240/S008). The Project Nightlight Study will now replace the previous Training Study as noted in Figure 4.

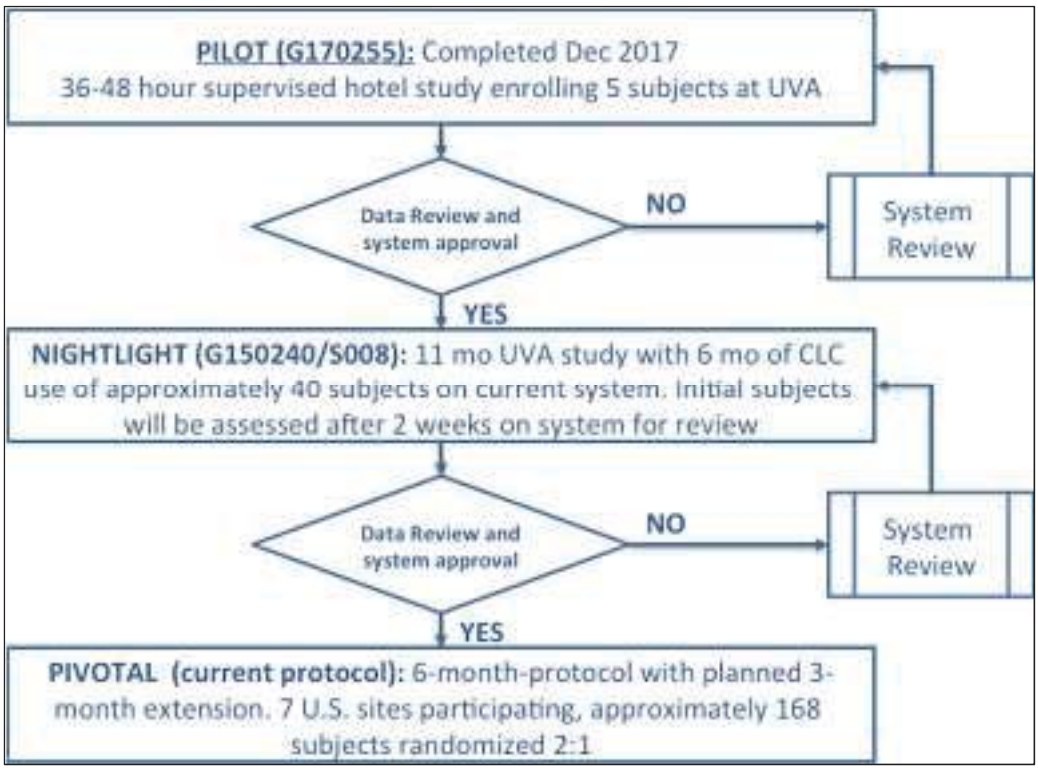

Figure 4: Sequence of planned studies leading to this pivotal trial of the Tandem X2 insulin pump with Control-IQ Technology

A successful pilot of 5 Adults (mean age 52.8 yrs; 3F/2M, mean A1c 6.5%) with Type 1 Diabetes was completed in December 2017. In this pilot study, the system was challenged with a variety of scenarios including: Pump disconnection, CGM sensor removal without stopping session, CGM sensor change, Basal Rate change, Cartridge Change, Extended Bolus, Calibration at non-ideal conditions, Stopping Control-IQ, Reset Sleep Time, Restaurant Meals and Exercise (treadmill/walk). The study demonstrated excellent connectivity with 98% time in closed-loop control and 94% time CGM is available during 196 hours of use.

Table 2. Pilot Study results based on time in closed-loop

METRIC (COMPUTED DURING CLOSED-LOOP USE)	OVERALL	DAYTIME	NIGHTTIME
Mean glucose (mg/dL)	**129**	**135**	**121**
Coefficient of variation (median)	27%	27%	21%
% below 54 mg/dL (median)	0.7%	0.0%	0.0%
% below 60 mg/dL (median)	1.1%	2.0%	0.0%
% below 70 mg/dL (median)	2.9%	4.1%	1.0%
Percent in range 70-180 mg/dL (mean)	**87%**	**82%**	**94%**
% above 180 mg/dL (median)	5%	8%	6%
% above 250 mg/dL (median)	0%	0%	0%
% above 300 mg/dL (median)	0%	0%	0%

Closed-Loop Control System

The Closed-Loop Control System contained in t-slim X2 with Control-IQ Technology is described in Master File MAF-2032/A008. Control-IQ Technology is derived from inControl previously described in IDE# G160097, G160181, G150240 and G140169/S010. The CLC is an "artificial pancreas" (AP) application that uses advanced closed loop control algorithms to automatically manage blood glucose levels for people with Type 1 Diabetes. The system modulates insulin to keep blood glucose in a targeted range. The system components include the t:slim X2 with Control-IQ Technology and the Dexcom CGM G6.

Figure 5. t:slim X2 with Control-IQ and Dexcom G6 system

1.2 Rationale

The objective of this randomized clinical trial is to 1) assess the efficacy and safety of the Control-IQ closed loop system over a 6 month period, the data from which may be used for subsequent PMA application for this system and 2) investigate longer term use of the system compared with switching to sensor-augmented pump therapy.

1.3 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 this.

1.3.1 Known Potential Risks

1.3.1.1 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.

1.3.1.2 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 fingersticks are part of the usual care for people with diabetes.

1.3.1.3 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.

1.3.1.4 Risk of Hypoglycemia

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

of hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery.

1.3.1.5 Risk 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.

1.3.1.6 Risk of Device Reuse

The study CGM system is labeled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The transmitter and receiver may be reused during the study after cleaning the device using a hospital-approved cleaning procedure. The transmitter is attached to the sensor but does not enter the skin and the receiver is a hand held device. Participants will be informed that FDA or relevant national authorities have approved these devices for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

The study insulin pump is labeled for single-patient use. During the study, this device may be reused after cleaning adhering to a hospital-approved cleaning procedure. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.) Participants will be informed that FDA or relevant national authorities typically approve the insulin pump device for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

The study blood glucose meter and blood ketone meter are labeled for single-patient use. During the study, only one person can use each device as there are rare risks that bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

1.3.1.7 Questionnaire

As part of the study, participants will complete questionnaires which include questions about their private attitudes, feelings and behavior related to the investigational equipment as well as managing diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

1.3.1.8 Other Risks

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

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

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

1.3.2 Known Potential Benefits

One purpose of this research is to reduce the frequency of hypoglycemia and severe hypoglycemic events. Hypoglycemia is the number one fear of many individuals and families with someone who has type 1 diabetes and this fear often prevents optimal glycemic control.

It is expected that this protocol will yield increased knowledge about using an automated closed-loop to control the glucose level and is intended to develop data to support a future PMA-application. The individual participant may not benefit from study participation.

1.3.3 Risk Assessment

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

1.4 General Considerations

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

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

There is no restriction on the number of participants to be enrolled by each site toward the overall recruitment goal.

The protocol is considered a significant risk device study, due to the fact that the closed loop system is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of having 168 participants enter the randomized trial, with the expectation that 150 participants will complete the 6-month randomized trial. A maximum of 225 individuals may be enrolled into screening for the study in order to achieve this goal.

Study participants will be recruited from 7 clinical centers in the United States without regard to gender, race, or ethnicity. There is no restriction on the number of participants to be enrolled by each site toward the overall recruitment goal.

A study goal will be to have the following minimum numbers of participants complete the trial in the specified subgroups at the time of enrollment:

- At least 50 participants with HbA1c ≥7.5% and 50 participants with HbA1c <7.5%
- At least 50 participants in the age range 14 to <26 and 50 participants ≥26 years old
- At least 30 participants who are on multiple daily injections (MDI) rather than pump
- At least 30 participants who are CGM-naïve (defined as not using a CGM in the prior 14 days)

2.1.1 Informed Consent and Authorization Procedures

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

For potential study participants ≥18 years old, the study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

For potential participants under 18 years of age, a parent/legal guardian (referred to subsequently as "parent") will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Potential participants meeting the IRB's minimum age of assent will be given a Child Assent Form to read and discuss with his/her parents and study personnel. If the parent and child agree to participate, the Informed Consent Form and Child Assent Form will be signed. A copy of the consent form will be provided to the participant and his/her parent and another copy will be added to the participant's study record.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

A participant is considered enrolled when the informed consent form has been signed.

2.2 Participant Inclusion Criteria

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

1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year
2. Familiarity and use of a carbohydrate ratio for meal boluses.
3. Age ≥14.0 years old
4. For females, not currently known to be pregnant

   If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing 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.
5. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact the participant in case of an emergency.
6. Willingness to suspend use of any personal CGM for the duration of the clinical trial once the study CGM is in use
7. Willingness to use a regular insulin pump during the study with no automatic insulin adjustment based on glucose level when assigned to participate in an SAP group
8. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol
9. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study.
10. Total daily insulin dose (TDD) at least 10 U/day
11. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (see section 2.3)

2.3 Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation.

1. Concurrent use of any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas).
2. Hemophilia or any other bleeding disorder
3. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk

4. Participation in another pharmaceutical or device trial at the time of enrollment or during the study
5. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc. or TypeZero Technologies, LLC, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

2.4 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by study personnel and local laboratory testing if needed to screen for exclusionary medical conditions.

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

2.4.1 Data Collection and Testing

A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or designee (a physician, fellow, nurse practitioner or a physician assistant).

The following procedures will be performed/data collected/eligibility criteria checked and documented:

- Inclusion and exclusion criteria assessed
- Demographics (date of birth, sex, race and ethnicity)
- Contact information (retained at the site and not entered into study database)
- Medical history
- Concomitant medications
- Physical examination to include:
  - Weight, height
  - Vital signs including measurement of blood pressure and pulse

- Blood draw for:
  - HbA1c level measured using the DCA2000 or comparable point of care device or local lab
  - Measurement performed as part of usual clinical care prior to obtaining informed consent for participation in the trial may be used
  - Measurement must be made within two weeks prior to enrollment
- Urine or serum pregnancy test for all women of child-bearing potential

Screening procedures will last approximately 1-2 hours.

Chapter 3: Run-In Phase

3.1 Run-in Phase Overview

This phase may begin immediately after enrollment is complete or may be deferred for a maximum of 28 days. The purpose of this run-in phase is to 1) assess compliance with study procedures, 2) to introduce the study CGM to study participants without current use of a CGM and 3) to introduce an insulin pump to participants who have not previously used an insulin pump.

Participants who do not currently use an insulin pump and a Dexcom G4, G5, or G6 CGM with readings captured on at least 11 out of the previous 14 days at the time of enrollment will be required to participate in the run-in phase. Participants will use the study CGM for a minimum of 11 days with a goal of at least 14 days during the run-in phase. Participants who are on MDI at enrollment will receive a study pump to use and will receive training as detailed below. All participants will receive training on the study CGM as detailed below. This will be an unblinded use of the study CGM.

Initiation of CGM

The participant will be provided with sensors and instructed to use the study CGM on a daily basis. Training will be provided to participants not experienced with CGM use as to how to use the CGM in real-time to make management decisions and how to review the data after an upload for retrospective review. Participants using a personal CGM prior to the study will discontinue the personal CGM beginning in this period.

The participant will be observed placing the sensor. The study CGM user's guide will be provided for the participant to take home.

Initiation of Pump

Pump-naïve participants who have not used a CGM in the 14 days prior to enrollment will first complete a CGM-only Run-in period of approximately 14 days prior to initiating study pump use.

Participants who are pump-naïve will be provided with a study pump similar to the pump used with the closed-loop system, but with the closed-loop control feature either absent or deactivated, and will be instructed to use the pump on a daily basis. An initial basal insulin profile will be customized on a per-participant basis. Total daily insulin dose will be reduced by approximately 20% as a general rule, with a recommended method outlined in a separate procedures manual. Further adjustments to total daily dose (TDD) and intraday basal rate profile may be made during the course of the run-in period.

Participants will complete training on the study pump as detailed below.

- The participant will be fully instructed on the study insulin pump. A qualified system trainer will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board (IOB) and correction boluses.

Additional topics are not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.

- The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed.
- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.

Blood Glucose and Ketone Testing

Participants will receive supplies for blood glucose and ketone testing.

- Blood glucose testing
  - Participants will be provided with a study blood glucose meter, test strips, and standard control solution to perform quality control (QC) testing at home per manufacturer guidelines.
  - All study blood glucose meters will be QC tested with at least two different concentrations of control solution if available during all office visits. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The participant will be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.
  - Participants will be reminded to use the study blood glucose meter for all fingerstick BGs during the study.
  - Participants will be given guidelines for treatment of low or high blood glucose.
- Blood ketone testing
  - Participants will be provided with a study blood ketone meter, test strips, and standard control solution to perform QC testing at home per manufacturer guidelines.
  - All study blood ketone meters will be QC tested with at least two different concentrations of control solution if available during all office visits. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The participant will be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.
  - Participants will be instructed to perform blood ketone testing as described in section 6.2.4
  - Participants will be given guidelines for treatment of elevated blood ketones

- Participants will be required to have a home glucagon emergency kit. Participants who currently do not have one will be given a prescription for the glucagon emergency kit.

Assessment of Successful Completion of the Run-in Phase

Enrolled participants will return approximately 14 days after the initiation of the run-in phase to assess progress or successful completion of the phase. If needed, one or more interim visits or phone contacts may occur to assist the participant with any system use issues. Visit procedures will include the following:

- Assessment of compliance with the use of the CGM (and study pump if applicable)
- Assessment of skin reaction in areas where a CGM sensor was worn
- Assessment of eligibility to continue to the RCT phase of the study

The CGM data (and pump data if applicable) will be downloaded and reviewed. CGM-naïve MDI participants who have completed an initial CGM-only use period without any safety issues will be transitioned to a study pump as described above and will begin home use of CGM use with study pump for approximately 14 days before returning to the clinic for another progress assessment. MDI participants will be contacted by study staff within approximately 24hrs, 72hrs, and 1 week after pump initiation to answer any questions related to device use prior to the 2 week visit. All subjects may have unlimited contact with the study team as needed.

To enter the randomized trial, participants must have obtained CGM readings on at least 11 out of the previous 14 days, and pump-naïve patients must have successfully used the study pump each day. If a participant fails to meet these criteria, or if it is determined that the participant will benefit from additional time with equipment training, the run-in period may be extended at the discretion of the investigator. One or two additional periods may occur, each a minimum of 11 days with a goal of at least 14 days, with another clinic visit to assess results after each period using the same criteria as above. The run-in duration will therefore vary from approximately 2 to 8 weeks, depending on the participant. Additional visits and phone contacts for further training are at investigator discretion.

An assessment of CGM and pump knowledge will be made and the participant must demonstrate sufficient competency to proceed to the RCT. The trainer and participant will review the individual items listed on the pump training checklist to ensure competency.

Participants who are unable to meet the CGM or study pump compliance requirements will be withdrawn from the study, as will participants who no longer meet all of the inclusion and exclusion criteria.

If the participant is eligible to continue in the study, study staff will follow the procedure for insulin pump optimization described below in section 3.2.

3.2 Optimization of Insulin Pump Settings

Data-driven optimization of pump settings will occur at the following times:

- Prior to Randomization:
  - At the Run-in Review Visit
- Following Randomization:

- At the 2-, 13-, and 26-week visits for all study participants (both the CLC and SAP Group).
- If the study participant contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

Data will be obtained from CGM and/or pump downloads at the visit. Adjustments to pump settings (basal rates, correction factor, insulin-to-carbohydrate ratio, etc.) will be made in response to major trends observed in the CGM data, with flexibility for clinicians to adhere to guidelines and practices established at each individual practice rather than a fixed set of heuristics for all sites.

Chapter 4: Randomization Visit

4.1 Randomization Visit

The visit may occur on the same day as the Screening or Run-in Review Visit, or on a subsequent day. If deferred, the randomization visit should occur no more than 14 days after screening (if Run-in skipped) or successful completion of the run-in phase.

A urine pregnancy test will be repeated for all females of child-bearing potential if this visit is not on the same day as the Screening Visit.

4.1.1 HbA1c

HbA1c will be measured using DCA Vantage or similar point-of-care (POC) device or local lab if this visit is not on the same day as the Screening Visit. A blood sample also will be drawn to send to the central laboratory for baseline HbA1c determination to be used in outcome analyses.

4.1.2 Baseline C-Peptide Assessment

A blood sample will be drawn to send to the central laboratory for a random, non-fasting C-peptide determination to characterize baseline residual insulin production. In conjunction, blood glucose may be measured using the study blood glucose meter or a blood sample may be drawn to send to the central laboratory for a blood glucose assessment.

4.1.3 Randomization

Eligible participants will be randomly assigned to one of two treatment groups in a 2:1 ratio:

1. CLC Closed-Loop Group
2. SAP Group

The participant's randomization group assignment is determined by completing a Randomization Visit case report form on the study website. The randomization list will use a permuted block design, stratified by clinical center.

The participant will be included in the data analysis regardless of whether or not the protocol for the assigned randomization group is followed. Thus, the investigator must not randomize a participant until he/she is convinced that the participant/parent will accept assignment to either of the two groups.

It was decided that it was more important to stratify randomization by site than by factors such as baseline time in range, HbA1c, or device use since these factors will be easier to adjust for in analysis than will site in view of the relatively small number at each site.

4.1.4 Questionnaires

Participants will complete a set of baseline questionnaires, described in section 7.2, prior to randomization. Participants assigned to the CLC group also will complete the Technology Expectation Survey after randomization.

Chapter 5: Randomized Trial Procedures

5.1 Procedures for the CLC Group

5.1.1 Study System Training

Participants assigned to the CLC group will receive study system training. These training sessions can occur on the same day or extend to up to one additional day if needed within 1-7 days from randomization; participants will not take the study system home until training has been completed.

For participants <18 years old, the parent/guardian will be trained on severe hypoglycemia emergency procedures including removal of the study pump and administration of glucagon. The parent/guardian will be asked to attend any/all of the other training procedures.

Study System Training and Initiation

Study System Training

Participants will receive study system training by a qualified trainer. The study system includes the Tandem t:slim X2 with Control-IQ technology and associated Dexcom G6 CGM.

CGM training will include:

- The participant will be instructed and supervised on how to insert the sensor and transmitter.
- The participant will learn how to calibrate the CGM unit
- The participant will learn how to access the CGM trace via the t:slim X2 with Control-IQ user interface
    - Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labeling of the study CGM device

Pump training will include:

- The participant will be fully instructed on the study insulin pump. A qualified system trainer will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board and correction boluses. Additional topics not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed.
- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.

- The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.

Pump training specific to the Control-IQ Technology functions will include:

- How to turn on and off Control-IQ technology.
- How to understand when Control-IQ is increasing or decreasing basal rates.
- How to administer a meal or correction bolus on the t:slim X2 with Control-IQ system
- What to do when exercising while using the system
- How to enable the sleep function and set the sleep schedule
- The participant will be assessed for understanding of the system interface and how to react to safety/alert messages.
- The participant will be given a User Guide as a reference.

System Initiation

The participant will be instructed to use the system in closed-loop mode except 1) when no calibrated CGM sensor is available or 2) if insulin is delivered by any means other than the study pump (e.g. injection of subcutaneous insulin via syringe in the event of infusion site failure). If insulin is delivered by any means other than the study pump, participant will be instructed to turn off Control-IQ for approximately four hours.

The participant will also be instructed to contact study 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 closed-loop use should be temporarily discontinued.

For participants <18 years of age, the participant's parent/legal guardian will be required to attend the training procedures.

Participants will be provided with sufficient supplies to last until the subsequent visit.

Participants will be provided with contact information and will be asked to call the study clinical staff for any health related issues and for technical issues with t:slim X2 with Control-IQ. Participants may use the study pump without Control-IQ activated and study CGM during periods of component disconnections or technical difficulties. Participants will also receive study staff contact information to ask any questions they may have during the study.

Study staff will discuss with the participant that routine contact is required and will make arrangements with the participant for the contacts. If the participant cannot be reached, the participant's other contact methods will be utilized, including the emergency contact. Participants who are not compliant with the arranged contacts on two separate occasions may be discontinued at the discretion of the investigator.

Upon completion of the t:slim X2 with Control-IQ training, study staff will document, using a checklist, that the participant is familiar with the function/feature and/or capable of performing each of the tasks specified.

Participants will be provided Hypoglycemia, Hyperglycemia and Ketone Guidelines (section 6.2) for when their glucose levels are >300 mg/dL for more than two hours or >400 mg/dL at any time or <70 mg/dL or ketones >0.6 mmol/L.

5.1.2 Home Use of the Study System

After training on the study system has been completed, participants will proceed with home use (meaning free-living use at work, home, etc.) of the t:slim X2 with Control-IQ technology system.

Participants may use available manufacturer-provided software and features of the study CGM related to mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose.

5.1.3 Study Device Download

Participants will be instructed to download the study device prior to each phone visit or on at least every 4 week basis throughout the remainder of the study.

5.1.4 1-Week Phone Contact

Study staff will perform a phone call with the participant within 7 (±1) days following randomization.

The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
    - Study staff will answer any questions related to device use

Participants will then complete an additional week of home use with the study system. Participants will return to clinic 14 (±3) days from the date of randomization.

5.1.5 2-Week Visit (Training Review and Insulin Pump Optimization)

The participant will be offered review training to address any questions on the use of the study device including meal bolus strategies and strategies related to pump use and exercise.

The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
- Study staff will answer any questions related to device use and follow the procedure for insulin pump optimization described in section 3.2 using the study CGM available data from the previous two weeks.
- The study blood glucose meter and study ketone meter will be downloaded and QC tested with at least two different concentrations of control solution if available.

5.2 Procedures for the SAP Group

Participants in the SAP group will use an insulin pump with no automated insulin delivery in conjunction with the study CGM, study blood glucose meter and study ketone meter. Participants not already using an insulin pump with no automated insulin delivery at enrollment will be provided with a study pump to use. Study pump training and/or study CGM training will be provided if the participant is initiating use of these devices at this point.

Participants may use available manufacturer-provided software and features of the study CGM related to mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose.

5.2.1 Study Device Data Download

Participants will be instructed to upload data from the study CGM using commercially available software prior to the 1-week phone contact and prior to the 2-week clinic visit for clinician review. Participants will be provided with any software and hardware needed to perform these data uploads.

5.2.2 1-Week Phone Contact

Study staff will perform a phone call with the participant within 7 (±1) days following randomization.

The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
    - Study staff will answer any questions related to device use

The participant will continue on SAP for a second week, then return to the clinic 14 (±3) days from the date of randomization.

5.2.3 2-Week Visit (Training Review and Insulin Pump Optimization)

The participant will be offered review training on the use of SAP during the remainder of the study, including meal bolus strategies and strategies related to pump use and exercise.

The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
- Study staff will review uploaded CGM data, answer any questions related to device use, and follow the procedure for insulin pump optimization described in section 3.2.
- The study blood glucose meter and study ketone meter will be downloaded and QC tested with at least two different concentrations of control solution if available.

The participant will be instructed to upload data from the CGM at least once every 4 weeks for the remainder of the study.

5.3 Follow-up Visits and Phone Contacts for Both Groups

The schedule for remaining follow-up visits and phone contacts is the same for both treatment groups. Study staff will discuss with the participant that periodic contact is required and will make arrangements with the participant for the contacts. If the participant (or parent/guardian, for participants less than 18 years old) cannot be reached, the participant's other contact methods will be utilized, including the emergency contact.

5.3.1 Follow-up Visits

Follow-up visits in clinic will occur at:

- 6 weeks (±1 week)
- 13 weeks (±1 week)
- 26 weeks (±1 week)

5.3.1.1 Procedures at Follow-up Visits

<u>Procedures performed in both groups at each visit, unless otherwise specified below:</u>

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
    - Download of device data (study system or personal pump and study CGM, study BG meter, study ketone meter)

<u>Procedures Specific to the 13- and 26-Week Visit</u>

- HbA1c determination using the DCA Vantage or similar point of care device
- Collection of a blood sample to send to the central laboratory for HbA1c determination
- Completion of questionnaires
- Weight measurement will be repeated, in addition to height for participants <21 years old
- Insulin Pump Optimization as described above

5.3.2 Phone Contacts

In addition to the 1-week phone contact described above for the respective treatment groups, the following phone contacts will be made:

- 4 weeks (±3 days)
- 9 weeks (±3 days)
- 17 weeks (±3 days)
- 21 weeks (±3 days)

At each phone contact the following procedures are performed in both treatment groups:

- Review of available CGM and/or system data to identify any safety issues associated with insulin pump settings and current diabetes management approach
    - Assessment of adverse events, adverse device effects, and device issues

Additional phone contacts may be performed as needed.

5.4 Early Termination Visit (If Applicable)

Participants will be asked to come for an end of study visit in the event of withdrawal or early termination.

5.5 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.

5.6 Participant Access to Study Device at Study Closure

Participant will return all investigational study devices and supplies (insulin pump, CGM and related supplies) at study closure. Participant may keep the study ketone meter and study glucometer if these devices are not marked for investigational use only.

Chapter 6: Study Devices

6.1 Description of the Investigational Device

6.1.1 Insulin Pump

The study system will include the Tandem t:slim X2 with Control-IQ technology.

6.1.2 Continuous Glucose Monitoring

The study CGM will include Dexcom G6 transmitter and sensors when using the Tandem t:slim X2 with Control-IQ technology. This may not be an FDA-approved device system at the start of the study, but may become approved during the course of the study. The CGM sensor will be replaced at least once every 10 days.

6.1.3 Blood Glucose Meter and Strips

Blood glucose levels will be measured using the study-assigned blood glucose meter (glucometer) and the CGM device will be calibrated if needed using the study glucometer and strips in accordance with the manufacturer's labeling.

6.1.4 Ketone Meter and Strips

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

6.1.5 Study Device Accountability Procedures

Device accountability procedures will be detailed in the site procedures manual.

6.1.6 Blood Glucose Meter Testing

- Participants will be provided with instructions to perform QC testing per manufacturer guidelines.
- All study blood glucose meters will be QC tested with at least two different concentrations of control solution if available during all office visits. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The participant will be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.
- Participants will be reminded to use the study blood glucose meter for all fingerstick blood glucose measurements.
- Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labelling of the study CGM device.

6.1.7 Blood Ketone Testing

- Participants to perform QC testing at home per manufacturer guidelines.
- All study blood ketone meters will be QC tested with at least two different concentrations of control solution if available during all office visits. A tested meter will not be used in a study

if it does not read within the target range at each concentration per manufacturer labeling. The participant will be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.

- Participants will be instructed on how to perform blood ketone testing.
- Participants will be given guidelines for treatment of elevated blood ketones.

6.2 Safety Measures

6.2.1 CGM Calibration

Throughout the study, participants will be instructed to calibrate the study CGM in accordance with manufacturer labelling.

6.2.2 System Failure

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

If the study system is unable to activate Control-IQ for any reason, the pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the user.

If the t:slim X2 detects a system error that does not allow the pump to operate, the Malfunction Alarm will display and the participant will be instructed to contact Tandem Technical Support via the study team.

6.2.3 Hypoglycemia Threshold Alert and Safety Protocol

During the course of the study, participants will be permitted to change the CGM low glucose threshold alert setting on their device or mobile app, but will be instructed to choose a value no less than 60 mg/dL.

The t:slim X2 with Control-IQ system will issue a predictive hypoglycemia alert (Control-IQ Low Alert) when the system predicts BG <70 mg/dL within the next 15 minutes (<80 mg/dL when exercise mode is activated).

If the participant receives a Control-IQ Low Alert, a message appears on the user interface (UI) that is accompanied by vibration followed by vibrations and/or sound if not acknowledged by the user in 5 minutes. This alert remains on the screen until acknowledged by the user. The user is prompted to test blood sugar and treat with carbs.

6.2.4 Hyperglycemia Threshold Alert and Safety Protocol

During the course of the study, participants will be permitted to change the CGM high glucose threshold alert setting on their device or mobile app, but will be instructed to choose a value no greater than 300 mg/dL.

The t:slim X2 with Control-IQ system will issue a predictive hyperglycemia alert (Control-IQ High Alert) when the system has increased insulin delivery, but detects a CGM value above 200 mg/dL and does not predict the value will decrease in the next 30 minutes.

If the participant receives a Control-IQ High Alert, a message appears on the UI that is accompanied by vibration followed by vibrations and/or sound if not acknowledged by the user in 5 minutes. This alert remains on the screen until acknowledged by the user. The user is prompted to check the site for occlusion and test blood glucose.

If a participant's CGM reading is >300 mg/dL for over 2 hours or ≥400 mg/dL at any point, the participant will be instructed to take the following steps:

- Perform a blood glucose meter check.
- If the blood glucose is >300 mg/dL, check for blood ketones with the study ketone meter.
- If the ketone level is >0.6 mmol/L, take correction insulin, change insulin (pump) infusion site and contact study staff.
- If a participant administers correction insulin via insulin syringe, participants will be instructed to turn Control-IQ off for approximately four hours.

Chapter 7: Testing Procedures and Questionnaires

7.1 Laboratory Testing

1. HbA1c:

- Performed locally at the Screening visit, Randomization visit, 13-week visit, and 26-week visit. The Screening visit test may be skipped if a local test result is already available within the prior 2 weeks.
- A blood sample will be obtained and sent to central lab at the Randomization visit, 13-week visit, and 26-week visit.

2. Urine Pregnancy:

- Performed locally for females of child-bearing potential at the Screening visit, Randomization visit, and 13-week visit. This will also be done anytime pregnancy is suspected.

7.2 Questionnaires

Questionnaires are completed at the Randomization Visit, Week 13 Visit, and Week 26 Visit. The questionnaires are described briefly below. The procedures for administration are described in the study procedures manual.

The following questionnaires will be completed at the randomization visit:

- Diabetes Specific Personality Questionnaire
- Clarke's Hypoglycemia Awareness Scale
- Fear of Hypoglycemia Survey (HFS-II)
- Hyperglycemia Avoidance Scale
- Hypoglycemia Confidence Scale
- Diabetes Distress Scale
- INSPIRE Survey
    - Technology Expectations Survey *(Closed-Loop participants only at randomization; SAP group will complete this survey at week 26 prior to starting closed-loop control)*

The following questionnaires will be completed at the Week 13 and Week 26 Visits:

- Clarke's Hypoglycemia Awareness Scale
- Fear of Hypoglycemia Survey (HFS-II)
- Hyperglycemia Avoidance Scale
- Hypoglycemia Confidence Scale
- Diabetes Distress Scale

- INSPIRE Survey
- Technology Acceptance Survey *(Closed-Loop participants only)*
    - System Usability Scale (SUS) *(Closed-Loop participants only)*

Diabetes Specific Personality Questionnaire

The Diabetes Specific Personality Questionnaire (26) is based on the original Six Factor Personality Questionnaire (27), a well-validated measure that was adapted for the diabetes-specific version of the questionnaire. The SFPQ is a measure of six personality dimensions each consisting of three facet scales, measured by 108 Likert items. The SFPQ facet scales are organized in terms of six factor scales.

Administration time is approximately 15 minutes.

Clarke's Hypoglycemia Awareness Scale

The scale (28) comprises eight questions characterizing the participant's exposure to episodes of moderate and severe hypoglycemia. It also examines the glycemic threshold for, and symptomatic responses to hypoglycemia. A score of four or more on a scale of 0 to 7 implies impaired awareness of hypoglycemia.

Administration time is approximately 5 minutes.

Hypoglycemia Fear Survey (HFS-II)/Low Blood Sugar Survey

The Hypoglycemia Fear Survey-II (29) was developed to measure behaviors and worries related to fear of hypoglycemia in adults with type 1 diabetes. It is composed of 2 subscales, the Behavior (HFS-B) and Worry (HFS-W). HFS-B items describe behaviors in which patients may engage to avoid hypoglycemic episodes and/or their negative consequences (e.g., keeping blood glucose levels above150 mg/dL, making sure other people are around, and limiting exercise or physical activity). HFS-W items describe specific concerns that patients may have about their hypoglycemic episodes (e.g., being alone, episodes occurring during sleep, or having an accident).

Administration time is approximately 10 minutes.

Hyperglycemia Avoidance Survey (HAS)/High Blood Sugar Survey

The HAS (30) reliably quantifies affective and behavioral aspects of hyperglycemia avoidance and is used to assess the extent of potentially problematic avoidant attitudes and behaviors regarding hyperglycemia in people with Type 1 diabetes (T1D).

Administration time is approximately 10 minutes.

Hypoglycemia Confidence Scale

The HCS (31) is a 9-item self-report scale that examines the degree to which people with diabetes feel able, secure, and comfortable regarding their ability to stay safe from hypoglycemic-related problems. It has been validated for use in adults with type 1 diabetes and insulin-using type 2 diabetes.

Administration time is approximately 5 minutes.

Diabetes Distress Scale

The Diabetes Distress Scale (32) is a measure of diabetes-related emotional distress and consists of a scale of 28 items. These include 7 items from each of four domains central to diabetes-related emotional distress. Patients rate the degree to which each item is currently problematic for them on a 6-point Likert scale, from 1 (no problem) to 6 (serious problem).

Administration time is approximately 10 minutes.

Technology Expectation and Technology Acceptance Surveys

The Technology Expectation and Technology Acceptance Surveys were developed for a Bionic Pancreas camp study (33). The 38 items in the Questionnaire were based on interviews conducted with individuals who had participated in previous Bionic Pancreas trials about their experience regarding the Bionic Pancreas. It was subsequently adapted to assess these same measures for the inControl closed-loop system. It assesses both positive and negative experiences with inControl, including blood glucose management, device burden, and overall satisfaction. Items were rated on a 5-point scale.

Administration time is approximately 10 minutes.

INSPIRE Survey

The INSPIRE (Insulin Delivery Systems: Perceptions, Ideas, Reflections and Expectations) survey was developed to assess various aspects of a user's experience regarding automated insulin delivery for both patients and family members. The surveys include various topics important to patients with type 1 diabetes and their family members based upon >200 hours of qualitative interviews and focus groups. The adult survey includes 31 items; the adolescent survey includes 28 items; and the parent survey includes 30 items. Response options for all surveys include a 5-point Likert scale from strongly agree to strongly disagree, along with an N/A option.

Administration time is approximately 5 minutes.

System Usability Scale (SUS)

The System Usability Scale (SUS) is a 10-item questionnaire that measures the overall usability of a system. It is a valid and reliable measure of the perceived usability of a system and is technology-agnostic. The questionnaire presents statements with five response options (anchoring the options from strongly disagree to strongly agree) and asks users to rate their agreement to the statements. User scores are transformed into a composite score, from 0 to 100, and this score is taken as an overall measure of the system's usability; higher scores indicate better perceived usability.

Administration time is approximately 5 minutes.

Chapter 8: Adverse Events, Device Issues, and Stopping Rules

8.1 Adverse Events

8.1.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation (see section 8.1.2 for reportable adverse events for this protocol).

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

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)).

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 (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form).

Device Complaints and Malfunctions: A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3). Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.

8.1.2 Reportable Adverse 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
2. An Adverse Device Effect as defined in section 8.1.1, unless excluded from reporting in section 8.2
3. An Adverse Event occurring in association with a study procedure
4. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
5. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

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

Pregnancy occurring during the study will be recorded.

8.1.2.1 Hypoglycemic Events

Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when the following definition for severe hypoglycemia is met: the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

8.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following 4 criteria is met:

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis
- blood ketone level ≥1.0 mmol/L and communication occurred with a health care provider at the time of the event
- blood ketone level ≥3.0 mmol/L, even if there was no communication with a health care provider

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

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; 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. Each adverse event form is reviewed by the Medical Monitor to verify the coding and the reporting that is required.

8.1.3 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:

Yes

There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

No

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

8.1.4 Intensity of Adverse Event

The intensity of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

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

- MODERATE: Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

8.1.5 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality.

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

8.1.6 Outcome of Adverse Event

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

- RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
    - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

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

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

8.2 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 on a Device Issue Form but will reported as an Adverse Event if the criteria for AE reporting described above are met:

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

8.3 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The occurrence of pregnancy will be reported on an AE Form.

8.4 Timing of Event Reporting

SAEs and UADEs must be reported to the Coordinating Center within 24 hours via completion of the online serious adverse event form.

Other reportable adverse events, device malfunctions (with or without an adverse event), and device complaints should be reported promptly by completion of an electronic case report form, but there is no formal required reporting period.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

Upon receipt of a UADE report, the Sponsor will investigate the UADE and if indicated, report the results of the investigation to the sites' IRBs, and the FDA within 10 working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b) (2). The Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitor

must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the Medical Monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

In the case of a device system component malfunction (e.g. pump, CGM, control algorithm), information will be forwarded to the responsible company by the site personnel, to be handled by its complaint management system.

8.5 Stopping Criteria

8.5.1 Participant Discontinuation of Study Device

Rules for discontinuing study device use are described below.

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- Participant pregnancy
- Two distinct episodes of DKA
- Two distinct severe hypoglycemia events as defined in section 8.1.2.1

If pregnancy occurs, the participant will be discontinued from the study entirely. Otherwise, even if the study device system is discontinued, the participant will be encouraged to remain in the study through the final study visit.

8.5.2 Criteria for Suspending or Stopping Overall Study

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in section 8.1.2.2), 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.The study Medical Monitor will review all adverse events and adverse device events that are reported during the study and will review compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the DSMB). The Medical Monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

8.6 Independent Safety Oversight

A Data and Safety Monitoring Board (DSMB) will review compiled safety data at periodic intervals (typically every 6 months). 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 also will be informed of any ADEs not meeting criteria for a UADE if the Medical Monitor requests the DSMB review. 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.

8.7 Risks

The potential risks associated with use of the study device are described in section 1.3.

Additional risks are minor and/or infrequent and include:

- Pain, bruising, redness, or infection from blood draws
- Loss of confidentiality
- Stress from completing quality of life questionnaires

Chapter 9: Miscellaneous Considerations

9.1 Drugs Used as Part of the Protocol

Participants will use either lispro or aspart insulin prescribed by their personal physician.

9.2 Prohibited Medications, Treatments, and Procedures

Participants using glulisine at the time of enrollment will be asked to contact their personal physician to change their prescribed personal insulin to lispro or aspart for the duration of the trial.

Treatment with any non-insulin glucose-lowering agent (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals) will not be permitted.

The investigational study devices (t:slim X2 insulin pump, study CGM systems) must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or diathermy treatment. Participants may continue in the trial after temporarily discontinuing use if requiring one of the treatments above.

9.3 Participant Compensation

Participant compensation will be specified in the informed consent form.

A maximum of $375 will be paid for completing the entire study. Participants will be paid $100 for completing 13- and 26-week visits and $50 for each separate scheduled visit that requires traveling to the research site. No additional payments will be provided for unplanned visits to the research site.

- Screening Visit: $25
- Run-in Visit/Randomization Visit: $50
- 2-week Visit: $50
- 6-week Visit: $50
- 13-week Visit: $100
- 26-week Visit: $100

9.4 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal.

9.5 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the

study. De-identified participant information may also be provided to Tandem for system evaluation purposes.

Chapter 10: Statistical Consideration

10.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the first tabulation of data by treatment group (ie, for DSMB review). The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

10.2 Statistical Hypotheses

The primary outcome for this study (6-month randomized trial) is CGM-measured % in range 70-180 mg/dL.

The hypotheses for the primary outcome are:

a. *Null Hypothesis*: There is no difference in mean CGM-measured % in range 70-180 mg/dL over 6 months between SAP and CLC

b. *Alternative Hypothesis*: The mean CGM-measured % in range 70-180 mg/dL over 6 months is different for SAP and CLC.

10.3 Sample Size

Sample size has been computed for the primary outcome (CGM-measured % in range 70-180 mg/dL). Data from the CGM arm of the JDRF CGM RCT from participants meeting the eligibility criteria for the current trial were used to project the distribution of % in range 70-180 mg/dL as measured by CGM for the SAP group in the proposed study.

The total minimum sample size was computed to be 123 for the following assumptions: (1) 2:1 [CLC:SAP] randomization, (2) 90% power, (3) a 7.5% absolute increase in % in range 70-180 mg/dL, (4) an effective SD of 12%, (5) and 2-sided type 1 error of 5%.

The total sample size has been increased to 168 to account for dropouts and to increase the number of participants who will be exposed to the CLC system for an enhanced safety and feasibility assessment.

10.4 Outcome Measures

10.4.1 Primary Efficacy Endpoint

- CGM-measured % in range 70-180 mg/dL

10.4.2 Secondary Efficacy Endpoints

10.4.2.1 Secondary Efficacy Endpoints Included in Hierarchical Analysis

The following secondary endpoints will be tested in a hierarchical fashion as described in section 10.7.1.

- CGM-measured % above 180 mg/dL
- CGM-measured mean glucose
- HbA1c at 26 weeks
- CGM-measured % below 70 mg/dL
- CGM-measured % below 54 mg/dL

10.4.2.2 Other Secondary Efficacy Endpoints

The following endpoints are considered exploratory. Type 1 error for these endpoints will be controlled using the false discovery rate (FDR) instead of the familywise error rate (FWER). See section 10.15 below.

CGM-Measured:

- % in range 70-140 mg/dL
- glucose variability measured with the coefficient of variation (CV)
- glucose variability measured with the standard deviation (SD)
- % <60 mg/dL
- low blood glucose index
- hypoglycemia events (defined as at least 15 consecutive minutes <70 mg/dL)
- % >250 mg/dL
- % >300 mg/dL
- high blood glucose index

HbA1c:

- HbA1c <7.0% at 26 weeks
- HbA1c <7.5% at 26 weeks
- HbA1c improvement from baseline to 26 weeks >0.5%
- HbA1c improvement from baseline to 26 weeks >1.0%
- HbA1c relative improvement from baseline to 26 weeks >10%
- HbA1c improvement from baseline to 26 weeks >1.0% or HbA1c <7.0% at 26 weeks

Questionnaires:

- Fear of Hypoglycemia Survey (HFS-II) – total score and 3 subscales:
  - Behavior (avoid)
  - Behavior (maintain high BG)
  - Worry
- Hyperglycemia Avoidance Scale – total score and 4 subscales:
  - Immediate action
  - Worry
  - Low BG preference
  - Avoid extremes
- Diabetes Distress Scale – total score and 4 subscales:
  - Emotional burden
  - Physician-related distress
  - Regimen-related distress
  - Interpersonal distress
- Hypoglycemia Confidence Scale – total score
- Clarke Hypoglycemia Awareness Scores
- INSPIRE survey scores
- System Usability Scale (SUS)

Other:

- Insulin
  - Total daily insulin (units/kg)
  - Basal: bolus insulin ratio
- Weight and Body Mass Index (BMI)

10.4.2.3 Safety Analyses

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

- Severe hypoglycemia
- Diabetic ketoacidosis
- Other serious adverse events and serious adverse device events

- Unanticipated adverse device effects

10.4.3 CGM Metrics Calculations

Randomization is preceded by two weeks of CGM run-in, which will be used in the calculation of baseline CGM metrics.

CGM data starting from randomization visit through the 6 month visit will be included in the calculation of each CGM metric. Percentages in range 70-180 mg/dL (and all other CGM-based metrics) will be calculated giving equal weight to each CGM point for each participant.

10.5 Analysis Datasets and Sensitivity Analyses

All analyses comparing the CLC arm with SAP arm will follow the intention-to-treat (ITT) principle with each participant analyzed according to the treatment assigned by randomization. All randomized participants will be included in the primary and secondary hierarchical analyses.

Safety outcomes will be reported for all enrolled participants, irrespective of whether the participants was randomized or the study was completed.

10.5.1 Per Protocol Analyses

If more than 5% of participants have fewer than 168 hours of post-randomization CGM data, the primary and secondary hierarchical analyses will be replicated excluding such participants.

The primary and secondary hierarchical analyses will be replicated only with participants from CLC group who used the system in CL mode for >80% overall and with participants from SAP group who used the sensor for >80% overall.

10.5.2 Other Sensitivity Analyses

Confounding

The primary analysis described below will include a pre-specified list of covariates. As an additional sensitivity analysis, any baseline demographic or clinical characteristics observed to be imbalanced between treatment groups will be added as covariates to the analyses of the primary and secondary hierarchical metrics. The determination of a meaningful baseline imbalance will be based on clinical judgement and not a p-value.

Exclude First 2 Weeks of CGM Data

As noted above in Section 10.4.3, calculation of CGM metrics will include all available post-randomization CGM data. As a sensitivity analysis, each of the primary and secondary hierarchical CGM metrics listed in 10.4.1 and 10.4.2.1 will be recalculated excluding the first two weeks of CGM data following the randomization visit. A parallel set of analyses will be done on these recalculated metrics.

Missing Data

It is 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 when using different methods. The following methods will be applied:

- Direct likelihood (primary analysis described below)
- Rubin's multiple imputation
- Available cases only

10.6 Analysis of the Primary Efficacy Endpoint

Summary statistics (mean ± SD or median (quartiles)) will be reported for the CGM-measured % in range 70-180 mg/dL and for differences from pre-randomization by treatment group.

Changes from run-in pre-randomization CGM wear to the 6-month post-randomization period in CGM-measured % in range 70-180 mg/dL between two treatment arms will be compared using a linear mixed effects regression model while adjusting for baseline CGM-measured % in range 70-180 mg/dL, age, prior CGM and pump use, and clinical center (random effect). Missing data will be handled using direct likelihood. Residual values will be examined for an approximate normal distribution. If residuals are highly skewed even after the transformation, then a transformation or robust statistical method (e.g., non-parametric or MM estimation) will be used instead. It is expected that the residual values for CGM-measured % in range 70-180 mg/dL will follow an approximate normal distribution.

10.7 Analysis of the Secondary Endpoints

Point estimated and confidence intervals for the treatment arm differences will be presented for all secondary metrics. The models will adjust for the corresponding baseline metric, age, prior CGM and pump use, and clinical center (random effect).

10.7.1 Hierarchical Analyses

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 with the model described above for the primary outcome) will proceed to the next outcome metric in the following order:

- CGM-measured % in range 70-180 mg/dL (primary outcome)
- CGM-measured % above 180 mg/dL
- CGM-measured mean glucose
- HbA1c at 26 weeks
- CGM-measured % below 70 mg/dL
- CGM-measured % below 54 mg/dL

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 six 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.

For example, in the hypothetical scenario depicted in the table below, the first four outcome variables have a significant result so testing continues to the fifth variable (CGM % below 70 mg/dL). The result is not significant for that fifth variable ($p = 0.06$) so testing stops. No formal hypothesis test is conducted for the sixth variable on the list in this example scenario.

Table 3. Example Hierarchical Test Results

HIERARCHICAL ORDER	OUTCOME VARIABLE	TREATMENT ARM P-VALUE	SIGNIFICANT?	ACTION
1st	CGM % 70-180 mg/dL (primary outcome)	0.001	Yes	Test next variable
2nd	CGM % above 180 mg/dL	0.02	Yes	Test next variable
3rd	CGM mean glucose	0.007	Yes	Test next variable
4th	HbA1c at 26 weeks	0.03	Yes	Test next variable
5th	CGM % below 70 mg/dL	0.06	No	Stop formal testing
6th	CGM % below 54 mg/dL	Not tested	Unknown	N/A

Regardless of the results of the hierarchical testing, summary statistics appropriate to the distribution will be tabulated by treatment arm for each hierarchical outcome. A 95% confidence interval for the treatment arm difference will also be calculated for all four hierarchical outcomes listed above. However, a confidence interval that excludes zero will not be considered a statistically significant result if an outcome variable higher on the hierarchical list failed reach statistical significance.

10.7.2 Other Endpoint Analyses

CGM-Measured Outcomes

The analyses for the secondary CGM-measured outcomes will parallel those mentioned above for the primary outcome.

HbA1c

Summary statistics (mean ± SD) will be reported for the central lab HbA1c at 26-weeks and for differences from pre-randomization by treatment group.

Change in HbA1c from baseline to 26 weeks will be compared between the two treatment arms using a linear model while adjusting for baseline HbA1c, age, prior CGM and pump use, and clinical center (random factor).

Missing data will be handled using direct likelihood in a regression model including all available central laboratory HbA1c measurements at baseline and 26 weeks visits. When available, the local HbA1c measurement will be included in the regression model as an auxiliary variable.

For the binary HbA1c outcomes listed above, risk-adjusted percentages by treatment group will be computed from a logistic regression model. The logistic regression will adjust for the same factors mentioned above for the analysis with HbA1c as a continuous factor (i.e., baseline HbA1c, age, prior CGM and pump use, and clinical site as a random effect).

Questionnaires and Other Outcomes

For questionnaires administered to both randomization groups, comparisons will be made using similar linear models as described above for the primary outcomes. Separate models will be run for the total score and each of the subscales listed above.

Similarly, for insulin, weight, and BMI metrics comparisons will be made using similar linear models as described above for the primary HbA1c analysis.

10.8 Safety Analyses

All randomized participants will be included in these analyses and all their post-randomization safety events will be reported.

The circumstances of all reportable cases of the following will be summarized and tabulated by treatment group:

- Severe hypoglycemia (as defined in section 8.1)
- Diabetic ketoacidosis (as defined in section 8.1)
- Ketone events defined as day with ketone level >1.0 mmol/L
- CGM-measured hypoglycemic events (≥15 minutes with glucose concentration <54 mg/dL)
- CGM-measured hyperglycemic events (≥15 minutes with glucose concentration >300 mg/dL)
- BG-measured hypoglycemic events (one BG record <54 mg/dL)
- BG-measured hyperglycemic events (one BG record >350 mg/dL)
- Worsening of HbA1c from baseline to 26 weeks by >0.5%
- Other serious adverse events (SAE) and serious adverse device events (SADE)
- Adverse device effects (ADE)
- Unanticipated adverse device effects (UADE)

For the following outcomes, mean ± SD or summary statistics appropriate to the distribution will be tabulated by treatment group:

- Number of SH events and SH event rate per 100 person-years
- Number of DKA events and DKA event rate per 100 person-years
- Any adverse event' rate per 100 person-years

If enough events, the numbers will be compared between the two treatment arms using a robust Poisson regression. The regression will adjust for the participant-reported number of events prior to the start of the study and site as random effect. The amount of follow up will be included as an offset covariate to compare the rates.

Comparison of safety outcomes between the two treatment groups only include those events occurring on or after randomization until the 26 week visit.

Any pre-randomization adverse events will be tabulated separately and will include participants who were never randomized.

10.9 Intervention Adherence

The following tabulations and analyses will be performed by treatment group to assess intervention adherence for the study:

- Sensor use – hours of use and percent time of use
- The daily frequency of downloaded BGM use

For CLC arm only, the following will be tabulated to assess adherence:

- % time in different operational modes per week - overall and by month

10.10 Adherence and Retention Analyses

The following tabulations and analyses will be performed by treatment group to assess protocol adherence for the study:

- Number of protocol and procedural deviations per participant along with the number and percentage of participants with each number of deviations
- Number of protocol and procedural deviations by severity with brief descriptions listed
- Flow chart accounting for all participants at all scheduled visits and phone contacts post treatment initiation to assess visit and phone completion rates
- Number of and reasons for unscheduled visits and phone calls
- Number of participants who stopped treatment and reasons

10.11 Baseline Descriptive Statistics

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

Will include:

- Age
- HbA1c
- Gender
- Race/ethnicity
- Income, education, and/or insurance status
- Insulin method before enrollment (pump vs. MDI)
- CGM use before enrollment
- Diabetes duration
- BMI
- C-peptide
- Scores for diabetes specific personality, quality of life, hypoglycemia awareness and fear questionnaires

10.12 Device Issues

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

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

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

- Performance metrics, describing the Control-IQ system and its components like:
  - % time CGM data were available to the Control-IQ system – overall and by month
  - % time in different operational modes per week - overall and by month
  - Rate of different failure events and alarms per 24 hours recorded by the Control-IQ system – overall and by month
- Technology Expectations Survey score at baseline and Technology Acceptance Survey score at 26 weeks

10.13 Planned Interim Analyses

No interim efficacy analysis is planned.

The DSMB will review safety data at intervals, with no formal stopping rules other than the guidelines provided in the participant-level and study-level stopping criteria (as defined in section 8.5 of the protocol).

10.14 Subgroup Analyses

In exploratory analyses, all primary outcomes found significant according to the hierarchical rules outlined in section 10.7.1 will be assessed separately in various subgroups and for continuous variables according to the baseline value as defined below. Tests for interaction with treatment group will be performed and further explored if an interaction will be found in the first place.

Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment group difference. In the absence of such an overall difference and if performed, subgroup analyses will be interpreted with caution. For continuous variables, results will be displayed in subgroups based on cutpoints although the analysis will utilize the variable as continuous, except for age which will be analyzed both as a continuous variable and in two age groups. If there is insufficient sample size in a given subgroup, the cutpoints for continuous measures may be adjusted per the observed distribution of values. Cutpoint selection for display purposes will be made masked to the outcome data.

- Baseline HbA1c
- Baseline CGM time spent <70 mg/dL
- Baseline CGM time spent >180 mg/dL
- Baseline CGM time 70-180 mg/dL
- Device use before the enrollment: pump/MDI, CGM/no CGM, and combinations of both
- Age
- Sex
- Race
- Clinical site

Additional analyses may be performed for subgroups defined based on the following baseline demographic/clinical characteristics.

- Body mass index
- Income, education, and/or insurance status
- Baseline scores for quality of life, hypoglycemia awareness and fear questionnaires
- C-peptide level

10.15 Multiple Comparison/Multiplicity

Primary Analysis

Since there will be a single comparison for the primary outcome (CGM-measured % 70-180 mg/dL), no adjustment is needed.

Secondary Hierarchical Analyses

The hierarchical testing procedure described above in section 10.7.1 will be used to control the overall type 1 error for the primary outcome plus five key secondary outcomes identified above.

All Other Secondary Analyses

For all above-mentioned secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure.

10.16 Exploratory Analyses

In addition to the analysis for the CGM-measured endpoints described earlier, separate analyses will be conducted for daytime and nighttime.

The CGM-measured analyses will be replicated with only CGM data when the closed-loop was active for the CLC group. The CGM data for the SAP group will be the same as mentioned above in the CGM Metrics Calculation section.

Chapter 11: Data Collection and Monitoring

11.1 Case Report Forms and Device Data

The main study data are collected through a combination of electronic case report forms (CRFs) and electronic device data files obtained from the study software and individual hardware components. These electronic device files and electronic CRFs from the study website are considered the primary source documentation.

When data are directly collected in electronic case report forms, this will be considered the source data. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

11.2 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.

11.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report

- Agent/Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

11.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 12: Ethics/Protection of Human Participants

12.1 Ethical 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.

12.2 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.

12.3 Informed Consent Process

12.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing 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 to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator 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. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants 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.

12.3.2 Participant and Data Confidentiality

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research and the University of Virginia Center for Diabetes Technology. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Jaeb research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Jaeb Center for Health Research and the University of Virginia Center for Diabetes Technology. Permission to transmit data will be included in the informed consent.

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