Clinical Acceptance of the Artificial Pancreas: the International Diabetes Closed Loop (*i*DCL) Trial

A Randomized Clinical Trial to Assess the Efficacy of Adjunctive Closed Loop Control Versus Sensor-Augmented Pump Therapy in the Management of Type 1 Diabetes

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Acronym	Abbreviation For
ADA	American Diabetes Association
AP	Artificial Pancreas
ATTD	Advanced Technologies & Treatments for Diabetes
AUC	Area Under the Curve
BAM	Basal Attenuation Module
BG	Blood Glucose
BIM	Basal Increase Modulator
BT/BTLE	Bluetooth, Bluetooth low energy
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CLC	Closed-Loop Control
CSII	Continuous Subcutaneous Insulin Infusion
CTR	Control-to-Range
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
DSMB	Data and Safety Monitoring Board
EC	European Commission
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAS	Hyperglycemia Avoidance Survey
HbA1c	Hemoglobin A1c
HCT	Helmsley Charitable Trust
HFS-II	Hypoglycemia Fear Survey
HCM	Hyperglycemia Correction Module
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
RCT	Randomized Controlled/Clinical Trial
RMB	Risk-Based Monitoring
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Sensor-Augmented Pump

Acronym	Abbreviation For
SD	Standard Deviation
SFPQ	Six Factor Personality Questionnaire
SH	Severe Hypoglycemia
SMBG	Self-Monitoring of Blood Glucose
SSL	Secure Sockets Layer
TDI	Total Daily Insulin
UADE	Unanticipated Adverse Device Effect
UI	User Interface
UVA	University of Virginia

CHAPTER 1: INTRODUCTION

1.1. Background and Rationale

The transition of closed-loop control (CLC, known as the "artificial pancreas") to everyday diabetes therapy is contingent upon the acceptance by patients and physicians of an advanced CLC system ensuring concerted work of continuous glucose monitors (CGMs), insulin pumps, and control algorithms. In 2011, a new pathway towards the development of such a system was charted by the Diabetes Assistant (DiAs) – a smart-phone multi-use platform designed at the University of Virginia (UVA)to operate in several treatment modes ranging from CGM or insulin pump support to overnight and 24/7 CLC. Since its introduction in 2011, DiAs has earned regulatory approvals in the U.S., France, Italy, Netherlands, and Israel; 3 different control algorithms have been implemented on the DiAs platform and used in 18 clinical trials, including long-term studies at home. To date, over 300 patients with type 1 diabetes have tested DiAs for over 220,000 hours of outpatient use. We can therefore affirm that reliable technology has been developed and sufficient data have been accumulated to warrant a large-scale clinical trial aiming to establish the artificial pancreas as a clinically accepted treatment for type 1 diabetes that is superior to the current sensor-augmented pump (SAP) therapies. A key distinction of our approach is that the artificial pancreas is not considered a single-function device–it is a platform for technology deployment that can run open- or closed-loop control modalities depending on physician recommendation, patient preference, or signal availability. Recently, we have built and tested a third-generation version of our DiAs system named inControl, as described below, to support larger-scale clinical trials.

1.2. Preliminary Studies

Figure 1 below presents the extensive sequence of innovative outpatient clinical trials done in the past 5 years since the introduction of our DiAs system:

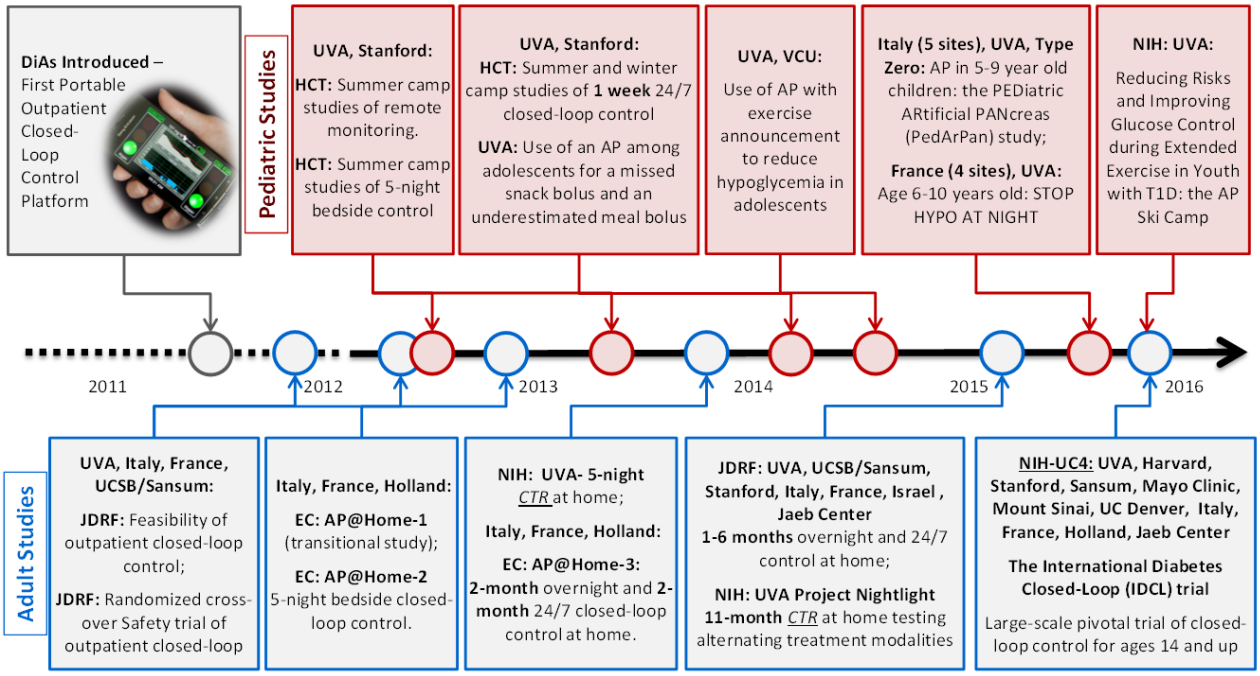

Figure 1: Past, current, and upcoming outpatient studies identified by their source of funding: JDRF, NIH, the Helmsley Charitable Trust (HCT), and the European Commission (EC)

These studies included multi-site and international trials done at several prominent clinical centers in the U.S. and overseas, ranging from early-feasibility 2-day studies in supervised outpatient environment to 6-months trials at home. Our overall strategy has been to test, re-test, and test again, in various conditions, clinical centers, and age groups. As noted above, these studies accumulated a wealth of data (*21 patient years of closed-loop control*) and AP know-how, which now allow us to transition to the large-scale International Diabetes Closed-Loop pivotal trial. The upper panel of Figure 1 includes pediatric studies, while the lower panel presents studies in adults.

Briefly, in 2012/2013 we completed two international multi-site trials, which confirmed the feasibility of DiAs and its efficacy to reduce hypoglycemia in the outpatient setting; both were selected for the *Diabetes Care* symposiums at the 2013 and 2014 American Diabetes Association (ADA) Scientific Sessions (1, 2). Three summer camp trials of remote monitoring (3), overnight CLC (4), and 24/7 CLC (5) confirmed the efficacy of DiAs in children with T1D. In Europe, AP@home ran two pilot trials to pave the way for the large-scale AP@Home-3 which included 2-month overnight and 2-month 24/7 CLC at home (6), which was the first study to report statistically significant reduction in HbA1c with CLC (7). The longest to-date (6-month) multi-center trial of 24/7 CLC at home was reported in February 2016 at the ATTD conference in Milan, Italy and showed very significant several-fold reduction in hypoglycemia without deterioration in HbA1c (8, 9). Adult studies now continue with Project Nightlight – *an 11-month trial* which compares dinner/overnight vs. 24/7 CLC in terms of glycemic outcomes and patient acceptance (10), and with the International Diabetes Closed-Loop Trial. Three new exciting pediatric studies complete the lineage presented in Figure 1: (i) the multi-center Italian PedArPan trial recruited 5–9-year-old children and their parents from 5 sites for a summer camp (11); (ii) the French Stop Hypo at Night trial compares the prevention of hypoglycemia in 7-12 year old children achieved by the Safety System described in the previous section vs. threshold low glucose suspend, and (iii) *an AP study on skis recruited 16 children at Wintergreen, Virginia in January 2016 to test the ability of the system to cope with extreme winter conditions and prolonged vigorous physical activity (5 hours of skiing daily for 5 days)* (12).

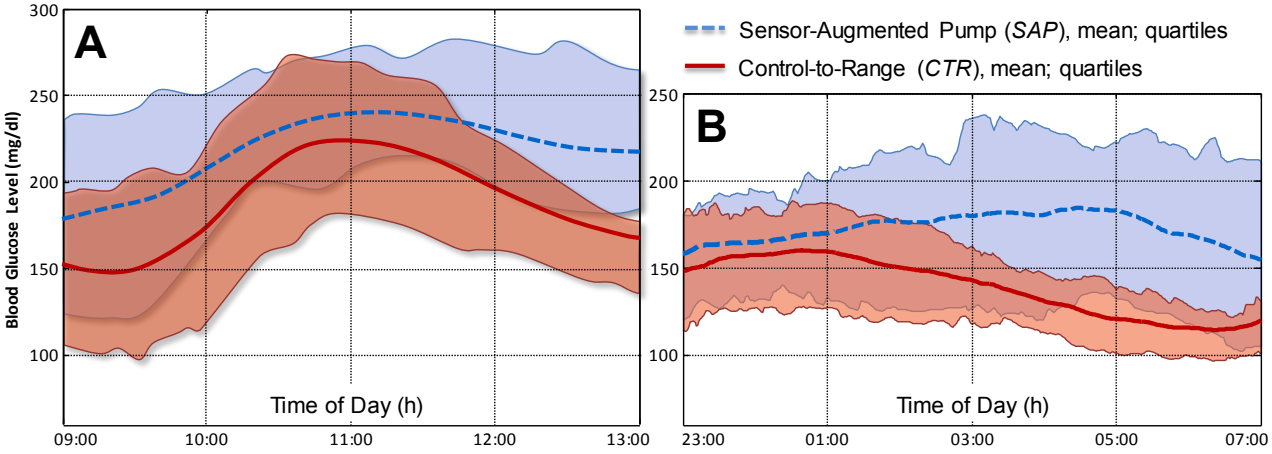

Figure 2: CLC in Adolescents Missing/Underestimating Pre-meal Bolus (A) and in Adults Overnight (B)

While our overall progress with the development and the clinical testing of a wearable artificial pancreas (AP) is depicted in Figure 1, the results below are of particular relevance to the proposed Study:

(1) CLC Algorithm Performance: We illustrate our expectations for this project with data from two studies that have tested the same CTR system we are planning to use now with adolescents missing or

underestimating their pre-meal boluses (13) and with adults during overnight control (14), presented in Figure 2, panels A and B:

In the first of these studies CLC reduced the extent and duration of postprandial BG excursions: mean BG of 197 vs. 235 mg/dL ($p<0.05$) on CLC vs. SAP (13). In the second study, CLC compared to SAP reduced mean BG level at 07:00h (119.3 vs. 152.9 mg/dL; $p<0.001$) and overnight (139.0 vs. 170.3 mg/dL; $p<0.001$) (14).

(2) JDRF Multi-Center 6-Month Trial of 24/7 Closed-Loop Control: In the summer of 2014, we initiated a two-phase long-term (6 months) trial evaluating DiAs in the natural environment. Phase 1 (1 month) recruited 30 patients with T1DM at 6 clinical centers: UVA, Stanford University, the William Sansum Diabetes Center, Santa Barbara, CA, the Universities of Padua (Italy) and Montpellier (France), and the Schneider Children's Medical Center of Israel (1). During Phase 1, subjects participated in 2 weeks of overnight-only and 2 weeks of 24/7 CLC. Phase 2 continued with N=14 patients at 4 of these sites (UVA, Stanford, Sansum, Padua), for 5 additional months of 24/7 CLC (9). The study was coordinated by the Jaeb Center for Health Research.

Median subject characteristics: age=45 years; duration of diabetes=27 years; total daily insulin=0.54 (U/kg/day); basal daily insulin=0.22 (U/kg/day); 10/4 male/female.

Results:

Figure 3 below presents the time within target range achieved during CLC in Phase 1 of this study during overnight CLC and during 24/7 CLC, compared to sensor-augmented pump. As seen in Figure 3, CLC achieved over 70% time in the target range overall, accompanied by significant reduction in hypoglycemia.

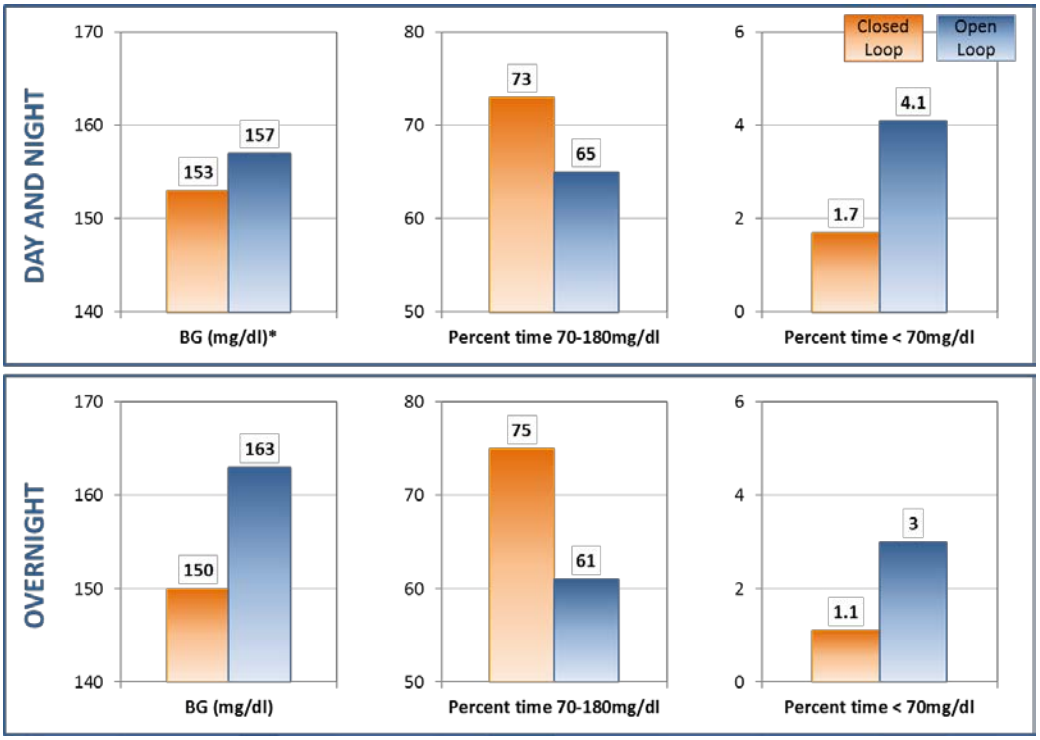

Figure 3: Summary of the results from Phase 1 which included 2 weeks of overnight CLC and 2 weeks of 24/7 CLC

During the 5-month Phase 2, CLC achieved over 75% time in the target range overall and separately during the day and during the night. The rest of the data were primarily distributed between 180 and 250 mg/dL. Extreme BG excursions were rare (Figure 4):

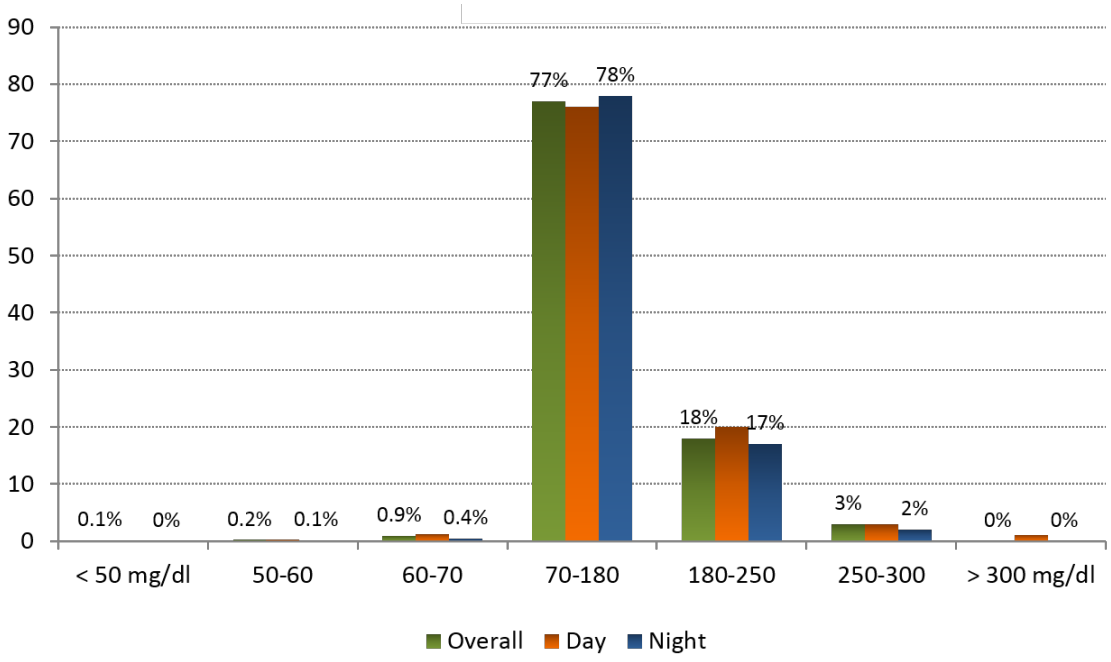

Figure 4: Summary of the results from Phase 2 – additional 5 months of 24/7 CLC

Overall, HbA1c was reduced from 7.2% at the baseline to 7.0% (p=0.16) at the end of the study. This was accompanied by a significant 3-fold reduction in the frequency of hypoglycemia from baseline to the last three months of CGM monitoring 4.1% vs. 1.3% (p<0.001). Improvement in HbA1c was highly correlated with the percent time of system use, r=0.59; in particular those with above-median system use (>70% of the time) achieved HbA1c reduction of 0.44%, from 7.19% at the baseline to 6.74% at the end of study (9).

Table 1 below presents a summary of the results:

Table 1: 6-month CLC Trial Key Results

	Baseline	End of Study	P-value
%CGM < 70 mg/dL (median (IQR))	4.1 (2.9-7.5)	1.3 (0.6-1.7)	<0.001
%CGM < 60 mg/dL (median (IQR))	2.2 (1.5-3.4)	0.3 (0.2-0.6)	<0.001
%CGM < 50 mg/dL (median (IQR))	1.0 (0.8-1.3)	0.1 (0.0-0.2)	<0.001
A1c (mean ± SD)	7.2 ± 0.6	7.0 ± 0.6	0.16
A1c for those with A1c >7.0 at baseline	7.5 ± 0.4	7.1 ± 0.7	0.12

Meta-Analysis of All DiAs Studies to Date:

Table 2 presents meta-analysis of 184,000 hours (21 patient years) of data from several previous studies that used the DiAs artificial pancreas platform over the past 5 years. These studies were conducted at several research centers in the U.S. and overseas and enrolled a total of 420 patients with type 1 diabetes. Despite the geographical and patient diversity, the across-site results were consistent:

Table 2: CLC Meta-Analysis

	% time within 70-180 mg/dL		Average BG (mg/dL)		% time < 70 mg/dL	
	CLC	SAP	CLC	SAP	CLC	SAP
Overall	71.7%	63.8%	152.4	158.3	2.0%	3.9%
Overnight	76.5%	60.7%	148.6	161.4	1.1%	3.1%

1.3. Closed-Loop Control System

inControl-AP 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 current mobile implementation of inControl-AP runs on a standard Android smartphone and uses Bluetooth (BT) and Bluetooth Low Energy (BLE) connectivity to communicate with a Continuous Glucose Monitor (CGM) and insulin pump. The system modulates insulin to keep blood glucose in a targeted range. inControl-AP runs on a modified release of the Android operating system. Modifications include the removal of unnecessary applications and functions, and fixes to the BT stack to permit communication with the insulin pump. While inControl-AP is an Android application with a JS/CSS UI, system upgrades during the study will be considered when new technology becomes available and is sufficiently tested. For example, new generations of CGM sensors or insulin pumps with embedded inControl-AP could become available for inclusion in this trial and could be used, provided that these new development do not change the core functionality of the system described below and in Figure 5.

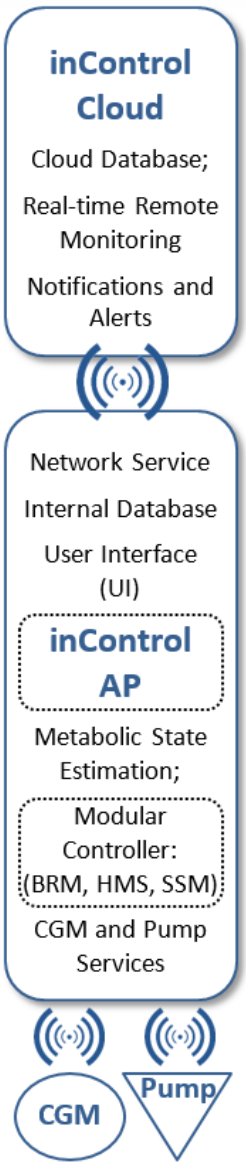

Figure 5: inControl-AP Schematic

The system services include the following processing elements:

- Core: handles timing and main loop calls, intercepts system messages and handles data changes
- Metabolic state estimation: calculates the patient's current metabolic state, including current and predicted blood glucose and IOB, and stores values in a database
- Controller: calls the modules that calculate algorithmic and manually requested insulin delivery quantities in sequence
    - UIM – User Input Module handles the delivery of insulin requested manually by the user which includes meal and correction boluses
    - BIM – Basal Increase Module increases basal delivery in response to estimated blood glucose levels based on a circadian target profile
    - HCM – Hyperglycemic Correction Module calculates a correction bolus in response to estimated blood glucose above its target
    - BAM – Basal Attenuation Module may reduce basal insulin delivery if the system determines a risk of hypoglycemia
- Supervisor: determines which dosing algorithm outputs are valid and active based on the current operating state of the system

The inControl system operates on a 5-minute cycle based on the highest frequency of input data. There are two insulin dosing modes (pump and closed loop) and three operating modes (normal, sleep and exercise). The combination of insulin dosing mode and operating mode determines what actions inControl will perform and what options are presented to the user.

Figure 6: Schematic of inControl-AP system hardware components

1.4. Synopsis of Study Protocol

1.4.1. Study Objective

The objective of the study is to assess the efficacy and safety of home use of a Control-to-Range (CTR) closed-loop (CL) system.

1.4.2. Study Design

The protocol is a 3-month parallel group multi-center randomized trial designed to compare Control-to-Range (CTR) closed-loop (CL) with sensor augmented pump therapy (SAP).

1.4.3. Major Eligibility Criteria

- Clinical diagnosis of type 1 diabetes, treated with insulin for at least 1 year
- Use of an insulin infusion pump for at least 6 months
- Age ≥14 years old
- HbA1c level <10.5% at screening
    - A study goal will be to have a minimum of 50 subjects with HbA1c ≥7.5% and 50 with HbA1c <7.5%.
- No use of glucose-lowering agents other than insulin in the 3 months prior to enrollment
- Willingness to establish network connectivity on at least a weekly basis either via local Wi-Fi network or via a study-provided cellular service

1.4.4. Sample Size

Approximately 126 subjects will enter into the randomized trial conducted at approximately 7 clinical sites in the United States.

1.4.5. Treatment Groups

Subjects in the trial will be randomly assigned in a 1:1 ratio to the Control-to-Range (CTR) Closed-Loop or sensor augmented pump therapy (SAP) groups, respectively.

1.4.6. Visit and Phone Contact Schedule

Subjects who used a personal CGM that is the same brand as the study CGM prior to the study for at least 21 of the prior 28 days will proceed directly to randomization. These subjects will have the personal CGM downloaded for capture of the two-week baseline data.

All other subjects will participate in the following CGM run-in phases requiring additional clinic visits as shown in Figure 7:

- Two-week period of blinded study CGM use to characterize baseline glycemic control; subjects using a personal CGM prior to the study will continue to use it during this period.
- Two-week period of unblinded study CGM use, with training in using CGM if necessary; subjects using a personal CGM prior to the study will discontinue the personal CGM beginning in this period.

After randomization, all subjects will have an initial two-week training period as shown in Figure 8:

- Participants in the SAP Group will use the study CGM and will continue to use their personal insulin pump, with a phone contact after one week to assess usage and reinforce CGM training if needed.
- Participants in the CTR Group will cease use of their personal insulin pump and will receive study pump training followed by inControl training and then use the inControl system at home (study pump, study CGM and inControl device). There will be a phone contact after one week to assess usage and reinforce pump, CGM and/or inControl training if needed.

As shown in Table 3, all subjects have the same post-randomization clinic visit and phone contact schedule, with the possible exception of an additional training session on a different day for CTR Group subjects if there is insufficient time at the randomization visit to train fully on the closed-loop system components. This training session will occur within one week of the Randomization Visit, and the remaining schedule is as follows:

- Visits after: 2 weeks, 5 weeks, 9 weeks, 13 weeks
- Phone contacts after: 1 week, 3 weeks

360 **Figure 7: Enrollment and Pre-Randomization Flow Diagram**

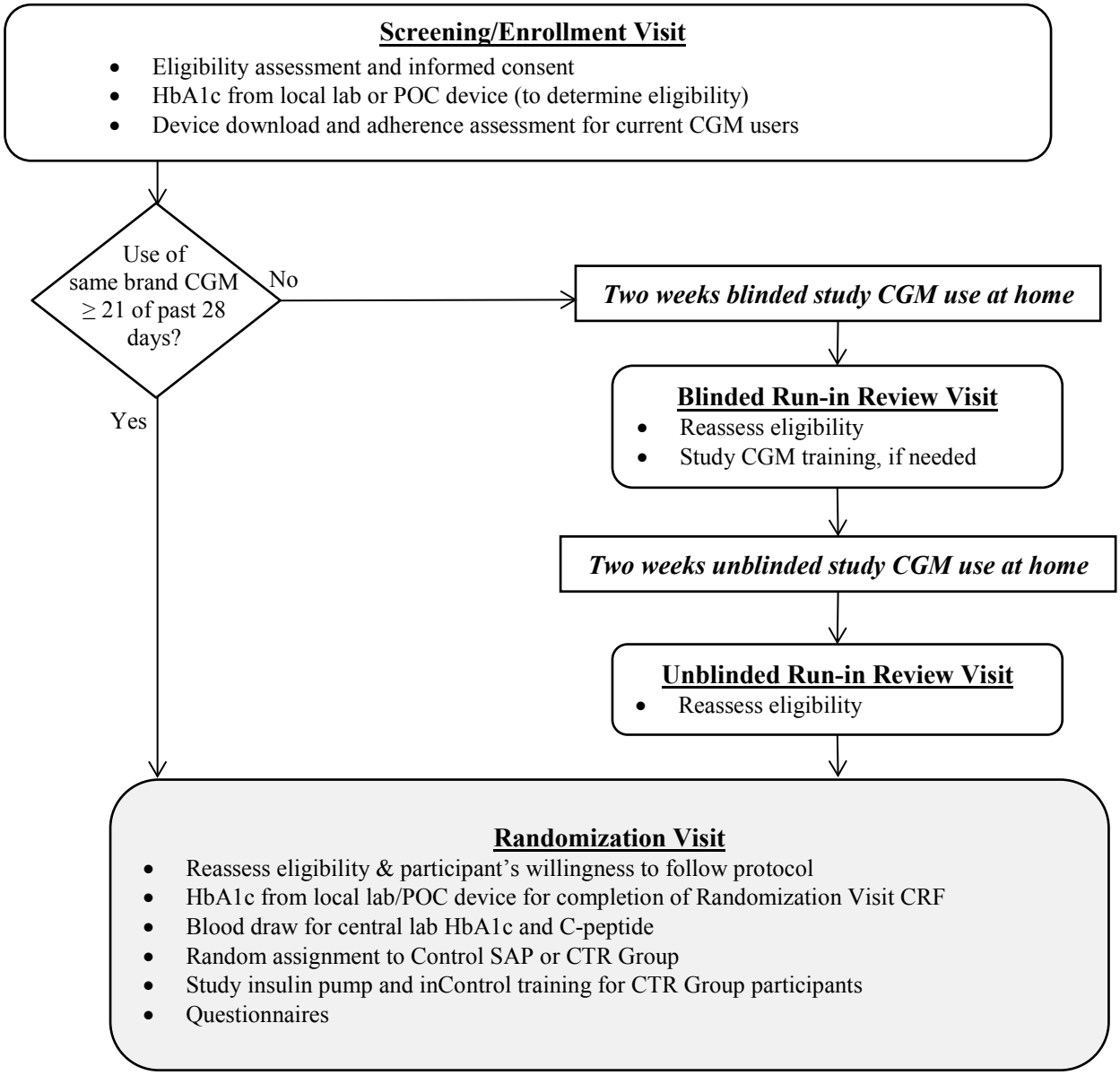

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Figure 8: Post-Randomization Flow Diagram

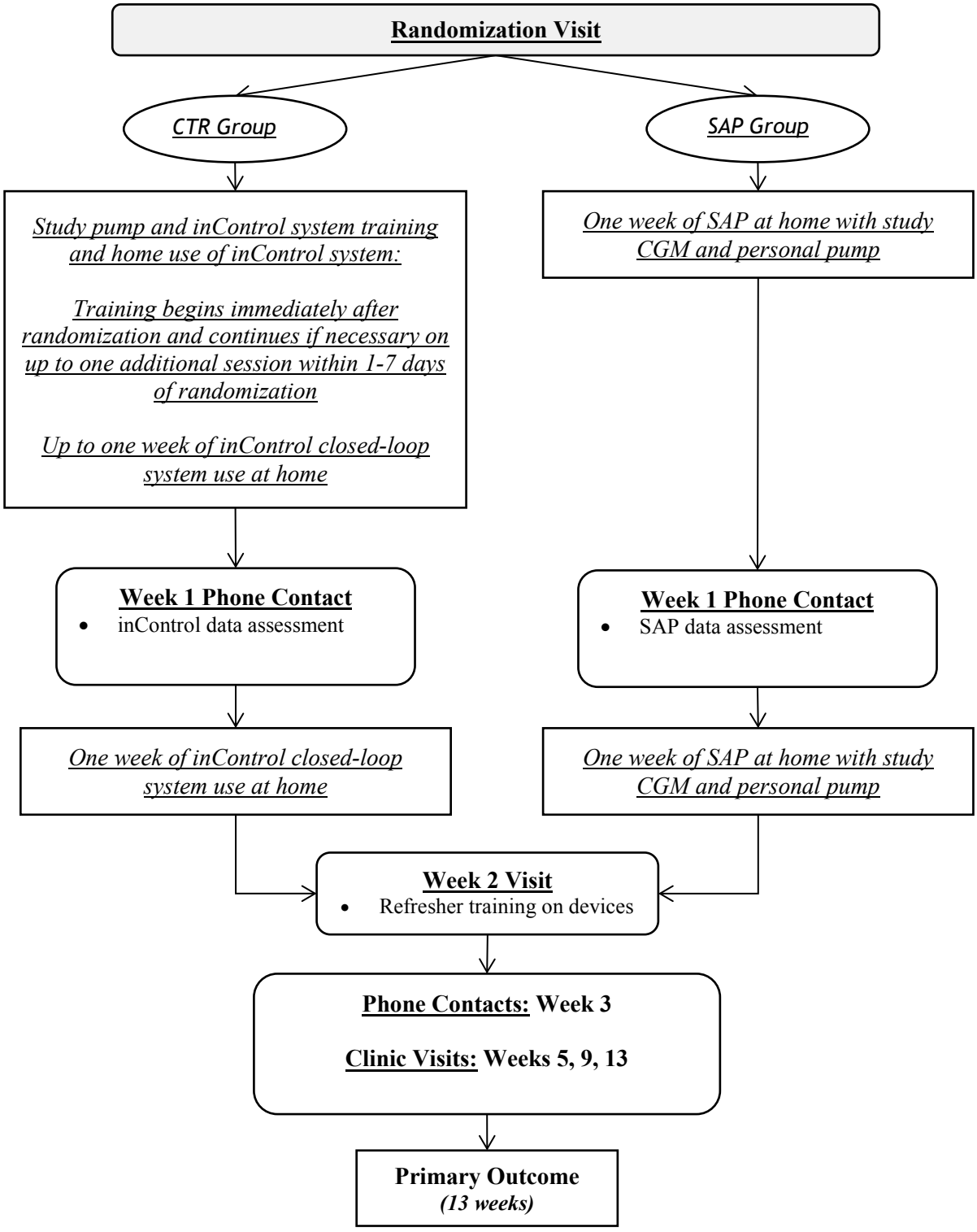

Table 3: Schedule of Study Visits, Phone Contacts, and Key Procedures (Randomization at Week 0)

Purpose	Screen/ Enroll	CGM run-in, if needed	Rand	Follow-Up					
Timing from Randomization	**0-6w prior**	**~2-3w prior**	**0**	**1w** ±3d	**2w** ±3d	**3w** ±3d	**5w** ±1w	**9w** ±1w	**13w** ±1w
Visit or Phone	**V**	**V[1]**	**V**	**P**	**V**	**P**	**V**	**V[2]**	**V**
Eligibility Assessment	X	X	X						
Blinded CGM (2 weeks)		X	X[3]					X	
HbA1c (DCA Vantage or similar point of care device, or local lab)	X		X						X
HbA1c (Central lab)			X						X
C-peptide (Central lab)			X						
Pregnancy test (female participants of child-bearing potential)	X		X						
Device data downloads	X	X	X		X		X	X	X
Review diabetes management and AEs		X	X	X	X	X	X		X
Optimization of insulin pump settings	X	X	X		X				
Clarke Hypoglycemia Awareness Scale, Hyperglycemia Avoidance Scale, Fear of Hypoglycemia Survey, Hypoglycemia Confidence Scale, INSPIRE Survey, and Diabetes Distress Scale			X						X
Diabetes Specific Personality Questionnaire			X						
Technology Expectations Survey (CTR group)			X						
Technology Acceptance Survey (CTR group)									X

[1] Visit not required for all subjects—refer to Figure 7 and Figure 8 above
[2] Non-medical visit; insertion of blinded CGM sensor and download of study device data only
[3] For CTR subjects only who are not using a CGM receiver whose data can be downloaded

1.4.7. Outcomes

Primary Efficacy Outcomes:

The co-primary outcomes are differences in CGM-measured metrics between baseline and 3-month post-randomization period:

- superiority in CGM-measured time below 70 mg/dL, and
- non-inferiority in CGM-measured time above 180 mg/dL

The study will be declared a success if a statistically significant superiority in CGM-measured time below 70 mg/dL along with a non-inferiority in CGM-measured time above 180 mg/dL is observed.

Main Safety Outcomes:

- Episodes of severe hypoglycemia
- Episodes of diabetic ketoacidosis (DKA)
- Other serious adverse events

1.5. 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).

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 subjects to be enrolled by each site towards 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.

Investigational device components may be used by study staff for the purpose of system training and troubleshooting as long as there is no insulin infusion.

CHAPTER 2: SUBJECT SCREENING AND ENROLLMENT

2.1. Study Population

Enrollment will proceed with the goal of randomizing 126 subjects and having at least 110 subjects with sufficient data to include in the primary analysis. A maximum of 200 subjects may be enrolled in the study in order to achieve the goal of randomizing 126 subjects.

In order to have a broad range of glycemic control among the subjects, a study goal will be to have a minimum of 50 subjects with HbA1c ≥7.5% and 50 with HbA1c <7.5%.

2.2. Eligibility and Exclusion Criteria

2.2.1. Eligibility

To be eligible for the study, a subject must meet the following criteria:

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) Use of an insulin pump for at least 6 months
3) Age ≥14 years old
4) HbA1c level <10.5% at screening
5) 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. Subjects who become pregnant will be discontinued from the study. Also, subjects who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.*
6) Willingness not to add non-insulin glucose-lowering agents (such as Pramlintide, Metformin, GLP-1 analogs, SGLT2 inhibitors) during the study
7) Willingness, if not assigned to the closed-loop group, to avoid use of any closed-loop control system for the duration of the clinical trial
8) Willingness to suspend use of any personal CGM for the duration of the clinical trial beginning with the unblinded study CGM run-in period
9) Willingness to establish network connectivity on at least a weekly basis either via local Wi-Fi network or via a study-provided cellular service
10) Currently using no insulins other than one of the following rapid-acting insulins at the time of enrollment: insulin lispro (Humalog), insulin aspart (Novolog), or insulin glulisine (Apidra)
11) Investigator has confidence that the subject can successfully operate all study devices and is capable of adhering to the protocol
12) For subjects <18 years old, living with one or more parent/legal guardian (referred to subsequently as diabetes care partner) committed to participating in study training for emergency procedures for severe hypoglycemia and able to contact the subject in case of an emergency.

2.2.2. Exclusion

The presence of any of the following is an exclusion for the study:

1) Medical need for chronic acetaminophen
2) Use of any glucose-lowering agent (such as Pramlintide, Metformin, GLP-1 analogs, SGLT2 inhibitors) in the 3 months prior to enrollment
3) Hemophilia or any other bleeding disorder
4) A condition, which in the opinion of the investigator or designee, would put the participant or study at risk including any contraindication to the use of any of the study devices per FDA labelling
    - *Individuals should not be enrolled with uncontrolled thyroid disease, renal failure (e.g., dialysis or eGFR <30), or unstable cardiovascular disease. Laboratory testing and other work up needed to determine that an individual is a suitable candidate for the study should be performed as part of usual care*.
5) Participation in another pharmaceutical or device trial at the time of enrollment or during the study
6) Use of a closed-loop system within the last month prior to enrollment
7) Employed by, or having immediate family members employed by 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

2.3. Authorization Procedures

Written informed consent must be obtained prior to performing any study specific procedures with the subject that are not part of the subject's routine care.

For eligible subjects 18 years of age or older, the study will be discussed with the subject and the subject will be provided with an Informed Consent Form to read and will be given the opportunity to ask questions. If the subject agrees to participate, the Informed Consent Form will be signed. A copy of the consent form will be provided to the subject and another copy will be added to the subject's clinic chart.

For eligible subjects under 18 years of age, the care partner will be provided with an Informed Consent Form to read and will be given the opportunity to ask questions. Each subject will be given a Child Assent Form to read and discuss with parents and study personnel. If the care partner and child agree to participate, the Informed Consent Form and Child Assent Form will be signed. A copy of the consent forms will be provided to the subject and his/her care partner and another copy will be added to the subject's clinic chart.

2.4. Screening and Enrollment Visit Logistics

Potential subjects 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. Subject exclusion will be at the discretion of the investigator based on study inclusion/exclusion criteria.

Subjects who do not initially meet study eligibility requirements may be rescreened once 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:

- Subject, and where indicated parent/guardian fully informed about the study and informed consent form/assent form signed according to IRB requirements
- Inclusion and exclusion criteria assessed
- Demographics (date of birth, gender, race and ethnicity, and socioeconomic indicators)
- Contact information
- Diabetic history
- Medical history
- Substance use history (drinking, smoking, and drug habits)
- Concomitant medications
- Physical examination to include:
    - Weight, height
        - Weight measurement will be repeated during the final study visit, in addition to height for subjects <21 years old
    - Vital signs including measurement of blood pressure and pulse
- HbA1c level measured using the DCA Vantage or similar point of care device or local lab (used to assess eligibility)
    - Measurement performed as part of usual clinical care up to two weeks prior to obtaining informed consent for participation in the trial may be used
- Urine or serum pregnancy test for all females of child-bearing potential

Blood draws for any other laboratory testing needed to determine that an individual is a suitable candidate for the study should be performed as part of usual care.

Subjects who are female and menstruating will be asked to keep a log to track menstrual cycles and will be given a paper log to record this information.

Screening procedures will last approximately 1-2 hours.

CHAPTER 3: CGM RUN-IN PHASE

3.1. CGM Run-in Phase Overview

Concurrent with the screening and enrollment visit, the subject will be assessed for the need for CGM run-in activities prior to randomization.

Subjects who used a personal CGM that is the same brand as the study CGM prior to the study for at least 21 of the prior 28 days will proceed directly to randomization. These subjects will have the personal CGM downloaded for capture of two-week baseline data.

All other subjects will participate in the following CGM run-in phases requiring additional clinic visits as shown in Figure 7:

- Two-week period of blinded study CGM use to characterize baseline glycemic control; subjects using a personal CGM prior to the study will continue to use it during this period.
- Two-week period of unblinded study CGM use, with training in using CGM if necessary; subjects using a personal CGM prior to the study will discontinue the personal CGM beginning in this period.

Subjects participating in the CGM run-in phase will receive appropriate training on incorporating CGM into their diabetes management. Training will include the hypoglycemia and hyperglycemia safety protocols in section 6.1 as well as instruction that study CGM readings are affected by acetaminophen use and may be inaccurate for at least 4 hours if a medication containing acetaminophen is taken.

Subjects will receive supplies for blood glucose and ketone testing during this period:

- Blood glucose testing
    - Subjects 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 subject 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.
    - Subjects will be reminded to use the study blood glucose meter for all fingerstick blood glucose measurements during the run-in period.
    - Subjects will be given guidelines for treatment of low or high blood glucose.
- Blood ketone testing
    - Subjects 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 subject 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.
    - Subjects will be instructed to perform blood ketone testing as described in Section 6.1.2.2.
    - Subjects will be given guidelines for treatment of elevated blood ketones
- Subjects will be required to have a home glucagon emergency kit. Subjects who currently do not have one will be given a prescription for the glucagon emergency kit.

3.2. Optimization of Insulin Pump Settings

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

- Prior to Randomization:
    - At the Enrollment Visit for study subjects that do not need to complete a CGM run-in
    - At the Blinded CGM Run-in Review and Unblinded CGM Run-in Review Visits for study subjects participating in the CGM Run-in
- Following Randomization:
    - At the Week 2 visit for all study subjects (both the CTR and SAP Group).
    - If the study subject contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

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.

3.3. Blinded CGM Use

At the screening visit, a CGM sensor will be placed for subjects who will complete the blinded CGM phase. The CGM receiver will be blinded so that the subject is not able to see the CGM glucose values. The subject will be instructed on sensor use including insertion of a new sensor after 7 days (or sooner if the sensor comes out) and will be asked to wear the sensor for 14 days. Additional sensors will be provided. Subjects that currently use a CGM may continue to use the personal CGM in addition to the blinded study CGM.

Subjects will be informed that in order to be eligible for the randomized trial, the blinded CGM must be used on a minimum of 11 out of 14 days.

3.3.1. Blinded CGM Assessment/Unblinded CGM Initiation Visit

Enrolled subjects will return 14 to 21 days after screening to assess the blinded CGM wear. The purpose of the visit will include the following:

- Assessment of compliance with the use of the CGM
- Assessment of skin reaction in areas where a CGM sensor was worn
- Initiation of unblinded CGM use and instructions on its use

3.3.2. Assessment of Blinded CGM

The CGM data will be downloaded and reviewed to assess whether the subject has used the CGM on at least 11 out of 14 days. If the subject is eligible to continue in the study, study staff will follow the procedure for insulin pump optimization described above in section 3.2.

Subjects who are unable to meet the CGM compliance requirement will be withdrawn from the study, unless the investigator believes that there were extenuating circumstances that prevented successful completion. In such cases, the investigator will contact the protocol chair to request approval to repeat this part of the run-in phase.

3.4. Unblinded CGM Use

3.4.1. Initiation of Unblinded CGM

The subject will be provided with sensors and instructed to use the CGM on a daily basis for 2 weeks. Training will be provided to subjects 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. Subjects using a personal CGM prior to the study will discontinue the personal CGM beginning in this period.

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

3.4.2. Assessment of Successful Completion of the Unblinded CGM Run-in Phase

Enrolled subjects will return 14 to 21 days after the initiation of the unblinded CGM visit to assess the unblinded CGM wear. The purpose of the visit will include the following:

- Assessment of compliance with the use of the CGM
- 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 will be downloaded and reviewed. To enter the randomized trial, subjects must have obtained CGM readings on at least 11 out of 14 days. If the subject is eligible to continue in the study, study staff will follow the procedure for insulin pump optimization described above in section 3.2

The exclusion criteria from screening will be reviewed again and if the subject is no longer eligible based on these criteria, he or she will be dropped from the study.

An assessment of CGM knowledge will be made and the subject must demonstrate sufficient competency to proceed to the RCT.

Subjects who are unable to meet the CGM compliance requirements will be withdrawn from the study, unless the investigator believes that there were extenuating circumstances that prevented successful completion. In such cases, the investigator will contact the protocol chair to request approval to repeat this part of the run-in phase.

CHAPTER 4: Randomized Trial

4.1. Randomization Visit

4.1.1. Timing of Visit

The randomization visit may occur concurrently with the Enrollment Visit for subjects who meet CGM use requirements described above. Otherwise, the visit will be concurrent with the Unblinded CGM Run-in Review Visit.

Subjects will receive supplies for blood glucose and ketone testing and associated use guidelines and a prescription for a glucagon emergency kit if needed, as described above. Subjects will be advised to contact the manufacturer's technical support center for technical issues with the study CGM and to call the study physician for any health related issues.

A urine pregnancy test will be repeated for all females of child-bearing potential who participated in the CGM run-in phase.

4.1.2. HbA1c

HbA1c will be measured using DCA Vantage or similar POC device or local lab. A blood sample will also be drawn to send to the central laboratory for baseline HbA1c determination to be used in outcome analyses.

4.1.3. 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.

4.1.4. Randomization

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

1. Control-to-Range (CTR) Closed-Loop Group
2. SAP Group

The subject'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 subject 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 subject until he/she is convinced that the subject/parent will accept assignment to either of the two groups.

4.1.5. Questionnaires

Subjects will complete a set of baseline questionnaires, described in section 5.1, prior to randomization. Subjects randomized into the CTR group will also complete an additional Technology Expectation Survey after randomization.

4.2. Procedures for the CTR Group

4.2.1. Study Pump Training and inControl Training

Subjects randomized to the CTR group will receive study pump training and inControl 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; subjects will not take the inControl system component home until training has been completed.

For subjects <18 years old, the diabetes care partner will be trained on severe hypoglycemia emergency procedures including removal of the study pump and administration of glucagon. The diabetes care partner may also attend any/all of the other training procedures as desired.

Pump training will include:

- The subject [and care partner] will be fully instructed on the study insulin pump. A qualified staff member 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, changing batteries, navigation through menus, bolus procedures including stopping a bolus, etc.
- The study team will assist the subject in study pump infusion site initiation and will start the subject on the study pump. The study pump will be programmed with the subject's usual basal rates and pump parameters. The subject's personal pump will be removed.
- The subject will be supervised with the study pump during at least one meal or snack bolus to ensure subject understanding of the pump features.
- The subject [and care partner] will be encouraged to review the literature provided with the pump, infusion sets, and meter remote after the training is completed.
- Subjects will be asked to perform fingerstick blood glucose measurements in accordance with the labelling of the study CGM device.

The subject [and care partner] will be trained by qualified study staff to use inControl to control the study pump, including meal announcement, meal bolusing, exercise, and switching back and forth between all operational modes (i.e. normal, sleep, and exercise) and insulin modes (closed-loop and pump).

Training will include a series of practice challenges using the different modes of the study system. Prior to initial use, the inControl system will be initialized by a study team member with each subject's individual parameters, including carbohydrate ratio, correction factor, and basal rate pattern.

Subjects will be provided Hypoglycemia, Hyperglycemia and Ketone Guidelines (section 6.1.2.2) for when their glucose levels are >300 mg/dL for more than one hour or >400 mg/dL at any time or <80 mg/dL or ketones ≥0.6 mmol/L.

Study team members will train the subject [and care partner] in performing specific tasks including the following:

- The study team will confirm the pump parameters entered in the system with the study physician.
- How to switch between Closed-Loop mode and Pump mode depending on circumstances, including the need to stop closed-loop for at least 4 hours if a medication containing acetaminophen is taken.
- How to calibrate the CGM unit during the study
- How to access the CGM trace from the sensor via the inControl user interface

- How to activate the "meal" screen of the inControl system any time insulin will be given with a meal and the "add correction" screen any time additional correction insulin is desired
- How to inform the system of hypoglycemia treatment via a "hypoglycemia treatment" button on the inControl user interface after glucose is consumed that is not accompanied by an insulin bolus
- What to do when exercising while using the system
- How to enable the sleep function when sleep schedule will differ from normal parameters
- How to perform blood ketone testing and perform rescue therapy actions with the glucagon kit
- The subject [and care partner] will be assessed for understanding of the system interface and how to react to safety/alert notification.
- Subjects will be reminded to perform fingerstick blood glucose measurements in accordance with the labelling of the study CGM device.
- The subject [and care partner] will be given a printed User Guide as a reference.

The subject will be instructed to use the system in closed-loop mode except when no calibrated CGM sensor is available.

The subject 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 (e.g. for the emergency treatment of a severe allergic reaction or asthma attack) or oral or injectable glucocorticoids to determine if closed-loop use should be temporarily discontinued.

Subjects will be given the inControl device and will be provided with sufficient supplies to last until the subsequent clinic visit.

Subjects will be provided with technical support or manufacturer contact information for technical issues with inControl, study insulin pump or study CGM and will be asked to call the study physician for any health related issues. Subjects may use the study pump and study CGM during periods of inControl disconnections or technical difficulties. Subjects will also receive study staff contact information to ask any questions they may have during the study.

4.2.2. Blinded CGM Insertion

Subjects in the CTR group who are not using a CGM receiver whose data can be downloaded will have an additional CGM sensor and transmitter placed and will be given a blinded CGM receiver to collect data from this sensor during the first two weeks following randomization. This will allow the clinician to retrospectively assess CGM data from this period at the 2-Week visit using the exact same tool that will be used for subjects in the SAP group.

4.2.3. Home Use of inControl System

After training on the study pump and inControl system has been completed, subjects will proceed with home use (meaning free-living use at work, home, etc.) of the inControl system.

Subjects will be instructed not to use any non-study software applications that are designed to receive real-time CGM values from the study CGM transmitter.

4.2.4. Study Device Data Transmission

Subjects will be instructed to establish network connectivity for the inControl system on at least a weekly basis throughout the remainder of the study either via local Wi-Fi network or via a study-provided cellular service to allow data synchronization with study servers.

4.2.5. 1-Week Phone Contact

Study staff will perform a phone call with the subject within 7 (±3) 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

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

4.2.6. 2-Week Visit (Training Review and Insulin Pump Optimization)

The subject will be offered review training to address any questions on the use of inControl and the study pump, including meal announcement, meal bolusing, exercise, and switching back and forth between all operational modes.

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 above in section 3.2 using the available downloaded CGM 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.

4.3. Procedures for the SAP Group

Subjects in the SAP Group will continue to use their personal insulin pumps in conjunction with the study CGM, blood glucose meter, and ketone meter. Subjects may use commercially available features of the study CGM system related to mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose.

4.3.1. Study Device Data Transmission

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

4.3.2. 1-Week Phone Contact

Study staff will perform a phone call with the subject within 7 (±3) 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 subject will continue on SAP for a second week, then return to the clinic 14 (±3) days from the date of randomization.

4.3.3. 2-Week Visit (Training Review and Insulin Pump Optimization)

The subject 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 above 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 subject will be instructed to upload data from the CGM receiver at least once every two weeks for the remainder of the study.

4.4. 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 subject that periodic contact is required and will make arrangements with the subject for the contacts. If the subject (or care partner, for subjects less than 18 years old) cannot be reached, the subject's other contact methods will be utilized, including the emergency contact.

4.4.1. Follow-up Visits

Follow-up visits will occur at:

- 5 weeks (±1 week)
- 9 weeks (±1 week)
- 13 weeks (±1 week)

4.4.1.1. Procedures at Follow-up Visits

Procedures performed in both groups at each visit, unless otherwise specified below:

- 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 CGM, study BG meter, study ketone meter, inControl cloud data, pump if supported)

Procedures Specific to the 9-Week Visit

A blinded CGM device will be inserted in subjects in both the CTR and SAP groups, to be worn for the subsequent two weeks for the purpose of:

- Obtaining CGM data for outcome assessment of subjects who have become non-adherent to use of the study CGM
- Obtaining CGM data from a sensor independent from closed-loop system operation to support assessment of bias in CGM-measured outcomes

Blinded CGM devices will be physically returned to the clinic or mailed to the clinic for assessment. If it is found that fewer than 14 days of data were captured, the subject may be asked to capture additional blinded data prior to the 13-week visit.

Procedures Specific to the 13-Week Visit

- 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 end-of-study questionnaires
- Weight measurement will be repeated, in addition to height for subjects <21 years old

4.4.2. Phone Contacts

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

3-Week Phone Contact

A phone call will be made to the subject or care partner at 3 weeks (±3 days) and the following procedures performed in both treatment groups:

- Review of available CGM and/or inControl 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

CHAPTER 5: QUESTIONNAIRES

5.1. Introduction

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 *(CTR group only)*

The following questionnaires will be completed at the final visit at week 13:

- 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 *(CTR group only)*

Each questionnaire is described briefly below. The procedures for administration are described in the study procedures manual.

5.2. Diabetes Specific Personality Questionnaire

The Diabetes Specific Personality Questionnaire (15) is based on the original Six Factor Personality Questionnaire (16), 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.

5.3. Clarke's Hypoglycemia Awareness Scale

The scale (17) comprises eight questions characterizing the subject'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.

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

The Hypoglycemia Fear Survey-II (18) 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 above 150 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.

5.5. Hyperglycemia Avoidance Survey (HAS) / High Blood Sugar Survey

The HAS (19) 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.

5.6. Hypoglycemia Confidence Scale

The HCS (20) 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.

5.7. Diabetes Distress Scale

The Diabetes Distress Scale (21) 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.

5.8. Technology Expectation and Technology Acceptance Surveys

The Technology Expectation and Technology Acceptance Surveys were developed for a Bionic Pancreas camp study (22). 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.

5.9. 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.

CHAPTER 6: SAFETY MEASURES

6.1. Safety Measures

6.1.1. CGM Calibration

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

6.1.2. Safety Measures for Open-Loop CGM Use

These measures apply to subjects in the SAP group throughout the course of the study and also to subjects in the CTR group during periods when the closed-loop system is not being used or is not communicating with the CGM device.

6.1.2.1. Hypoglycemia Threshold Alarm and Safety Protocol

All subjects will initially be required to set the CGM hypoglycemia threshold alarm to a value no less than 60 mg/dL. During the course of the study, subjects will be permitted to change this setting, but will be instructed to choose a value no less than 60 mg/dL.

If a subject receives a CGM hypoglycemia threshold alarm or notes that the CGM glucose is below the hypoglycemia threshold alarm value, confirmatory fingerstick testing will be performed if required by CGM labelling and the subject will be instructed to treat hypoglycemia with ~16 grams of fast-acting oral glucose.

6.1.2.2. Hyperglycemia Threshold Alarm and Safety Protocol

All subjects will initially be required to set the CGM hyperglycemia threshold alarm to a value no greater than 300 mg/dL. During the course of the study, subjects will be permitted to change this setting, but will be instructed to choose a value no greater than 300 mg/dL.

If a subject receives a CGM hyperglycemia threshold alarm or notes that the CGM glucose is above the hyperglycemia threshold alarm value, confirmatory fingerstick testing will be performed if required by CGM labelling.

If a subject's CGM reading is ≥300 mg/dL for over 1 hour, or ≥400 mg/dL at any point, the subject user manual instructs the subject to take the following steps:

- Perform a blood ketone measurement with the study ketone meter. Subjects will also be encouraged to check ketones if they are clinically concerned.
- Correction insulin may be taken per the subject's usual routine.
- Subjects will be instructed to change their pump site and administer correction insulin via insulin syringe or pen for ketones ≥0.6 mmol/L and to additionally notify study staff for ketones ≥3.0 mmol/L.

6.1.3. Safety Measures Specific to Control-to-Range (CTR) Closed-Loop Group

6.1.3.1. Insulin Dosing

In Closed-Loop mode, all dosing is supervised by a dedicated basal attenuation module. Insulin injection for meal boluses must be manually confirmed, and insulin on board (IOB) constraints avoid inappropriate insulin stacking. In the case of a system crash or any interruption of communication

between inControl and the insulin pump, the pump will revert to the preprogrammed basal delivery within a short period of time (maximum 30 minutes). Each bolus is checked by the algorithm to ensure that it does not exceed a maximum threshold depending on whether the bolus is for a meal, for a correction, or for usual basal delivery.

6.1.3.2. Hypoglycemia Safety Protocol

The inControl system will issue a hypoglycemia alarm if the CGM is <70 mg/dL or when the system predicts BG <70 mg/dL within the next 15 to 30 minutes. The system also includes an additional threshold alarm that may be configured by study staff per subject preference.

If the subject receives a hypoglycemia alarm from inControl, a message appears on the UI that is accompanied by vibration and sound. This alert recurs if not acknowledged by the user. The user is prompted with a checklist to do the following:

- Check blood glucose
- Treat with fast acting carbohydrates

6.1.3.3. Hyperglycemia Safety Protocol

The inControl system will issue a predictive hyperglycemia alarm if the system detects prolonged resistance to insulin treatment and the BG is estimated to be above 200 mg/dL.

If the subject receives a hyperglycemia alarm from inControl, a message appears on the UI that is accompanied by vibration and sound. This alert recurs if not acknowledged by the user. The user is prompted with a checklist to do the following:

- Confirm hyperglycemia with a fingerstick
- Consider possible reasons including missed boluses for carbs, infusion site problems, pump occlusions, insulin degradation, sickness, and menstruation

If a subject's CGM reading is ≥300 mg/dL for over 1 hour, or ≥400 mg/dL at any point, the subject user manual instructs the subject to take the following steps:

- Perform a blood ketone measurement with the study ketone meter. Subjects will also be encouraged to check ketones if they are clinically concerned.
- Correction insulin may be taken per the subject's usual routine.
- Subjects will be instructed to change their pump site and administer correction insulin via insulin syringe or pen for ketones ≥0.6 mmol/L and to additionally notify study staff for ketones ≥3.0 mmol/L.

6.1.3.4. Remote Monitoring

The inControl remote monitoring portal (inControl Cloud) automatically logs system data such as CGM values, insulin delivery details, and system alarms and allows data from any inControl device to be monitored remotely in real-time, provided the device has Wi-Fi or cellular data connectivity.

Clinical site personnel may perform ad hoc real-time monitoring during the study in response to subject questions or to troubleshoot system problems. However, the system will not be configured to send automated notification messages regarding subject glycemic control or potential system malfunctions to these personnel.

Technical personnel may also perform ad hoc real-time monitoring during the study to support clinical personnel with subject questions and troubleshooting. In addition, the system will log information regarding potential system malfunctions to a central location for periodic technical monitoring.

6.1.3.5. CGM Sensor Connection Failure

If the CGM signal becomes unavailable for >20 minutes, Closed-Loop mode will not operate. If the pump is connected, the system will revert to Pump mode and deliver insulin with the most recent insulin dosing parameters programmed in the system for that individual. Resumption of Closed-Loop will occur automatically by the system once CGM signal is available again.

6.1.3.6. Pump Connection Failure

If inControl is unable to establish required pump connectivity for >20 minutes, the system will revert to Stopped mode and display a message accompanied by vibration or sound. The insulin pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the controller once the 0% temporary basal rate last directed by inControl times out. Alternatively, the subject can cancel the temp basal on the insulin pump and immediately resume basal insulin administration.

6.1.3.7. Study System Failure

If the study system stops working for more than 30 minutes, the pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the controller.

CHAPTER 7: ADVERSE EVENTS, DEVICE MALFUNCTIONS, POTENTIAL RISKS, AND STOPPING RULES

7.1. 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.

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: A device complication or complaint is something that happens to a device or is 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.

Device Malfunction: 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)

7.2. 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 7.1, unless excluded from reporting in section 7.3

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

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.

7.2.1. 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 loss of consciousness. 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.

7.2.2. Hyperglycemic Events/Diabetic Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following criteria is met: (1) the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below, or (2) in the absence of DKA if evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis.

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.

7.2.3. 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.

7.2.4. 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.

7.2.5. 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.

7.2.6. Outcome of Adverse Event

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

- RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- 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.
- 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).

- 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.

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.

7.3. 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 7 days
- 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 don't meet criteria for AE reporting

7.4. Pregnancy Reporting

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

7.5. Timing of Event Reporting

Serious or unexpected device-related adverse events must be reported to the Coordinating Center within 24 hours via completion of the online serious adverse event form.

Other reportable adverse events and device malfunctions (with or without an adverse event) will be reported within 3 days of the investigator becoming aware of the event by completion of an electronic case report form.

Device complaints not associated with device malfunction or an adverse event must be reported within 7 days of the investigator becoming aware of the event.

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 ten 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.

Device malfunctions will be handled by the Sponsor or designee as described below. In the case of a CGM transmitter or sensor device malfunction, the Coordinating Center will be contacted and the Sponsor will be notified accordingly.

7.6. Data and Safety Monitoring Board

The DSMB will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. Details regarding review will be documented in standalone DSMB procedural documentation.

7.7. Potential Risks and Side Effects

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 subjects with type 1 diabetes and subjects will be closely monitored for this. When wearing sensors and insulin infusion sets there is always a risk of skin rashes, allergic reactions to the tape, or infections at the insertion site. There is always a risk for a small piece of a sensor remaining under the skin or a sensor or infusion set breaking off under the skin.

7.7.1. 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.

7.7.2. 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.

7.7.3. Subcutaneous Catheter Risks (CGM)

Subjects 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 subject 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 subject should be further instructed to notify the study coordinator immediately if this occurs.

7.7.4. 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 subject 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.

7.7.5. 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.

7.7.6. Risk of Device Reuse

The study CGM system is labeled for single-patient use only. The sensor (the component of the system that enters the skin) will be single-patient 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 handheld device. Subjects 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.) Subjects will be informed that FDA or relevant national authorities have approved 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.

7.7.7. Psychosocial Questionnaires

As part of the study, subjects will complete psychosocial questionnaires which include questions about their private attitudes, feelings and behavior related to 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.

7.7.8. Other Risks

Some subjects 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 subjects will be carefully instructed about proper use of the sensor.

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

7.8. 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 the prospect of direct benefit to the subjects and general benefit to others with diabetes.

7.9. Study Stopping Criteria

7.9.1. Subject Discontinuation of Study Treatment

Rules for discontinuing closed-loop use (if randomized to CTR group) or study CGM use (if randomized to the SAP group) are as follows:

1. The investigator believes it is unsafe for the subject to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or subject behavior contrary to the indications for use of the device that imposes on the subject's

safety—e.g., SAP subject with recurring hypoglycemia due to large correction boluses based on CGM values without confirmatory fingerstick (assuming contraindicated by CGM labelling); or CTR subject with recurring hypoglycemia due to over-boluses in closed-loop with the expectation that the system will prevent hypoglycemia

2. The subject requests that the treatment be stopped
3. Subject pregnancy

In addition, closed-loop use will be discontinued if either of the following occurs:

1. Two distinct episodes of severe hypoglycemia as defined in section 7.1 related to automated insulin delivery
2. Two distinct episodes of DKA as defined in section 7.1 related to automated attenuation of insulin delivery

Even if study treatment is discontinued, the subject will remain in the study and will be encouraged to participate in study activities such as scheduled phone calls, clinic visits, device downloads, blinded CGM use, and HbA1c measurements, with priority given to trying to have the subject complete the 13-week visit.

7.9.2. Criteria for Suspending/Stopping Overall Study

In the case of a system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in Section 7.1) during closed-loop control either due to excess insulin administration or inappropriate suspension that occurs more than one time, enrollment visits, randomization visits, and all use of the closed-loop system in the study 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.

As stated in Section 7.6, the study DSMB will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. The DSMB will request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

CHAPTER 8: MISCELLANEOUS CONSIDERATIONS

8.1. 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. This research is a definitive step on the path towards development of a fully closed-loop system. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the subjects and general benefit to others with diabetes.

8.2. Subject Compensation

Subjects will be compensated $50 (or local equivalent) for each separate clinic visit during the study.

8.3. Subject Withdrawal

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

8.4. Confidentiality

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

CHAPTER 9: STATISTICAL CONSIDERATIONS

The approaches to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study.

The co-primary outcomes for this study are CGM-measured % below 70 mg/dL and % above 180 mg/dL over a 3-month period. The intervention will be considered effective if both of the following comparisons between two treatment arms (SAP vs. CTR) are statistically significant ($p < 0.05$):

- superiority test for % time CGM values below 70 mg/dL and
- non-inferiority test for % time CGM values above 180 mg/dL (non-inferiority limit = 5%).

9.1. Sample Size

Sample size has been computed using co-primary outcomes of time <70 mg/dL (superiority) and time >180 mg/dL (non-inferiority). Data from the CGM arm of the JDRF CGM RCT from subjects meeting the eligibility criteria for the current trial were used to project the distribution of % below 70 and above 180 mg/dL over 3 months as measured by CGM for the SAP group in the proposed study.

The total sample size was computed to be 110 for the following assumptions: (1) 1:1 randomization, (2) 90% power, with adjustment to account for the two co-primary analyses, (3) a 50% relative reduction in time <70 mg/dL (or absolute reduction of 2.0% assuming baseline of 4.0%) with an effective SD of 2.8% and 2-sided type 1 error of 5%, and (4) a non-inferiority limit of 5% for the treatment group comparison of time >180 mg/dL and assuming there is a true difference of 2.5% favoring the CTR group, with an effective standard deviation of 11% and a 1-sided type 1 error of 2.5%. The sample size was increased to 126 to account for subjects with insufficient data to include in the primary analysis (see section 9.2).

The Appendix provides further details of the sample size assumptions and computations.

9.2. Calculation of Outcome Metrics and Handling of Missing Data

CGM Metrics

Randomization is preceded by two weeks of blinded CGM run-in or by presenting at least three weeks of personal CGM data. The two weeks of blinded run-in or the last two weeks of personal CGM data will be used in the calculation of baseline CGM metrics.

Per protocol design, the first two weeks following the randomization visit involve a training schedule for both groups. CGM data during this time will not be included in the calculation of the outcome CGM metrics. Unblinded CGM data starting from Week 3 post-randomization through the 3 month visit will be included in the calculation of each CGM metric. Missing (or less than 168 hours) post-randomization unblinded sensor data will be imputed using all available post-randomization blinded data. Subjects with any amount of post-randomization unblinded or blinded data will be included in CGM analyses. Percentages <70 and >180 mg/dL will be calculated giving equal weight to each CGM point for each subject.

The two weeks of blinded CGM data collected after 9 weeks will not be used for the primary outcome; except for imputations as mentioned above.

HbA1c

If the 3-month visit is completed but an HbA1c measurement from the central laboratory is not available, a local HbA1c measurement made at the clinical site at the 3-month visit will be used if available. In such cases the HbA1c value used in the analysis will be computed from a regression line using the available lab-local HbA1c pairs. A similar imputation will be done for any missing lab HbA1c values at baseline or other visits. If neither measurement at 3 months is available, then the HbA1c value will be considered missing and the subject will be excluded from all HbA1c analyses.

9.3. Primary Analyses

The primary analysis will follow the intention-to-treat principle. It will include all randomized subjects, the data from whom will be analyzed in the group to which the subjects were assigned through randomization.

The intervention will be declared effective only if a statistically significant result (p-value<0.05) is obtained for both co-primary outcomes. The type 1 error is therefore not inflated by two co-primary outcomes.

9.3.1. Changes in CGM-Measured % below 70 mg/dL from Run-in to 3-Months Post-Randomization Period between the Two Treatment Arms

Summary statistics (median, quartiles) will be reported for the CGM % <70 mg/dL by treatment group.

Changes from run-in pre-randomization CGM wear (data generated as described above) to the 3-month post-randomization period in CGM-measured % <70 mg/dL between two treatment arms will be compared using a linear mixed effects regression model with a log(x+0.005) transformation while adjusting for the baseline CGM % <70 mg/dL and clinical center (random effect). Residual values will be examined for an approximate normal distribution. If values are highly skewed even after the transformation, then an alternate transformation or robust statistical method (e.g., non-parametric or MM estimation) will be used instead.

9.3.2. Changes in CGM-Measured % above 180 mg/dL from Run-in to 3-Months Post-Randomization Period between the Two Treatment Arms

Summary statistics (median, quartiles) will be reported for the CGM % >180 mg/dL by treatment group.

Changes from run-in pre-randomization to over 3-months post-randomization in CGM-measured % >180 mg/dL between two treatment arms will be compared using a linear mixed effects regression model; while adjusting for % >180 during run-in, and clinical center (random effect). A 2-sided 95% confidence interval for the difference between treatment arms will be generated. Separate two-sided p-values will be calculated to test non-inferiority and superiority. Since non-inferiority is often denoted in terms of a one-sided test, it is worth noting that a two-sided test at alpha = 0.05 gives the same rejection region in the right tail as a one-sided test at alpha = 0.025. It is also worth noting that the additional hypothesis test for superiority does not inflate the overall alpha since a type 1 error can only occur if the two-sided 95% confidence interval fails to contain the true difference. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or robust statistical method (e.g., non-parametric or MM estimation) will be used instead.

9.4. Secondary Efficacy Analyses

In secondary analyses, treatment group differences will be assessed for additional CGM metrics and HbA1c. For all secondary analyses (including sections 9.5, 9.6, and 9.7), the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure with <0.10 as the threshold for statistical significance.

Secondary glycemic metrics based on CGM data will include the following outcomes:

CGM Metrics Related to Overall Control

- mean glucose
- % in range of 70-180 mg/dL
- % in range 70-140 mg/dL
- glucose variability measured with the coefficient of variation

CGM Metrics Related to Hypoglycemia

- % <60 mg/dL
- % <54 mg/dL
- low blood glucose index
- hypoglycemia events (defined as at least 15 consecutive minutes <70mg/dL)

CGM Metrics Related to Hyperglycemia

- % >250 mg/dL
- % >300 mg/dL
- high blood glucose index

The analyses for the above CGM will parallel those mentioned above for the primary % below 70 mg/dL outcome, with the exception that a transformation will not be used for those metrics with a distribution that is approximately normally distributed. Summary statistics will be reported mean ± SD or median (quartiles) as appropriate to the distribution.

A comparison of primary and secondary results during the daytime and overnight will be made.

HbA1c

Change in HbA1c from baseline to 13 weeks will be compared between the two treatment arms using a linear model while adjusting for baseline HbA1c and clinical center (random factor).

Several binary outcomes will be compared between treatment groups using central lab HbA1c values.

- HbA1c <7.0% at 13 weeks
- HbA1c <7.5% at 13 weeks
- HbA1c improvement from baseline to 13 weeks $\geq$0.5%
- HbA1c improvement from baseline to 13 weeks $\geq$1.0%
- HbA1c relative improvement from baseline to 13 weeks $\geq$10%
- HbA1c improvement from baseline to 13 weeks $\geq$1.0% or HbA1c <7.0% at 13 weeks

Our goal is to minimize the amount of missing data and it is worth noting that all statistical methods for handling missing data rely on untestable assumptions and there is no one correct way to handle missing data. If some HbA1c data will be missing, in addition to the completer-only analyses

mentioned above, sensitivity analyses will be perform in order to confirm that the conclusions do not rely on the statistical methods employed for handling missing data. Replication of the HbA1c analyses with imputed data for subjects with missing both local and central lab HbA1c at 13 weeks will be done using two methods:

- Rubin's multiple imputation and
- Direct likelihood

9.5. Additional Treatment Group Comparisons

- Insulin
  - Total daily insulin (units/kg)
  - Basal: bolus insulin ratio
- Weight and Body Mass Index
- Clarke Hypoglycemia Awareness Scores
- INSPIRE survey scores

The analyses for the above metrics will parallel those mentioned above for the secondary efficacy outcomes.

9.6. Quality of Life Questionnaires

The following questionnaires will be completed at baseline and at 13 weeks:

- 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

For each questionnaire, mean ± SD values or percentiles appropriate to the distribution will be given by randomization group for the total score and each subscale. 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.

9.7. Subgroup Analyses

In exploratory analyses, the two primary outcomes (% <70 and >180 mg/dL) 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 (as continuous variable and in the two subgroups ≥7.5% and <7.5%)
- Baseline CGM time spent <70 mg/dL
- Baseline CGM time spent >180 mg/dL
- Age: As a continuous variable and in these subgroups
    - <25
    - ≥25
- Gender
    - Female
    - Male
- Race
    - White
    - Non-White (split if sample size allows)
- 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

9.8. Safety Analyses

All randomized subjects 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 7.1)
- Diabetic ketoacidosis (as defined in Section 7.1)
- Other serious adverse events (SAE) and serious adverse device events (SADE)
- 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

The numbers will be compared between the two treatment arms using robust Poisson regression and the percentage of subjects with at least one event will be compared using Fisher's exact test.

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

9.9. Additional Tabulations and Plots

The following tabulations will be performed according to treatment group without statistical testing:

- baseline demographics and clinical characteristics, including Diabetes Specific Personality Questionnaire score
- flow chart accounting for all subjects for all visits
- visit and phone contact completion rates for each follow-up visit
- number and reasons for unscheduled visits and phone calls
- number of subjects who stopped treatment and reasons
- sensor use – hours of use and days with any sensor use per week - overall and by month
- The daily frequency of downloaded BGM use - overall and by month
- Sensor performance metrics (difference, absolute relative difference, and International Organization for Standardization criteria) – if applicable, by sensor version.
- % time CGM data available
- protocol deviations
- device malfunctions requiring study team contact and other reported device issues
- 24 hours plots with median line and IQR bands for % CGM <70 mg/dL, >180 mg/dL, mean, 70-180 mg/dL, and coefficient of variation

9.10. Tabulations in CTR Arm Only

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

- performance metrics, describing the inControl system and its components
- % time CGM data were available to the inControl System
- hours of different CL mode use per week - overall and by month
- Technology Expectations Survey score at baseline and Technology Acceptance Survey score at 13 weeks

9.11. Sensitivity Analyses

If more than 5% of subjects have fewer than 168 hours of post-randomization CGM data, the two co-primary analyses will be replicated excluding such subjects.

9.12. Other Analyses

Additional analyses that will be detailed in the Statistical Analysis Plan will include the following:

- Blinded CGM data
    - Treatment group comparisons paralleling the unblinded CGM data analyses
    - Comparison of blinded and unblinded CGM data from the same time periods
    - Comparison of unblinded CGM data from the blinded time periods versus the unblinded CGM data from the rest of the follow-up period
- Effect of menstrual cycle to glycemic control and comparison of treatment groups during different menstrual cycle periods.

CHAPTER 10: DATA COLLECTION AND MONITORING

10.1. 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.

10.2. 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 to 21 Code of Federal Regulations (CFR) 812.

The data of most importance for monitoring at the site are subject 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
- 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.

APPENDIX: Sample Size Estimation for the *i*DCL Trial

The objective of this clinical trial is assess the efficacy and safety of home use of a standard Control-to-Range (sCTR) closed-loop (CL) system with minimal central safety monitoring compared with sensor augmented pump therapy (SAP) in subjects with type 1 diabetes. The CL system was primarily designed to reduce hypoglycemia while also keeping hyperglycemia under control. Given this design, a co-primary of superiority in hypoglycemia along with a non-inferiority in hyperglycemia are proposed for the study.

Major eligibility criteria are:

- Clinical diagnosis of type 1 diabetes
- Use of an insulin infusion pump for at least 6 months
- Age ≥14.0 years old

Primary Analyses

The primary analysis in this study will be a combination of two different hypothesis tests comparing the two treatment arms:

- CGM percent time below 70 mg/dl (superiority)
- CGM time above 180 mg/dl (non-inferiority)

1. Using JDRF CGM RCT data to estimate sample size

The JDRF CGM RCT was a parallel group 12-months randomized trial comparing open loop CGM use and self-monitoring of blood glucose (SMBG) versus SMBG alone. Data from the treatment /CGM group in the JDRF CGM RCT were used to estimate CGM data in the control group of the proposed study. CGM data for the first 2 weeks were used to simulate a mock run-in phase, the next 2 weeks were discarded, and the next 13 weeks were used to estimate time below 70 mg/dl and time above 180 mg/dl means and variances.

There were N=125 subjects randomized to open-loop CGM use who met the following criteria:

- using a pump for at least 6 months,
- age ≥14.0 years,
- at least 168 hours of CGM data (i.e. at least 50%) during the 2-week mock run-in phase.

2. Primary Analysis

The co-primary outcomes are:

- superiority in CGM-measured time below 70 mg/dl, and
- non-inferiority in CGM-measured time above 180 mg/dl over 3 months (non-inferiority limit of 5%).

The study will be declared a success only if both tests listed above reject the null hypothesis.

CGM time below 70 mg/dl

Among all 125 subjects in the JDRF data, the mean % below 70 mg/dl over 13 weeks = 4.0%, the mean % below 70 mg/dl during the 2 weeks run-in phase = 3.7%, and the correlation between the two = 0.74. The SD for % below 70 mg/dl over 13 weeks = 3.3% (95% CI: 2.9%, 3.8%). A more conservative correlation of 0.5 was used for an effective SD = 2.8% (95% CI: 2.5%, 3.3%).

CGM time above 180 mg/dl

Among all 125 subjects in the JDRF data, the mean % above 180 mg/dl over 13 weeks = 27%, the mean % above 180 mg/dl during the 2 weeks run-in phase = 27%, and the correlation between the two = 0.80. The SD for % above 180 mg/dl over 13 weeks = 13% (95% CI: 11%, 15%). A more conservative correlation of 0.5 was used for an effective SD = 11% (95% CI: 10%, 13%).

Combined inference

For the primary analysis, the intervention will be considered effective only if both co-primary outcomes are found to be statistically significant. Instead of inflating the type 1 error, requiring both comparisons to be statistically significant slightly inflates type 2 error. The lower bound for the overall combined power to reject both null hypothesis will be computed using Bonferroni adjustments.

The total sample size was computed to be 110 for the following assumptions:

- 1:1 randomization scheme,
- 90% overall power that accounts for the two co-primary analyses,
- A 50% relative reduction in time <70 mg/dL of (i.e., 4.0% vs. 2.0% absolute time) with an effective SD of 2.8% and 2-sided type I error of 5%,
- A non-inferiority limit of 5% for the treatment group comparison of time >180 mg/dL and assuming there is a true difference of 2.5% favoring the CTR group, with an effective standard deviation of 11% and a 1-sided type I error of 2.5%.

The assumptions above with a sample size of N=110 give statistical power:

- 96% for the hypoglycemia comparison (superiority) and
- 94% power for the hyperglycemia comparison (non-inferiority).

Using a Bonferroni bound, the overall power that both tests will reject the null hypothesis is at least 94% + 96% - 100% = 90%.

4. Summary

For the primary analysis, the intervention will be considered effective if a statistically significant reduction in % below 70 mg/dl along with an equivalence in % above 180 mg/dl over 3 months (with a non-inferiority limit of 5%) will be found (co-primary outcomes). Assuming an overall power >90%, an effective SD of 2.8% and a 50% relative reduction in % below 70 mg/dl (or absolute reduction of 2.0% assuming baseline of 4%) along with an effective SD of 11%, an improvement of 2.5%, and a non-inferiority limit of 5% in % above 180mg/dl, a minimum total sample size of 110 is needed.

The final sample size was selected to be 126 to account for possible non-compliance or dropout.

REFERENCES

1.Kovatchev B, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Anderson SM, Brown SA, Chernavvsky DR, Breton MD, Farret A, Pelletier MJ, Place J, Bruttomesso D, Del Favero S, Visentin R, Filippi A, Scotton R, Avogaro A, Doyle FJ, 3rd: Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 36:1851-1858, 2013

2. Kovatchev BP, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Anderson SM, Brown SA, Chernavvsky DR, Breton MD, Mize LB, Farret A, Place J, Bruttomesso D, Del Favero S, Boscari F, Galasso S, Avogaro A, Magni L, Di Palma F, Toffanin C, Messori M, Dassau E, Doyle FJ, 3rd: Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care 37:1789-1796, 2014

3. DeSalvo DJ, Keith-Hynes P, Peyser T, Place J, Caswell K, Wilson DM, Harris B, Clinton P, Kovatchev B, Buckingham BA: Remote glucose monitoring in camp setting reduces the risk of prolonged nocturnal hypoglycemia. Diabetes Technol Ther 16:1-7, 2014

4. Ly TT, Breton MD, Keith-Hynes P, De Salvo D, Clinton P, Benassi K, Mize B, Chernavvsky D, Place J, Wilson DM, Kovatchev BP, Buckingham BA: Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp. Diabetes Care 37:2310-2316, 2014

5. Ly T, Chernavvsky DR, Satin-Smith M, DeSalvo DJ, Shanmugham S, Keith-Hynes PT, Breton MD, Buckingham BA: Closed-loop control with DIAS vs. sensor-augmented pump therapy in adolescents and young adults with type 1 diabetes at camp In Advanced Technologies and Treatments for Diabetes (ATTD*)* Paris, France, 2015, p. 99-L

6. Kropff J, Del Favero S, Place J, Toffanin C, Visentin R, Monaro M, Messori M, Di Palma F, Lanzola G, Farret A, Boscari F, Galasso S, Magni P, Avogaro A, Keith-Hynes P, Kovatchev BP, Bruttomesso D, Cobelli C, DeVries JH, Renard E, Magni L: 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. Lancet Diabetes Endocrinol 3:939-947, 2015

7. Renard E:. Reduction of hyper- and hypoglycemia during two months with a wearable artificial pancreas from dinner to breakfast in patients with type 1 diabetes. In Boston, MA American Diabetes Association 75th Scientific Sessions, 2015, p. poster 940-P

8. Anderson S:. First New Year's Night on closed-loop control (CLC) at home: Case reports from a multi-center international trial of long-term 24/7 CLC In American Diabetes Association 75th Scientific Sessions Boston, MA, 2015, p. 223-OR

9. Kovatchev B:. JDRF Multi-Center 6-Month Trial of 24/7 Closed-Loop Control
In Advanced Technologies and Treatments for Diabetes (ATTD): Plenary Session Milan, Italy, 2016

10. Kovatchev B:. Closed-loop control modalities in type 1 diabetes: Efficacy and system acceptance. In Advanced Technologies and Treatments for Diabetes (ATTD*)* Paris, France, 2015

11. Del Favero S:. A multicenter randomized cross-over Italian pediatric summer camp: AP vs SAP in 5-8 year old children
In Advanced Technologies and Treatments for Diabetes (ATTD): Plenary Session Milan, Italy, 2016

12. Chernavvsky DR:. Closed-loop control during extended winter-sport exercise in youth with T1DM: Results from the first AP ski camp. In Advanced Technologies and Treatments for Diabetes (ATTD): Data Club Session Milan, Italy, 2016

13. Chernavvsky DR, DeBoer MD, Keith-Hynes P, Mize B, McElwee M, Demartini S, Dunsmore SF, Wakeman C, Kovatchev BP, Breton MD: Use of an artificial pancreas among adolescents for a missed snack bolus and an underestimated meal bolus. Pediatr Diabetes 17:28-35, 2016

14. Brown SA, Kovatchev BP, Breton MD, Anderson SM, Keith-Hynes P, Patek SD, Jiang B, Ben Brahim N, Vereshchetin P, Bruttomesso D, Avogaro A, Del Favero S, Boscari F, Galasso S, Visentin

R, Monaro M, Cobelli C: Multinight "bedside" closed-loop control for patients with type 1 diabetes. Diabetes Technol Ther 17:203-209, 2015
15. Gonder-Frederick L, Shepard J, Vajda K, Wakeman C, McElwee M, Kovatchev B: Personality traits and BG profile improvements with continuous glucose monitoring use. Diabetes 61 (Suppl 1):808-P, 2012
16. Jackson DN, Ashton MC, Tomes JL: The six-factor model of personality: Facets from the Big Five. *Personality & Individual Differences* 21:391-402, 1996
17. Clarke WL, Cox DJ, Gonder-Frederick L, Julian D, Schlundt D, Polonsky W: Reduced Awareness of Hypoglycemia in Adults With IDDM: A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 18:517-522, 1995
18. Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, Cox DJ: Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. Diabetes Care 34:801-806, 2011
19. Singh H, Gonder-Frederick L, Schmidt K, Ford D, Vajda K, Hawley J, Cox DJ: Assessing Hyperglycemia Avoidance in People with type 1 Diabetes. Diabetes Management 4:263-271, 2014
20. Polonsky WH, Fisher L, Hessler D, Edelman SV. Investigating Hypoglycemic Confidence in Type 1 and Type 2 Diabetes. Diabetes Technol Ther. 2017;19(2):131-6.
21. Polonsky WH, Fisher L, Earles J, Dudl RJ, Lees J, Mullan J, Jackson RA: Assessing psychosocial distress in diabetes: development of the diabetes distress scale. Diabetes Care 28:626-631, 2005
22. Weissberg-Benchell J, Hessler D, Polonsky WH, Fisher L: Psychosocial Impact of the Bionic Pancreas During Summer Camp. J Diabetes Sci Technol, 2016