UNIVERSITY of VIRGINIA

CENTER *for* DIABETES TECHNOLOGY

DEPARTMENT *of* PSYCHIATRY *and* NEUROBEHAVIORAL SCIENCES
DEPARTMENT *of* MEDICINE/ENDOCRINOLOGY *and* METABOLISM

The VRIF Trial: Hypoglycemia Reduction with Automated-Insulin Delivery System

Version Number: v1.2

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LIST OF ABBREVIATIONS

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

Chapter 1: Background Information

1.1 Introduction

The Tandem X2 insulin pump with Control-IQ Technology is a third-generation closed-loop control (CLC) system retaining the same control algorithm that was initially tested by UVA's DiAs system and then implemented in the TypeZero's inControl system. DiAs is described in 13 IDEs (see IDEs 1-12 and 14 in the list below) and inControl is described in IDEs G160097, G160181, G150240, G140169/S010. For complete algorithmic and clinical background, we refer to these IDEs and to a number of scientific publications that describe glycemic control outcomes and clinical impressions from the use of these systems (see list of peer-reviewed papers and scientific presentations under Bibliography). Overall, this control algorithm has been implemented in two mobile platforms (DiAs and inControl) and has been tested in 30 clinical trials by 450 adults and children with type 1 diabetes for over 300,000 hours of use to date in the U.S. and overseas.

As described in the Background, this project is a result from a sequence of clinical trials that have tested extensively the control system and in several centers in the U.S. and overseas. The following 19 IDEs reflect this progress:

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

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

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

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

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

IDE #G130142: Closed loop control in adolescents using heart rate as exercise indicator; 7/16/13;

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

IDE #G140066: Full day and night closed-loop with DiAs platform; 5/9/14.

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

IDE #G140089: Outpatient control-to-range: Safety and efficacy with day-and-night in-home use; 6/6/2014;

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

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

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

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

IDE #G160097: Clinical Acceptance of the Artificial Pancreas: the International Diabetes Closed-Loop (iDCL) Trial/Research Site Training Protocol; 06/03/16.

IDE#G160181: PROTOCOL 1 for "Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed Loop (iDCL) Trial; 09/21/16

IDE#G170255: Protocol 3 for "Pilot Trial of t:slim X2 with Control-IQ Technology";11/16/17 and IDE#G170255/S001 Protocol 3 for "Training Study of t:slim X2 with Control-IQ Technology"; 11/16/17. NCT03368937

IDE#G170267: "Real-Time Monitoring and Glucose Control During Winter-Sport Exercise in Youth with Type 1 Diabetes: The AP Ski Camp Continued"; 11/21/17. NCT03369067

IDE #G180053: Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed Loop (iDCL) Trial. A Pivotal Study of t:slim X2 with Control-IQ Technology, approved on 04/13/2018; NCT03563313

A successful pilot of 5 adults (mean age 52.8 yrs; 3F/2M, mean A1c 6.5%) with Type 1 Diabetes was completed in December 2017 using the Tandem Control-IQ Technology. In this adult pilot study, the system was challenged with a variety of scenarios including: Pump disconnection, CGM sensor removal without stopping session, CGM sensor change, Basal Rate change, Cartridge Change, Extended Bolus, Calibration at non-ideal conditions, Stopping Control-IQ, R0.

Reset Sleep Time, Restaurant Meals and Exercise (treadmill/walk). The study demonstrated excellent connectivity with 98% time in closed-loop control and 94% time CGM is available during 196 hours of use.

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

Table 1. Pilot Study results based on time in closed-loop

Following the Adult pilot trial, a pilot trial (G170267) with 12 children, 6-12 years of age, comparing Sensor-Augmented Pump (SAP) vs Artificial Pancreas (AP) (Tandem t:slim X2 with Control IQ) in two 72 hours period. Results shown that the mean blood glucose measurd by CGM (Dexcom G6) improved from 180.1 mg/dL when in SAP vs. 153.6 mg/dL when using AP, (p

value 0.025). Time in range measured 70-180 mg/dL also improved from 53.1% when in SAP vs 71.4% when in AP (p value 0.069) without increased of hypoglycemia <70 mg/dL, which showed a tendency to reduce when in AP going from 2.1% SAP vs 1.7 in AP. Hyperglycemia measured >180mg/dL; >250mg/dL and >300mg/dL all reduced significantly comparing SAP vs AP as follow: 44.9% vs 26.8% p=0.04; 16.2% vs 7.3% p=0.05 and 5.3% vs 2.9 % p=<0.001, respectively.

The data of these two aforementioned studies have not been published yet.

Closed-Loop Control System

The Closed-Loop Control System contained in Tandem t-slim X2 with Control-IQ Technology is described in Master File MAF-2032/A007. Tandem Control-IQ Technology is derived from TypeZero's inControl previously described in IDE# G160097, G160181, G150240 and G140169/S010. The CLC, also called "artificial pancreas" (AP), is an application that uses advanced algorithms to automatically manage blood glucose levels for people with Type 1 Diabetes. The system modulates insulin to keep blood glucose in a targeted range. The system components include the Tandem t:slim X2 with Control-IQ Technology and the Dexcom CGM G6.

Figure 1. t:slim X2 with Control-IQ and Dexcom G6 system

1.2 Rationale

The objective of this pilot study is (i) to test the use AP system as a viable therapy treatment for two vulnerable populations: 6-10 year-old and adults older ≥65 years old (ii) to assess cognitive function and Quality of Life (QoL) variables in children and elderly patients with T1D and examine whether improved glycemic control defined by stable (more than 70% of the day in glycemic range 70-180 mg/dL) control positively influences cognitive function and patient reported outcomes related to QoL (iii) obtain preliminary data to be able prepare for larger-scale and with more subject clinical trials. A parent/guardian of the enrolled children will also be asked to participate in all trainings, complete parental Patient-Report Outcomes (PRO) Questionnaires, and collect sleep patterns while wearing the actigraph watch.

At this moment, no studies have directly tested the neurocognitive impact of this AP technology; thus, this proposed study would be the first to bridge this substantial knowledge gap. This clinical

trial will enroll subjects from two population that are most vulnerable to suffer neurocognitive sequelae if their diabetes is not well controlled; thus, the impact of the results will be maximized. We hypothesized that by maintaining good glycemic control and reducing glucose variability in these two vulnerable populations, we may prevent, improve, and/or avoid further cognitive impairments. Hence, one of the major objectives of this study is to assess the impact of the use of an automated-insulin delivery (AID) system in Type 1 Diabetic children (ages 6-10 years of age) and older adults (65 years and older) as well as look at the relationship that diabetes control may have in neurocognitive functioning and other parameters of psychosocial well-being.

1.3 Study Design Overview

This is an open label, non-randomized safety and feasibility pilot study intended to evaluate the influence that good glycemic control using AP may have in the neurocognitive function on two populations that are most vulnerable to suffer neurocognitive deleterious consequences of not well-controlled T1D: (a) young children 6-10 years old, (b) parent of child participant, and (c) older adults 65 years of age and older. Up to 15 subjects in each age group for a period of 8-10 weeks will be studied. During the trial, participants will complete neurocognitive tests during interventions and answering QOL questionnaires at baseline and before and after each intervention. The first study phase will be up to 2 weeks of a training period to allow participants to get acquainted with the use of the study CGM if they are not familiar with the use of the device. This training period will be followed by a 4-week sensor-augmented pump (SAP) period using a study CGM and the subject's personal insulin pump. The subjects will return to clinic at the completion of the SAP period and will be trained on the Tandem t:slim X2 with Control-IQ and G6 CGM. At the completion of the system training session, subjects will begin 4-weeks of Closed-Loop Control (CLC).

Patient-Report Outcomes (PRO) Questionnaires will be provided to study subjects at baseline, after completion of SAP and after completion of CLC. In addition, Ecological Momentary Assessments (EMAs) will be provided Older Adult and Child participants to evaluate neurocognitive function in all its domains: (i) Attention and Execution, (ii) Memory and Learning (iii) Sensorimotor and (iv) Language will be evaluated during the last fourteen days of each intervention period. Actigraphy data will also be collected in the last fourteen days of the SAP and CLC periods by participating adults and by children and their parent/caregiver. This study's pilot test data in a small number of subjects will be used to inform the development of future, larger-scale studies of the relationship between CLC in daily function and QoL in people with T1D.

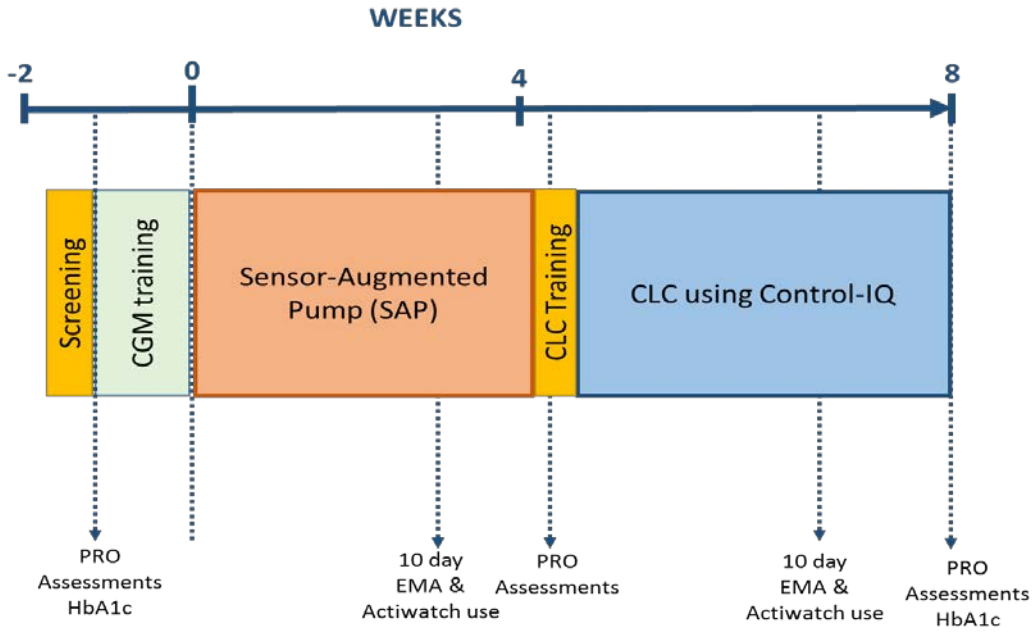

Figure 2. Study Design

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of having 45 participants complete the randomized trial.

- 15 Older Adults – 65 years of age and older
- 15 Children - 6-10 years of age
- 15 Parents – one parent /guardian for the child participant

A maximum of 68 individuals may be enrolled into screening for the study in order to achieve this goal. This is a single site study conducted at the University of Virginia Center for Diabetes Technology (UVA CDT).

For the purpose of this study, "*participants*" or "*study subjects*" will reflect the Children and Older Adults subjects.

2.1.1 Informed Consent and Authorization Procedures

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

For potential study participants ≥65 years old, the study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

For potential participants under 18 years of age, a parent/legal guardian (referred to subsequently as "parent") will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Potential participants meeting the IRB's minimum age of assent will be given a Child Assent Form to read and discuss with his/her parents and study personnel. If the parent and child agree to participate, the Informed Consent Form and Child Assent Form will be signed. A copy of the consent form will be provided to the participant and his/her parent, and another copy will be added to the participant's study record if a paper copy is signed; otherwise, the signed informed consent will be stored electronically. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

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

2.2 Participant Inclusion Criteria

Older Adults and Child participants must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year, using insulin for at least 1 year and using an insulin pump for at least 6 months.

2. Familiarity and use of a carbohydrate ratio for meal boluses by participants and families participating.
3. Age 6-10 years old or 65 years or older
4. Hemoglobin A1c <10%
5. For females of child-bearing potential, not currently known to be pregnant

   A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
6. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact the participant in case of an emergency.
7. Willing to disable any automated insulin delivery functionality on a personal insulin pump during study, such as Medtronic 670G in auto mode. Predictive low blood glucose suspend, such as Tandem insulin pump with Basal-IQ, will be allowed.
8. Investigator has confidence that the participant and family can successfully operate all study devices and is capable of adhering to the protocol.
9. Willingness to switch to lispro (Humalog) or aspart (Novolog) and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study.
10. Total daily insulin dose (TDD) at least 10 U/day.
11. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial

2.3 Participant Exclusion Criteria

Older Adults and Child participants meeting any of the following exclusion criteria at baseline will be excluded from study participation.

1. Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment.
2. Diagnosis of Diabetic Ketoacidosis in the 12 months prior to enrollment.
3. Uncontrolled cardiac disease (e.g. recent myocardial infarction, severe congestive heart failure).
4. Cerebrovascular accident in the 12 months prior to enrollment.
5. Uncontrolled resting arterial hypertension (>160/90 mm Hg).
6. Conditions that would make use of a CGM difficult (e.g., blindness, severe arthritis, immobility).
7. Current use of oral/inhaled glucocorticoids or other medications, which in the judgment of the investigator would be a contraindication to participation in the study.

8. Concurrent use of any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas).
9. Hemophilia or any other bleeding disorder
10. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk
11. Participation in another pharmaceutical or device trial at the time of enrollment or during the study
12. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc., or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial.

2.4 Screening Procedures

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

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

2.4.1 Data Collection and Testing

A medical history performed within 3 months of screening appointment or a standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or designee from the study team.

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

- Inclusion and exclusion criteria assessed
- Demographics (date of birth, sex, race and ethnicity)
- Contact information
- Medical history
- Concomitant medications
- Physical examination to include:
    - Weight, height
    - Vital signs including measurement of blood pressure and pulse
- Blood draw for:
    - HbA1c level will be measured using the DCA2000, a comparable point of care device or local laboratory (i.e. LabCorp). Measurement performed as part of usual clinical care

prior to obtaining informed consent for participation in the trial may be used

- Measurement must be made within two weeks prior to enrollment

- Urine or serum pregnancy test for all women of child-bearing potential
- Subject's personal insulin pump may be downloaded at this appointment.

2.4.2 Patient-Report Outcomes (PRO) & Neurocognitive Assessments

All participants will be asked to complete PRO Questionnaires on three occasions: after the Screening (Baseline) Visit, after SAP phase and after CLC phase. Note that parents of children will also complete PROs which will be used to assess impact of their child's use of CLC on parental psychosocial status.

Construct	**PRO/QOL Questionnaires**
Fear of Hypoglycemia	Hypoglycemia Fear Survey (Adult, Parent and Child Versions)
Diabetes-related distress and burden	Problem Areas in Diabetes (Adult, Parent and Child Versions)
Sleep	Pittsburgh Sleep Quality Index (PSQI) and Child Sleep Habits Questionnaire (CSHQ)
Depression	Center for Epidemiological Science Depression Scale (Adult Version) Children's Depression Inventory (Child Version)
Technology Acceptance	Technology Acceptance Questionnaire (Adult/Parent/Child Versions) *

*The Technology Acceptance Questionnaire will not be given at the Screening Visit.

Table 2. PRO & OQL Questionnaires

2.4.3 Study Contact during Study

Contact with study subjects will be done as follow: after baseline and during training period, at initiation of SAP period and regular contact approximately every 10-14 days. For approximately the last 14 days, contact will be more frequent to remind patients to use the daily dairy entries and to wear the actigraphy watch. The following will occur:

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

Participants may have unscheduled calls during the study period if required for additional device training or other unanticipated needs.

Chapter 3: Study Equipment Training

3.1 Initiation of CGM

The CGM training may begin immediately after enrollment is complete or may be deferred for a maximum of 60 days. The purpose of this training is to introduce the study CGM to study participants that are not already familiar with its use.

Older Adults and Child participants will use the study CGM for up to approximately 14 days during the training phase. All participants will receive training on the study CGM as detailed below. This will be an unblinded use of the study CGM.

The participant will be provided with sensors and instructed to use the study CGM on a daily basis. Training will be provided to participants not experienced with CGM use as to how to use the study CGM in real-time to make management decisions and how to review the data after an upload (if needed) for retrospective review. Participants using a personal CGM prior to the study will discontinue the personal CGM. A study CGM will be provided to all study participants at the training session.

The participant will be observed placing the sensor. The study CGM user's guide will be provided for the participant to take home. The study team will be sure that the participant and their parent will leave the clinic knowing how to use proper use the CGM. The study team will be available for any questions.

Study subjects and parents may use the Dexcom Apps on their personal phone to monitor CGM values and alerts in real-time during the SAP phase.

3.2 Blood Glucose and Ketone Testing

Older Adults and Child participants will receive supplies for blood glucose and blood ketone testing.

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

Participants will be given guidelines for treatment of low or high blood glucose.

- Blood ketone testing
    - Participants will be provided with a study blood ketone meter and test strips.
    - All study blood ketone meters will be QC tested with control solution at the onset of the study. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The participant will be instructed to contact study staff for a replacement of the meter or test strips.
    - Participants will be instructed to perform blood ketone testing as described in section 6.2.5
    - Participants will be given guidelines for treatment of elevated blood ketones
- Participants will be required to have a home glucagon emergency kit. Participants who currently do not have one will be given a prescription for the glucagon emergency kit.

3.3 Optimization of Insulin Pump Settings

Data-driven optimization of pump settings can occur any time during the study, particularly if the study participant contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

3.4 Neurocognitive Ecological Momentary Assessments (EMAs) collected with Daily Diary Data

The purpose of collecting EMAs in this study is to evaluate and compare neurocognitive function at different times during the day (i.e. when blood glucose may be high or low), with high variability (SAP phase) vs. well blood glucose (BG) controlled (CLC phase). In particular, EMA methods are used to capture individuals' experiences (e.g., symptoms, affect, and behaviors) in real-world contexts and in near-real time. EMAs involve current behavior ratings and repeated assessments over time and is ideally suited to identify temporal antecedents and consequences of glucose variability in T1D patients. The EMAs will be then used to study particular neurocognitive functions over several days at random time samplings. The intent is to capture these assessments in periods of greater glucose variability versus periods of tighter control. EMAs, (aka Daily Dairy Assessment), will collect the data as a Daily Dairy may be placed on a digital device such as a smart phone or iPod, iTouch Smartwatch.

Participants will be asked to complete a Daily Diary at three to four time points for approximately the last 14 days of SAP phase, and approximately the last 14 days of CLC phase. The Daily Diary Assessments should take about 7 days to complete but may take slightly longer; therefore, subjects may be asked to begin the daily diaries a few days earlier in order to complete a total of at least 40 entries (~4 entries per day). Each Daily Diary entry will take no longer than five minutes to complete.

- Given the target number of 45 participants, an approximate 1,200 data sets (Daily Dairy entries) for analysis may be reviewed.
- For the proposed study, the subject will access the diary from a study cell phone or iTouch, will prompt the participant to respond to an EMA. These prompts will occur at 3-4 random intervals during a 14 hr period, with the participant setting the beginning and end time for daily prompts. Participants would be able to “skip” Diary entries when prompts occur at

inconvenient times (e.g. while driving, at school). The Daily Diary Assessment would require participants to complete: 1) a Symptom and Mood Checklist with items rated on a 7 point (0 – 6) visual analogue Likert Scale, 2) two brief cognitive tests (mental subtraction and digit span, this will be adapted according to age), and 3) Self-Ratings of performance on cognitive tests.

- For cognitive testing, mental subtraction was chosen because it is a task that has proven reliably sensitive to BG changes in our previous research. For the adult participants, the test will consist of 10 mental subtraction problems with a minuend three digits long and one digit subtrahend. No problem will be presented more than one time and the minuend and subtrahend will be randomly generated. Participants will use the number pad to enter their answer. Both the participant's answer and the time to complete the ten problems will be recorded. The questions will be adapted children participants. For example, younger kids may be presented with pictographic images that will have to recognize, colors, number of each animal drawing presented, etc.
- The second cognitive test, Digit or iconographic (for younger children) Span, was chosen as a measure of working memory which has been shown by previous research to be sensitive to both hypo-and hyperglycemia. The task will consist of 10 Working Memory Digit or iconographic (according to age) Span problems.

3.5 Actigraphy Watch

- Another important aspect to be studied in this trial will be the evaluation of sleep disturbances, an important factor in daily QoL. During approximately the last 14 days of each period, Older Adults, Children, and their Parents will be also asked to wear an Actigraphy watch to record sleep patterns. Objective sleep data will be collected via innovative latest generation actigraphy technology. Actigraphy technology is highly accurate and convenient as demonstrated in two decades of research. Specifically, actigraphy units are non-invasive, low cost, have the ability to continuously monitor sleep in real-world settings for several weeks/months, and are made of robust materials, making them particularly dependable when used with children.
- Our proposed study would be the first to *simultaneously obtain* objective measurements of sleep in <u>both</u> young children with T1D and their parents alongside other key variables. To clarify, the adult participant will wear the watch during the overnight hours. In the case of children, both the child with T1D and a parent will be wearing the Actiwatch 2 and Actiwatch PRO, respectively. Subjects will be asked to begin wearing the watch 1 hour before bed and during overnight period (~7PM-7AM) during approximately the last 14 days of the SAP and CLC periods.

Chapter 4: SAP Phase

4.1 Initiation of SAP Phase

Participants will utilize their personal pump and continue use of the Study CGM. Enrolled participants will start the SAP period after the study team and study MD are sure that the CGM is working as intended and all the questions are answered. This could start at home but if further training needed, one or more interim visits or phone contacts may occur to assist the participant with any system use issues. The SAP study phase will last about 28 days.

4.1.1 HbA1c

HbA1c will be measured using the DCA2000, a comparable point of care device or local laboratory.

4.1.2 Patient-Report Outcomes Questionnaires and EMA

Participants will complete a set of Patient-Report Outcomes Questionnaires, described in

Construct	**PRO/QOL Questionnaires**
Fear of Hypoglycemia	Hypoglycemia Fear Survey (Adult, Parent and Child Versions)
Diabetes-related distress and burden	Problem Areas in Diabetes (Adult, Parent and Child Versions)
Sleep	Pittsburgh Sleep Quality Index (PSQI) and Child Sleep Habits Questionnaire (CSHQ)
Depression	Center for Epidemiological Science Depression Scale (Adult Version) Children's Depression Inventory (Child Version)
Technology Acceptance	Technology Acceptance Questionnaire (Adult/Parent/Child Versions) *

*The Technology Acceptance Questionnaire will not be given at the Screening Visit.

Table 2 after completing the SAP period. EMA will be completed approximately during the last 14 days of SAP. Actigraphy will also be used during approximately the last 14 night period as described.

4.1.3 Study Device Download

Participants will be instructed to download the study devices on a weekly basis and prior to each visit if needed if the visit is delayed for any particular reason and the memory of the device may not support additional data storage. The study team may also download all devices at baseline and at the end of each intervention period (SAP and CLC).

Chapter 5: CLC Phase

5.1 Procedures for the CLC Phase

5.1.1 Study System Training

Participants will receive study system training. These training sessions can occur on the same day or extend up to one additional day if needed within approximately 7 days from the end of SAP; participants will not take the study system (Tandem t:slim X2 with Control-IQ) home until training has been completed. The CLC study phase will last about 28 days.

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

Insulin Pump Optimization will occur at this visit.

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

5.1.1.1 CGM Training for CLC Phase

CGM training will include:

- The participant will be instructed and supervised on how to insert the sensor and transmitter.
- The participant will learn how to calibrate the CGM unit
- The participant will learn how to access the CGM trace via the t:slim X2 with Control-IQ user interface
- Participants will be asked to perform fingerstick blood glucose measurements (if needed) in accordance with the labeling of the study CGM device
- Parent(s)/guardian(s) will be required to use the Dexcom App to monitor their child's CGM trends and alerts in real-time during the CLC phase.

5.1.1.2 Insulin Pump Training for CLC Phase

Insulin pump training will include:

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

- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed. Infusion sets manufactured by Tandem will be provided to the study subject and a sample list is below and may be provided in different cannula lengths (e.g. 6mm or 9mm) and tubing lengths (e.g. 23 or 43 inch):
    - ❖ Tandem Autosoft Line (e.g. Autosoft 30, Autosoft 90, Autosoft XC)
    - ❖ Tandem Varisoft
    - ❖ Tandem TruSteel

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

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

5.1.2 System Initiation

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

The participant will also be instructed to contact study staff during periods of illness with an elevated temperature >101.5 degrees Fahrenheit (38.6 degrees Celsius), periods of significant illness, or during periods of use of medications such as epinephrine for the emergency treatment of a severe allergic reaction or asthma attack in addition to use of oral or injectable glucocorticoids to determine if closed-loop use should be temporarily discontinued.

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

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

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

also receive study staff contact information to ask any questions they may have during the study.

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

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

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

5.1.3 Home Use of the Study System

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

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

5.1.4 Study Device Download

Participants will be instructed to download the study device on a weekly basis and prior to each visit if needed if the visit is delayed for any particular reason and the memory of the device may not support additional data storage. The study team may also download all devices at baseline and at the end of each intervention period (SAP and CLC).

5.1.5 Patient-Report Outcomes Questionnaires and EMA

Participants will complete a set of Patient-Report Outcomes Questionnaires (

Construct	**PRO/QOL Questionnaires**
Fear of Hypoglycemia	Hypoglycemia Fear Survey (Adult, Parent and Child Versions)
Diabetes-related distress and burden	Problem Areas in Diabetes (Adult, Parent and Child Versions)
Sleep	Pittsburgh Sleep Quality Index (PSQI) and Child Sleep Habits Questionnaire (CSHQ)
Depression	Center for Epidemiological Science Depression Scale (Adult Version) Children's Depression Inventory (Child Version)
Technology Acceptance	Technology Acceptance Questionnaire (Adult/Parent/Child Versions) *

*The Technology Acceptance Questionnaire will not be given at the Screening Visit.

Table 2) after completing the CLC period. EMAs (Daily Dairy) will be completed during approximately the last 14 days of CLC. Actigraphy will also be used during approximately the last 14 night period as described.

At the end of this period the following will happen:

1. All devices will be download (e.g. CGM, personal insulin pump, glucometer, ketone meters, actigraphy watch)
2. The Patient-Report Outcomes Questionnaires
3. Assessment of compliance with study device use by review of any available device data after each phase
4. Assessment of adverse events, adverse device effects, and device issues
5. HbA1c determination using the DCA Vantage, local laboratory, or similar point of care device
6. A Diabetes and Technology Interview: "Expectations and Satisfaction in Diabetes Technology: how the artificial pancreas is seen and experienced by senior users and caregivers of children with T1DM." This survey may be completed via telephone or email with the subject. Telephone surveys will be audiorecorded.
    a. Parents/Caregivers of minor subjects will receive the Interview Schedule for Parents/Caregivers and adult subjects will receive the Interview Schedule for Participants/Users.

5.2 Unscheduled Visits

Participants may have unscheduled visits during the study period if required for additional device training or other unanticipated needs per the study investigator discretion.

5.3 Participant Access to Study Device at Study Closure

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

Chapter 6: Study Devices

6.1 Description of the Study Devices

6.1.1 Insulin Pump

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

6.1.2 Continuous Glucose Monitoring

The study CGM will include Dexcom G6 transmitter and sensors when using the Tandem t:slim X2 with Control-IQ technology. The CGM sensor will be replaced at least once every 10 days.

6.1.3 Blood Glucose Meter and Strips

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

6.1.4 Ketone Meter and Strips

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

6.1.5 Study Device Accountability Procedures

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

6.1.6 Blood Glucose Meter Testing

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

6.1.7 Blood Ketone Testing

- All study blood ketone meters will be QC tested with control solution, if available. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The participant will be instructed to contact study staff for a replacement of the meter or test strips.
- Participants will be instructed on how to perform blood ketone testing.

- Participants will be given guidelines for treatment of elevated blood ketones.

6.1.8 Actigraphy Watches

Actigraphy watches will be provided and used by the Older Adult, Child, and Parent subjects. They will be instructed to fit the watch 1 hour before bed and using it overnight (~7 PM - ~7AM) during approximately the last 14 days of each period: SAP and CLC.

Actigraphy watches: https://www.usa.philips.com/healthcare/product/HC1046964/actiwatch-spectrum-activity-monitor) by Philips Respironics.

For adults:
https://www.usa.philips.com/healthcare/product/HC1046964/actiwatch-spectrum-activity-monitor

For children:
https://www.usa.philips.com/healthcare/product/HC1044809/actiwatch-2-activity-monitor

6.2 Safety Measures

6.2.1 CGM Calibration

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

6.2.2 CGM Sensor Failure

If the CGM experiences loss of signal or sensor failure during Closed-Loop mode, the subject will be encourage to establish reconnection with the sensor or replace the sensor as soon as possible within 24 hours.

6.2.3 System Failure

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

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

If the Tandem t:slim X2 detects a system error that does not allow the pump to operate, the Malfunction Alarm will display with instructions to contact Tandem Technical Support. However, the study subject will be advised to contact the study team to troubleshoot these events.

6.2.4 Hypoglycemia Threshold Alert and Safety Protocol

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

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

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

6.2.5 Hyperglycemia Threshold Alert and Safety Protocol

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

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

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

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

- Perform a blood glucose meter check.
- If the blood glucose is >300 mg/dL, check for blood ketones with the study ketone meter.
- If the ketone level is >0.6 mmol/L, take correction insulin, change insulin (pump) infusion site and contact study staff.
- If a participant administers correction insulin via insulin syringe, participants will be instructed to turn Control-IQ off for approximately 4 hours.

Chapter 7: Testing Procedures and Questionnaires

7.1 Laboratory Testing

1. HbA1c:

- Performed locally at the Screening visit. Blood test may be obtained within 2 weeks prior to enrollment.
- HbA1c level will be measured using the DCA2000, a comparable point of care device or local laboratory

Urine or Serum Pregnancy:

- A serum or urine pregnancy test will be required for women who are in childbirth potential at the screening visit. Test must be negative to participate in the study.
- A serum or urine pregnancy test will be required for women who are in childbirth potential at the study equipment training session (prior to the start of CLC). Test must be negative to participate in the study.

7.2 Patient-Report Outcomes (PRO) Questionnaires

Questionnaires are completed at the Baseline, end of SAP phase and the end of the CLC phase. The questionnaires are described in

Construct	**PRO/QOL Questionnaires**
Fear of Hypoglycemia	Hypoglycemia Fear Survey (Adult, Parent and Child Versions)
Diabetes-related distress and burden	Problem Areas in Diabetes (Adult, Parent and Child Versions)
Sleep	Pittsburgh Sleep Quality Index (PSQI) and Child Sleep Habits Questionnaire (CSHQ)
Depression	Center for Epidemiological Science Depression Scale (Adult Version) Children's Depression Inventory (Child Version)
Technology Acceptance	Technology Acceptance Questionnaire (Adult/Parent/Child Versions) *

*The Technology Acceptance Questionnaire will not be given at the Screening Visit.

Table 2.

Chapter 8: Risks Associated with Clinical Trial

8.1 Potential Risks and Benefits of the Investigational Device

Risks and benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia, hyperglycemia and ketone formation are always a risk in participants with type 1 diabetes and participants will be monitored for these events.

8.1.1 Known Potential Risks

8.1.1.1 Venipuncture Risks

A hollow needle/plastic tube will be placed in the arm for taking blood samples. Blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

8.1.1.2 Fingerstick Risks

About 1 drop of blood will be removed by fingerstick for measuring blood sugars and sometimes HbA1c or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as fingersticks are part of the usual care for people with diabetes.

8.1.1.3 Subcutaneous Catheter Risks (CGM)

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

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

8.1.1.4 Risk of Hypoglycemia

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

8.1.1.5 Risk of Hyperglycemia

Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. A CGM functioning poorly and significantly under reading glucose values could lead to inappropriate suspension of insulin delivery.

8.1.1.6 Risk of Device Reuse

The study CGM system is labeled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The transmitter and receiver may be reused during the study after cleaning the device as instructed in the G4 Platinum Professional Cleaning and Disinfection Guide. The transmitter is attached to the sensor but does not enter the skin. The receiver is a hand-held device. Participants will be informed that FDA or relevant national authorities have approved these devices for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

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

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

8.1.1.7 Questionnaire

As part of the study, participants will complete questionnaires which include questions about their private attitudes, feelings and behavior related to the investigational equipment as well as managing diabetes. 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.

8.1.1.8 Audio Taping

As part of the study, participants will complete a semi-structured in-person or phone interview that will be audio recorded. Participant voices will be recorded on an audio recording device. To protect participant privacy, participants will be instructed to not identify themselves or any personally identifying information as to not contain any HIPAA identifiers – participants will be referred to by subject number or false name and will be instructed to not discuss any personally identifying information during the interview. Audio recordings will be transferred to a secure drive, after which the recording will be deleted from the individual recording device. If a HIPAA identifier is discovered in the recording, the transcription will omit this.

8.1.1.9 Other Risks

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

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

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

8.1.2 Known Potential Benefits

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

It is expected that this protocol will yield increased knowledge about using an automated closed-loop to control the glucose level. The individual participant may not benefit from study participation.

8.1.3 Risk Assessment

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

8.2 General Considerations

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

Data will be directly collected in electronic case report forms which will be considered the source data.

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

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

9.1 Adverse Events

9.1.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation (see section 9.1.2 for reportable adverse events for this protocol). Only adverse events related to study participation will be reported.

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.

Device Complaints and Malfunctions: A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3).

9.1.2 Reportable Adverse Events

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

1. A serious adverse event

An Adverse Device Effect as defined in section 9.1

An Adverse Event occurring in association with a study procedure

Hypoglycemia meeting the definition of severe hypoglycemia as defined below

Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

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

Pregnancy occurring during the study will be recorded.

9.1.2.1 Hypoglycemic Events

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

9.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis

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

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

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

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and

- Treatment provided in a health care facility

All reportable Adverse Events—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—will be reported on an adverse event form online. Each adverse event form is reviewed by the Medical Monitor to verify the coding and the reporting that is required.

9.1.3 Relationship of Adverse Event to Study Device

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

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

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

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

9.1.4 Intensity of Adverse Event

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

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

9.1.5 Coding of Adverse Events

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.

9.1.6 Outcome of Adverse Event

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

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

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

9.2 Device Issues

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

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

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

9.3 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The pregnancy itself will not be considered an adverse event.

9.4 Timing of Event Reporting

Serious, Unexpected adverse events will be reported to the Medical Monitor and IRB within 7 calendar days. The FDA will be notified within ten working days of the Coordinating Center 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.

Unanticipated Problems that are not adverse events or protocol deviations will be reported to the Medical Monitor and IRB within 7 calendar days. This might include a Data Breach.

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

9.5 Stopping Criteria

9.5.1 Participant Discontinuation of Study Device

Rules for discontinuing study device use are described below.

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- Participant pregnancy
- More than one distinct episode of either severe hypoglycemia or DKA, if attributable to the device, as defined in section 9.1.2.1

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

9.5.2 Criteria for Suspending or Stopping Overall Study

In the case of a system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in section 9.1.2.2), use of the study device system will be suspended while the problem is diagnosed.

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

9.6 Risks

The potential risks associated with use of the study device are described in section 8.1.

Chapter 10: Miscellaneous Considerations

10.1 Drugs Used as Part of the Protocol

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

10.2 Prohibited Medications, Treatments, and Procedures

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

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

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

10.3 Participant Withdrawal

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

10.4 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. De-identified participant information may also be provided to Tandem for system evaluation purposes.

Chapter 11: Statistical Consideration

11.1 Statistical and Analytical Plans

This is a pilot trial with an n=30 total with fifteen participants in each age group. This in a feasibility/pilot study and therefore is not powered. The goal of this trial is the estimation of the treatment effect size.

11.2 Outcomes

(i) Primary: CGM-measured % in range 70-180 mg/dL.

CGM time in range 70-180 mg/dL during SAP and CLC (1 month each) using Repeated Measures ANOVA will be analyzed. Effect size will be determined using the Cohen-D methodology.

(ii) EMAs during each period (SAP vs CLC) will be obtained and analyzed comparing time to answer and accuracy of answers. Data will be analyzed using repeated measures ANOVA, for each test category.

(iii) Sleep patterns will also be collected after each period for quantity and quality by the use of the actigraphy watch and compare SAP vs CLC.

11.3 Sample Size

Sample size has been determined from a convenience sample of 45 subjects (15 children age 6-10 y.o, 15 parents of the enrolled children, and 15 older adults, age 65 and older) for the primary outcome (CGM-measured % in range 70-180 mg/dL).

This is a pilot trial with the main goal of obtaining preliminary data for further application.

The total sample size has been increased to 68 to account for a possible 50% dropouts/withdraws.

11.3.1 Secondary or Safety Outcomes

- CGM-measured % >180
- CGM-measured % 250 mg/dL
- CGM-measured % >300
- CGM-measured % < 70 mg/dL
- CGM-measured % <54 mg/dL
- glucose variability measured with the coefficient of variation (CV)
- glucose variability measured with the standard deviation (SD)
- % <60 mg/dL
- low blood glucose index
- hypoglycemia events (defined as at least 15 consecutive minutes <70 mg/dL)

- high blood glucose index
- HbA1c
- Severe hypoglycemia
- Diabetic ketoacidosis
- PROs:
  - Technology acceptance: after each phase
  - Diabetes distress: Baseline, and after each phase
  - Fear of hypoglycemia: Baseline and after each phase
  - Depression: Baseline and after each phase
- Other serious adverse events and serious adverse device events
- Unanticipated adverse device effects

Chapter 12: Data Collection and Monitoring

12.1 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 are considered the primary source documentation.

12.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations.

12.3 Quality Assurance and Monitoring

Study team 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.

12.4 Protocol Deviations

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

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

Chapter 13: Ethics/Protection of Human Participants

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent Procedures and Documentation

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

The participants should have the opportunity to discuss the study or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.3.2 Participant and Data Confidentiality

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or device company supplying study product may inspect all documents and records required to be maintained by the investigator. The clinical study site will permit access to such records.

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

Study individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical site be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Virginia Center for Diabetes Technology.

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