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School of Medicine  
Center for Diabetes Technology

**Project Nightlight:  
Efficacy and System Acceptance of Dinner/Night vs.  
24hr Closed Loop Control**

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## Chapter 1 INTRODUCTION

### 1.1 Background and Rationale

As advancements in technology continue, we propose the use of the inControl Diabetes Management Platform for this protocol. It remains a smartphone-based, artificial pancreas platform that automatically controls insulin delivery with an advisory system that generates real-time recommendations for meals, basal rates, bolus calculations and exercise decisions. This cloud based system provides real-time monitoring as well as retrospective analysis on data. The data generated are stored at an inControl Cloud permitting the research team and support networks to observe blood glucose values in real-time if needed. The insulin dosing strategies used in this device are the same strategies currently used in DiAs. This system is identical to the system approved by the FDA in IDE G150221/S002.

***In 2009 we initiated one of the first NIH studies dedicated to engineering and clinical testing of closed-loop control (CLC) of type 1 diabetes. Since then, we have achieved key milestones and derived conclusions which enabled further research in this rapidly growing field. Notably, we proposed the idea that the artificial pancreas is not a single all-in-one device but a network encompassing the patient in a digital treatment ecosystem that can offer and alter different treatment modalities in real time depending on the patient's clinical state.***

This new notion was reflected in: (1) Our modular engineering design of CLC algorithms, which now allows various treatment modalities to be initiated and swapped without interruption; (2) The Diabetes Assistant (DiAs) – *the first portable CLC hub* using a smart phone to run control algorithms and specifically designed to be operated by the patient, which is now used in a number of outpatient studies in the U.S. and in Europe, and (3) The Unified Safety System (USS Virginia) – the first CLC algorithm *engineered to adapt its mode of operation during the course of every night*, first mitigating after-dinner hyperglycemia and then sliding the patient to a target morning glucose of 120mg/dl, thereby resetting his/her metabolic state for a new day.

Using these technologies, we now propose to compare in a randomized cross-over trial the *long-term efficacy of three treatment modalities* –

SAP=sensor-augmented pump only

USS+SAP (d)=SAP during day and CLC starting at dinner and continuing overnight

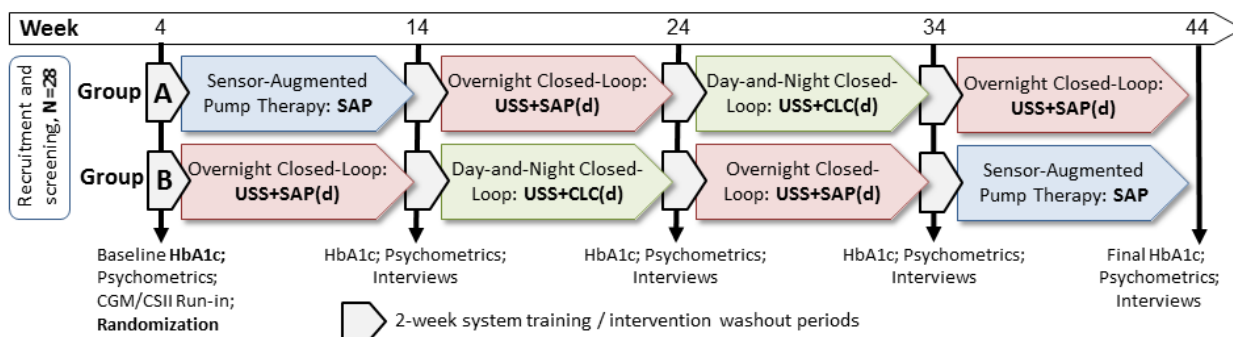
USS+CLC (d)=24-hour Day and Night Closed Loop Control

We plan to randomize up to 110 patients with type 1 diabetes into two different treatment sequences:

**Group A** following the sequence SAP→USS+SAP(d)→USS+CLC(d)→USS+SAP(d), and

**Group B** following the sequence USS+SAP(d)→USS+CLC(d)→USS+SAP(d)→SAP.

These treatment modality sequences are presented in the figure below, and are color coded to match the color-coding of active control modules relevant to each treatment modality presented in Figure 1:



**Figure 1: Design of One 11-month Study Session**

Each treatment modality will continue for 8 weeks – sufficient time to address the following specific aims:

**SA1: Dinner/Night CLC achieved by USS+SAP(d) will be superior to SAP alone in terms of:** (1) Improved HbA1c without increasing the risk for hypoglycemia; (2) Reduced incidence and risk for hypoglycemia overnight, and (3) Reduced fear of hypoglycemia and improved diabetes quality of life scores.

**SA2: CLC during the day achieved by USS+CLC(d) will preserve the benefits of USS+SAP(d) and will be superior to USS+SAP(d) in terms of:** (1) Increased time within target range of 70-180mg/dl during the day; (2) Reduced risk for hypoglycemia, particularly during and after exercise, and (3) Reduced postprandial glucose variability.

**SA3: CLC system acceptance evaluated by individual structured interviews and technology acceptance scores will be:** (1) Superior, for USS+SAP(d) compared to SAP alone, i.e. adding USS in the evening and overnight will increase patients’ acceptance of CLC, and (2) Marginally inferior, for USS+CLC(d) compared to USS+SAP(d); i.e. some patients would prefer SAP alone during the day due to perceived increased system complexity.

## 1.2 Preliminary Studies

This protocol benefits from extensive study of the Artificial Pancreas system with over 184,000 hours of clinical use with various component structures.

Two recent trials present examples particularly relevant to the proposed clinical studies: [Efficacy and Safety of Overnight CLC in Children and Adolescents with Type 1 Diabetes \(UVA and Stanford\)](#): In 2013, we tested USS Virginia to determine its overnight safety and efficacy in a summer-camp setting: 20 subjects were randomized to CLC using DiAs or SAP (sensor-augmented pump), completing 54 CLC and 52 SAP nights. On nights when DiAs was active for at least 6h, the median time spent in range was 73% for CLC vs. 55% for SAP, p=0.012. Less time was spent below 70mg/dl on CLC vs. SAP, p<0.001; there were **no hypoglycemic episodes below 60mg/dl on CLC**.

Figure 2 presents the data distributions on CLC vs. SAP across several BG ranges. The study concluded that USS Virginia is effective in improving time spent in range, as well as reducing nocturnal hypoglycemia in children and adolescents with type 1 diabetes in a summer camp setting.

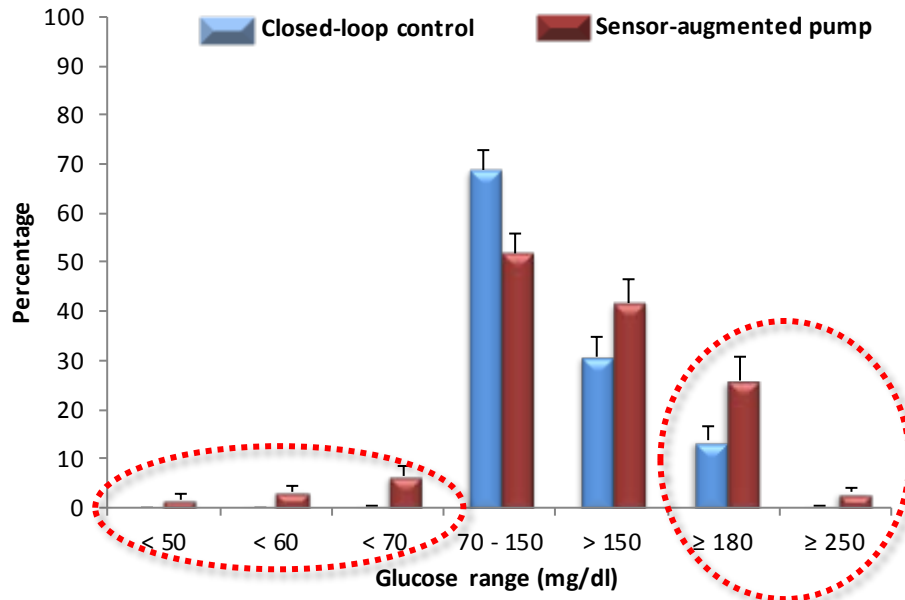


Figure 2: % time within several glucose ranges during overnight closed-loop vs. sensor augmented pump in summer camps for children with type 1 diabetes

Overnight Control in Adults with Type 1 Diabetes (UVA and Univ. of Padova): In this study, 10 subjects spent 5 nights on USS Virginia vs. 5 nights on SAP, in random order. CLC resulted in over 30mg/dl lower average BG and over 25% higher time within target range. The mean morning BG on CLC was 119.3mg/dl; thus the USS performed exactly to its design specification—reset BG to 120mg/dl by 7AM (Figure 3).

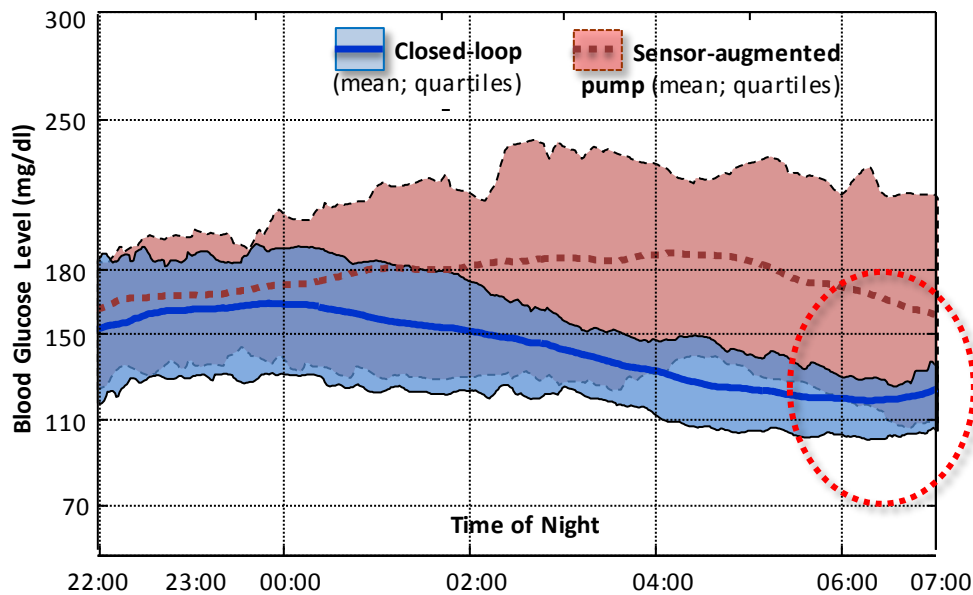


Figure 3: Glucose distribution during overnight closed-loop (blue) vs. sensor augmented pump (red)

Overnight glucose correlated with glucose control on the next day,  $r=0.52$ ,  $p<0.01$ ; peak BG and BG variability during the day (USS inactive) were improved after CLC nights as well. Details are given in the table below.

Main Outcomes of this Study	Sensor-Augmented Pump	Closed-Loop Control	P-value
Average Blood Glucose at 7AM	152.9	119.3	<0.001
Average Blood Glucose (mg/dl)	170.3	139.0	<0.001
Percent time within 70-180mg/dl	59.1%	85.4%	<0.001
Percent time below 70mg/dl	1.56%	0.55%	0.06

*These results support the significant glycemic benefits of using USS Virginia overnight and indicate strongly that control during days following well-controlled nights is correspondingly improved. Thus, evaluation of this system is warranted in long-term clinical trials with outcomes gauged by accepted metrics of glucose control.*

### 1.3 Study Objective

Overall, we expect to establish that a distinct overnight CLC modality (USS Virginia) combined with SAP therapy during the day is a viable precursor to future adaptable therapeutic schemes, achieving glycemic control that is superior to SAP alone and optimal balance between system complexity and perceived benefits.

### 1.4 Closed-Loop Control System

A general description of the Artificial Pancreas Platform devices identified below will be used in the Closed-Loop Control System. New generations of CGMs and insulin pumps with embedded inControl-AP could become available for inclusion in this trial and could be used providing these new developments do not change the core functionality of the system.

For the inControl Platform, (see Figure 4-Panel A):

- inControl Diabetes Management Platform – a smart-phone Artificial Pancreas medical platform;
- CGM – study CGM connected to the AP using low power Bluetooth communication protocols;
- Insulin Pump – insulin pump connected to AP system via wireless Bluetooth.
- Remote Monitoring Server connected to inControl Cloud via 3G or local Wi-Fi network, and
- Modular Closed-Loop Control Algorithm Running on the AP system, which is of Control-to-Range (CTR) class

We have successfully completed a pilot study of the Tandem t:slim X2 with Control-IQ Technology. This pilot study included 5 adults (mean HbA1c 6.5%) using the system between 36-48 hours, and was successfully completed with 86% mean time in target range of 70-180 mg/dL and 2.8% median time below 70 mg/dL. The system maintained connectivity 98% of the intended

time in closed-loop. Given the positive results from this pilot study, we now plan to incorporate t:slim X2 with Control-IQ Technology in this protocol as well.

For the Tandem-G6 configuration, (see Figure 4-Panel B):

The Closed-Loop Control System contained in t-slim X2 with Control-IQ Technology is described in Master File MAF-2032/A003 and has been approved in G170255 and G170267. Control-IQ Technology is derived from inControl previously described in IDE# G160097, G160181, G150240 and G140169/S010. The CLC is an “artificial pancreas” (AP) application that uses advanced closed loop control algorithms to automatically manage blood glucose levels for people with Type 1 Diabetes. The system modulates insulin to keep blood glucose in a targeted range. The system components include the t:slim X2 with Control-IQ Technology and the Dexcom CGM G6 (Fig. 4-B).



Figure 4. AP System Components: Panel A – G4+Roche pump configuration; Panel B – G6+Tandem Control IQ

## 1.5 Protocol Overview

### 1.5.1 Sample Size

Up to 110 adult subjects age  $\geq 18$  to  $< 70$  years old will be enrolled so that approximately 76 subjects complete the entire study at University of Virginia, allowing for up to 31% attrition rate due to the duration of the study protocol).

### 1.5.2 Protocol Summary

For the proposed studies, the AP system will be deployed with different functionalities at different stages of the trial, resulting in variation in what the subject will be responsible for and what the system will drive. A trial outline is contained in Figure 1 and visits detailed in Figure 5.

#### Study Phases without the AP system



CGM Run-in Phase: Study participants will begin with a maximum 2 week run-in period during which they will have a CGM (i.e. sensor-augmented pump therapy or CGM+CSII) but otherwise be on their usual diabetes management with respect to BG monitoring, pump basal rates, insulin-to-carbohydrate ratios and correction factors. This is necessary because some of the study participants will not have had experience with CGMs in the past.

Study Pump Run-in Phase: All subjects will have a run-in period on the study pump of up to two week duration. Subjects who have had prior experience with the study pump may either skip this run-in phase or may require a shorter run-in period depending on their proficiency with the study pump.

Sensor-Augmented Pump (SAP) Therapy: During this phase, the subject is on the study CGM and their personal insulin pump. There are no predictive or control algorithms. The subjects will administer basal and bolus insulin using their usual home insulin parameters.

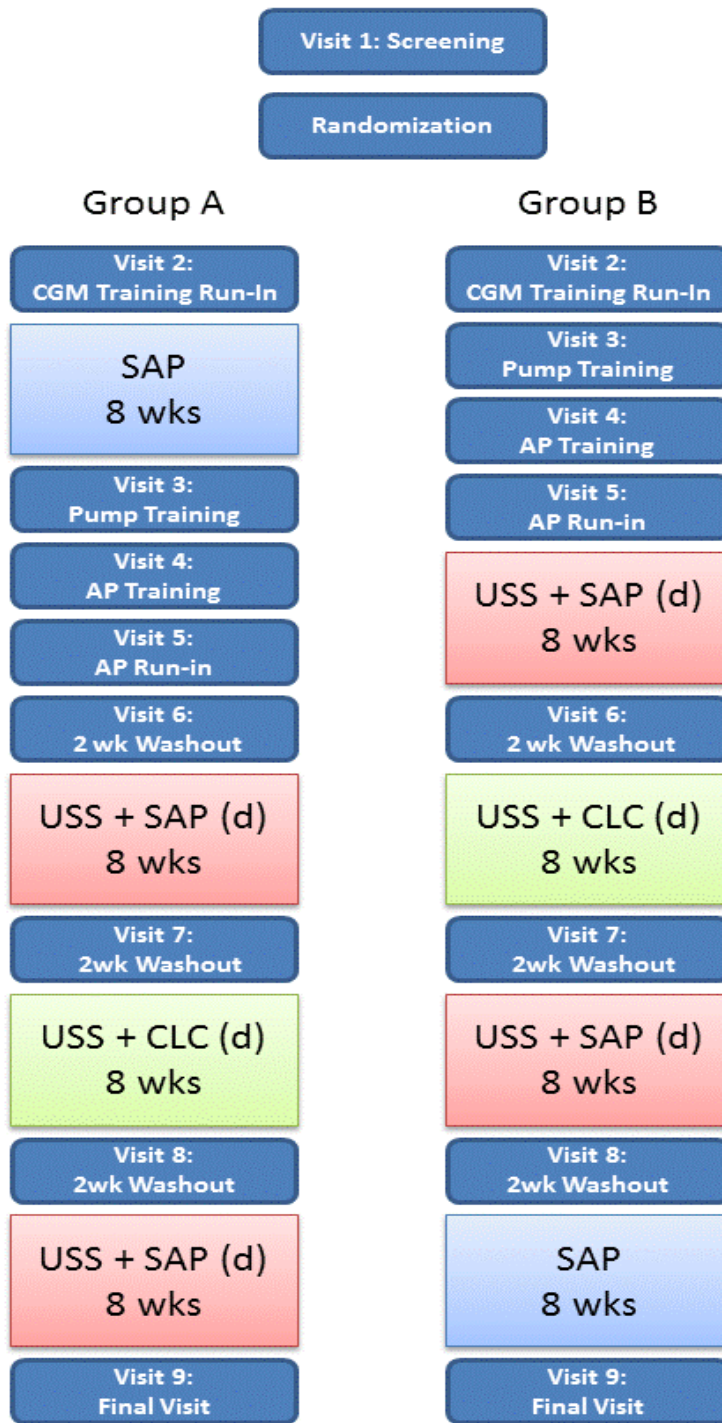
### **Study Phases with the AP System**

AP system Run-In Phase: Subjects who have not had recent use of the system (more than approximately 2 weeks of use in the past 6 months or more than 2 months of use in the past year) will complete an up to 2-week home use period with the full system in pump only (open loop) configuration where no closed loop algorithms are activated. Subjects who have had prior experience with the system as defined above will not be required to do Visit 5.

USS+SAP (d): USS Virginia plus SAP during the day (d). Subjects will be using the study pump and CGM with the AP system in Pump mode (open loop only, no closed loop algorithms running). The subject will activate the USS Virginia Closed-Loop Control as early as pre-dinner but is expected to activate CLC by bedtime. The subject will continue in Closed-Loop Control until the time of awakening in the morning. The USS will monitor CGM and insulin-on-board data and predicts the patient's risk of hypoglycemia and adjust insulin delivery accordingly.

USS+CLC (d): USS Virginia and Closed Loop Control over 24 hours. This arm will test fully-integrated closed-loop control (CLC) system. When hypoglycemia is predicted, the USS reduces basal rate insulin to prevent hypoglycemia, or issues an alert that signals that carbohydrates are required to treat hypoglycemia. The USS also generates alerts about correction bolus requests that are considered potentially dangerous, or meal bolus requests that require user approval prior to delivery.

Figure 5: Visit flow diagram



## Chapter 2 SUBJECT ENROLLMENT AND STUDY INITIATION

### 2.1 Study Population

We anticipate recruiting up to 110 subjects, ages  $\geq 18$  and  $< 70$  years. An equal number of males and females will be recruited, and all racial/ethnic groups will be eligible for participation. Based on our experience, we expect that approximately 76% in each arm will complete the study (N=64) and has been increased to account for inclusion of new devices. The randomization will aim to balance the age/gender distributions of the participants in the two groups and to match the groups by baseline HbA1c.

### 2.2 Eligibility and Exclusion Criteria

#### 2.2.1 Eligibility

To be eligible for the study, a subject must meet the following criteria at time of screening:

- Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year and an insulin pump for at least 6 months
- Criteria for documented hyperglycemia (at least 1 must be met):
  - i. Fasting glucose  $\geq 126$  mg/dL
  - ii. Two-hour OGTT glucose  $\geq 200$  mg/dL
  - iii. HbA1c  $\geq 6.5\%$  documented
  - iv. Random glucose  $\geq 200$  mg/dL with symptoms
  - v. No data at diagnosis is available but the participant has a convincing history of hyperglycemia consistent with diabetes
- Criteria for requiring insulin at diagnosis (1 must be met):
  - i. Participant required insulin at diagnosis and continually thereafter
  - ii. Participant did not start insulin at diagnosis but upon investigator review likely needed insulin (significant hyperglycemia that did not respond to oral agents) and did require insulin eventually and used continually
  - iii. Participant did not start insulin at diagnosis but continued to be hyperglycemic, had positive islet cell antibodies – consistent with latent autoimmune diabetes in adults (LADA) and did require insulin eventually and used continually
- Age  $\geq 18$  and  $< 70$
- 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 pregnancy test will be required for all premenopausal women who are not surgically sterile. Subjects who become pregnant will be discontinued from the study.
- Demonstration of proper mental status and cognition for the study
- Currently using an insulin-to-carbohydrate ratio to calculate meal bolus sizes
- Access to internet and/or cell phone service at home and work
- Ability to access the Internet and upload study data.
- An understanding of and willingness to follow the protocol and sign the informed consent

- Willingness to switch to lispro (Humalog) or aspart (Novolog) if using glulisine (Apidra).

### 2.2.2 Exclusion

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

- Admission for diabetic ketoacidosis in the 12 months prior to enrollment
- Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment
- History of a seizure disorder (except hypoglycemic seizure), unless written clearance is received from a neurologist and not currently on a seizure medication
- Cystic fibrosis
- Coronary artery disease or heart failure, unless written clearance is received from a cardiologist or primary care provider
- Pregnancy, breast-feeding, or intention of becoming pregnant over time of study procedures
- A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
  - Inpatient psychiatric treatment in the past 6 months
  - Presence of a known adrenal disorder
  - Abnormal liver function test results (Transaminase >2 times the upper limit of normal); testing required for subjects taking medications known to affect liver function or with diseases known to affect liver function
  - Abnormal renal function test results (calculated GFR <60 mL/min/1.73m<sup>2</sup>); testing required for subjects with diabetes duration of greater than 5 years post onset of puberty
  - Active gastroparesis
  - If on antihypertensive, thyroid, anti-depressant or lipid lowering medication, lack of stability on the medication for the past month (except thyroid medication requires 2 months) prior to enrollment in the study
  - Uncontrolled thyroid disease (TSH undetectable or >10 mIU/L); testing required within 6 months prior to admission for subjects with a goiter, positive antibodies, or who are on thyroid hormone replacement, and within one year otherwise
  - Abuse of alcohol or recreational drugs
  - Infectious process not anticipated to resolve prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis).
  - Uncontrolled arterial hypertension (Resting diastolic blood pressure >90 mmHg and/or systolic blood pressure >160 mmHg).
  - Oral steroids
  - Uncontrolled microvascular complications such as current active proliferative diabetic retinopathy defined as proliferative retinopathy requiring treatment (e.g. laser therapy) in the past 12 months.
  - A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication or

- disease in the judgment of the investigator will affect the completion of the protocol
- Basal Rates <0.1 units/hour or minimal total daily basal rates <2.40 units/day.
  - Use of the following drugs and supplements during the study:
    - Acetaminophen
    - Medications being taken to lower blood glucose, such as Pramlintide, Metformin, GLP-1 Analogs such as Liraglutide, and SGLT-2 inhibitors intended to lower blood glucose. Subjects who are on these agents either intermittently or continuously prior to the trial or at the time of screening will be asked to consult with their personal care provider prior to determining whether they can discontinue these agents.
    - Beta-blockers or nutraceuticals intended to lower blood glucose may not be initiated during the trial. Subjects who are on beta-blockers or nutraceuticals intended to lower blood glucose at the time of enrollment may continue on those medications/supplements if the doses have been stable for  $\geq 6$  months.
    - Any other medication that the investigator believes is a contraindication to the subject's participation

### **2.3 Informed Consent, Eligibility Assessment and Baseline Data Collection**

The study will be discussed with the subject. The subject will be provided with the 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 chart.

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

Subjects will be evaluated for study eligibility through the elicitation of a medical history, documentation of a physical examination (by study personnel or local MD) 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 and lab results.

#### **2.3.1 Historical Information and Physical Exam**

A history will be elicited from the subject and extracted from available medical records with regard to the subject's diabetes history, current diabetes management, other past and current medical problems, past and current medications, and drug allergies. A standard physical exam (including vital signs and height and weight measurements) will be either performed by the study investigator/ designee (study staff) or a physical exam from the subject's personal physician within 6 months will be reviewed.

#### **2.3.2 HbA1c**

HbA1c level will be measured at baseline using the method utilized by the clinic as part of patient care: DCA2000 or equivalent NGSP-certified point-of-care method or local laboratory. HbA1c measurements performed within 4 weeks of randomization may be used.

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## Chapter 3 STUDY PROTOCOL

### 3.1 Visit 1 – Screening

At the Screening Visit, the following procedures will be performed / criteria will be checked and documented:

#### Eligibility Screening Events (to be completed prior to randomization):

- Signed and dated informed consent
- HbA1c assessment via blood draw or fingerstick and DCA2000 or equivalent NGSP-certified point-of-care method (value -4 weeks prior to randomization acceptable)
- Inclusion and exclusion criteria
- Demographics (date of birth, gender, race and ethnicity)
- Diabetic history
- Medical history
- Substance use history (drinking, smoking, and drug habits)
- Concomitant medications
- Physical examination (by study staff or subject's personal MD within 6 mos.)Urine or serum pregnancy test for all premenopausal women who are not surgically sterile
- Blood draw for:
  - Chemistry panel for subjects with diabetes duration of greater than 5 years post onset of puberty (values within 6 months prior to enrollment acceptable).
  - Liver function tests in subjects taking medications known to affect liver function or diseases known to affect liver function (values within 6 months prior to enrollment acceptable).
  - TSH within 6 months for subject with a goiter, positive antibodies, or who are on thyroid hormone replacement. A normal TSH within the past year is otherwise acceptable.
  - Hematocrit

#### Non-Eligibility Screening Events:

- Weight, height (by study staff or subject's personal MD within 3 mos.)
- Blood pressure and heart rate (by study staff or subject's personal MD within 1 mo.)
- Questionnaires (may be completed electronically):
  - *inControl Technology Expectations Questionnaire (administered prior to starting inControl)*
  - *inControl Technology Acceptance Questionnaire (administered at subsequent time points after starting inControl)*
  - *DSPQ\_Diabetes Specific Personality Questionnaire (administered at onset of trial only)*
  - *Clarke Hypoglycemia Awareness Questionnaire*
  - *DDS\_Diabetes Distress Scale*
  - *High Blood Sugar Survey*
  - *HFS-II (Part 1 and 2) (Adult Low Blood Sugar Survey)*
- All blood glucose meters used in the study (either personal or study provided glucometers) will be QC tested with at least two different concentrations of control solution if available at the start 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 subject will be instructed to perform quality control testing of the BG meter at home per manufacturing guidelines, and to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails the testing.

- Subjects will be asked to perform SMBG measurements at least 4 times daily (before meals, and at bedtime) throughout the study. Subjects will be reminded to use the same glucometer for all finger sticks and calibrations and to only use SMBG values (not CGM values) to guide treatment decisions. **Subjects will use their personal glucometer throughout the study** but will be provided with a study glucometer if needed.
- Subjects will be provided with a study blood ketone meter and test strips. All study blood ketone meters will be QC tested at the start of the study with at least two different concentrations of control solution if available. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling.
- Subjects will be asked to obtain a glucagon kit per usual care guidelines from their personal physician. If subject is unable to obtain, study physicians may provide a prescription for the subject to obtain at their local pharmacy.

The total amount of blood to be withdrawn during this screening visit is ~9 cc. The visit will last approximately 2-4 hours.

### **3.1.1 Pilot Study**

Prior to implementation of inControl use at home, we will conduct a pilot study of up to 4 subjects using inControl under supervision. This may occur within this protocol or another protocol/IDE (G150221). These subjects will have an approximately 48 hour visit to a research house/hotel. These subjects will be under closed loop control with continuous remote monitoring. We will have a technician and medical personnel (e.g. nurse, EMT) with the subjects at all time. The data will be reviewed by the DSMB and, if no serious adverse events and approved by the DSMB, subjects will continue to be enrolled as described in this protocol.

### **3.2 Randomization**

A subject who meets all the inclusion and exclusion criteria will be enrolled in the study. After completion of the eligibility criteria, the participant will be randomized to one of the two arms: Group A and Group B as described and illustrated in Figure 1.

Subjects who are randomized to Group A will start SAP within four weeks of completing Visit 2; Visit 3 and Visit 4 will occur following completion of SAP.

Subjects who are randomized to Group B will proceed directly to Visit 2, Visit 3 and 4.

All training and run-in visits were structured to accommodate subjects who are experienced with the system or system components as well as subjects who have little to no experience with the system or system components. As a result, training/run-in visits may be combined as described in the protocol depending on the skill level of the individual subject.

### 3.3 Visit 2 – CGM Training and Run-In

Visit 2 may occur concurrently with Visit 1.

- A urine pregnancy tests may need to be repeated in premenopausal women who are not surgically sterile if Visit 2 occurs more than 6 weeks after their Visit 1.
- Current CGM use will be evaluated, data may be downloaded for any CGM currently in use.
- Eligible subjects will receive study CGM training including proper insertion, calibration and maintenance of the CGM sensor. Training will be tailored to their individual experiences.
- Subjects will take one of three paths forward in the study based on prior CGM experience:
  - **Dexcom CGM users with use in the past 12 weeks**  
These subjects will not require any further CGM run-in.
  - **Non-Dexcom CGM users (current or past users) or Dexcom CGM users with last use more than 12 weeks prior**  
These subjects will be given study CGM supplies and move into an up to 1-week home use period with the study CGM to confirm the ability to use the CGM successfully. Subjects may skip this CGM run-in period if subject demonstrates adequate CGM skills.
  - **CGM non-users**  
These subjects will be given study CGM supplies and move into an up to 2-week home use period with the study CGM to confirm the ability to use the CGM successfully and to help establish baseline glycemic control during frequent CGM use. Subjects will be contacted weekly by study staff to review CGM use.
- If the subject has not demonstrated adherence to use of CGM after any applicable run-in period, study staff may discontinue that subject at their discretion.
- Subjects will be required to set the CGM hypoglycemia threshold alarm to a value no less than 60 mg/dl and the CGM hyperglycemia threshold alarm to a value no greater than 300 mg/dl.

### 3.4 Visit 3 - Study Pump Training and Run-In Period

Visit 3 may occur concurrently with Visit 1 and 2.

Subjects will have supervised training on the study pump as described below.

Study staff will review subject's pump parameters by manual review and/or download of personal insulin pump.

All subjects will have a run-in period on the study pump of up to two weeks duration. Subjects who have had prior experience with the study pump may skip or require a shorter run-in period.

The pump run-in period may overlap with any required CGM run-in period.

Pump training will include:

- The subject will be fully instructed on the study insulin pump. A qualified staff member or pump 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 be 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 will be encouraged to review the literature provided with the pump, infusion sets, and other pump related supplies after the training is completed.

### **3.5 Visit 4 – Closed Loop Training Visit**

Visit 4 will occur just prior to starting the first session of Closed-Loop Control to ensure that the training is in close proximity to the initiation of the system in closed loop control (for Group B this will occur earlier than Group A).

Visit 3 and 4 may occur concurrently for inControl users. For subjects starting on the Tandem-G6 system, Visit 3 and 4 will be concurrent.

Visit 4 will consist of a ~5-10 hour training session in a transitional setting at a research house, hotel or clinic during which the subject will be trained to use the system to control the study pump, including meal announcement, meal bolusing, exercise, and switching back and forth between Pump (open-loop) mode and Stopped mode. Subjects may be asked to view study materials at home (e.g. User Guides and/or study videos on the Use of the AP System) prior to coming to Visit 4. This visit may shorter than 5-10 hours depending on the subject's proficiency with the system as well as prior experience.

A serum or urine pregnancy test will be collected for all premenopausal women who are not surgically sterile.

Prior to initial use, the system will be initialized with each subject's individual parameters, including carbohydrate ratio, correction factor, and basal rate pattern.

Study team members will train the subject in performing specific tasks including the following:

- The study team will confirm the pump parameters entered in the system with the subject.
- How to switch the system between Pump mode (open-loop, preprogrammed basal insulin delivery) and Stopped mode depending on circumstances. For the Tandem-G6 system, this will consist of turning Control-IQ off.
- How to calibrate the CGM unit during the study.
- How to access the CGM trace on the user interface.
- How to activate the meal screen of the system any time insulin will be given with a meal or any time additional correction insulin is desired.
- How to inform the system of hypoglycemia treatment on the user interface.
- What to do in when engaging in strenuous exertion
- How to perform blood ketone testing and perform rescue therapy actions with the glucagon kit

- The subject will be assessed for understanding of the system interface and how to react to safety/alert messages.
- The subject will be given a AP system User Guide relevant to their system (Appendix A-10) as a reference.

The subject must be able to complete system-related tasks independently to be eligible to continue in the study.

### **3.6 Visit 5 - AP System Run-In phase: Home Use in Pump Only (Open Loop) Configuration**

Eligible subjects who have not had recent use of the system (more than ~2 weeks of use in the past 6 months or more than ~2 months of use in the past year) will complete up to 2-week home use period with the full system in pump only (open loop) configuration where no closed loop algorithms are activated. Subject will be instructed not to start closed loop during this run-in phase. Subjects who have had prior experience with the AP system as defined above will not be required to do Visit 5. Subjects who are demonstrating proficiency, as determined by the study physician, may have a shorter open loop run-in phase with a minimum of 5 days duration. Criteria for proficiency is listed in section 3.11.

For the inControl system, remote monitoring will be available during this period for the purposes of data collection and ad hoc assessment of system performance by study team. The study team will be available for the subject to contact during this phase. Study staff will contact the subject and review data on the Remote Monitoring once daily. The subject may contact the study staff at any time.

For the Tandem-G6 system, remote monitoring will not be available. Study staff will contact the subject daily to assess difficulties with the use of the system. The subject may contact the study staff at any time. If the study team requires additional information, the subject may be asked to upload the pump at home so that the study can review data on the t:connect website.

### **3.7 Visit 6 + Visit 7 + Visit 8 Washout Following Completion of the Each Study Phase**

At the completion of the each phase of the study, subjects will have up to a two week washout prior to proceeding to the next phase.

First Phase: Group A 8 weeks of SAP; Group B 8 weeks of USS +SAP(d)

Second Phase: Group A 8 weeks of USS +SAP(d); Group B 8 weeks of USS + CLC(d)

Third Phase: Group A 8 weeks of USS + CLC(d); Group B 8 weeks of USS +SAP (d)

Fourth Phase: Group A 8 weeks of USS + SAP(d); Group B 8 weeks of SAP

Visit 6 may occur concurrently with Visits 3, 4 and 5. During this time, subjects may continue on the study pump if Visit 4 has been completed or switch to their own personal pump. Subjects will either come to the study site or complete the following locally: HgbA1c, and psychometric questionnaires (Appendix A-11)

**Individual Structured Interviews [Optional]:** Subjects will be asked to participate in an individual structured interview after using the AP system (Group A= after visit 7, 8, 9; Group B=after visit 6, 7, 8).

These structured interviews will be audiotaped to assist staff in recording subjects' responses. These interviews may be conducted in person or over the phone. The audio recordings will be labeled with the study subject ID number and will be stored with other study documentation.

Data will be downloaded from study devices, glucometer and personal pump (during SAP) by one of several methods: locally by the subject and sent to study staff, by study staff at time of a visit or devices not in use being mailed to the study staff for downloading.

### **3.8 Visit 9 - End of Study Visit**

At the completion of the final phase of the study, subjects will complete their final visit. Subjects will resume their personal pump. Subjects will either come to the study site or complete the following locally: HgbA1c, questionnaires, and may participate in an individual structured interview.

Data will be downloaded from study equipment, glucometer and personal pump (during SAP) by one of several methods: locally by the subject and sent to study staff, by study staff at time of a visit or equipment mailed to the study staff for downloading.

### **3.9 Study Procedures during SAP**

- Study subjects will be using the study CGM (Dexcom G4) and either their home pump or study pump for 8 weeks. Subjects using the Tandem-G6 system during AP phases will use their home pump during SAP.
- Subjects will be following their usual home insulin parameters. There are no predictive algorithms running for insulin administration.
- Subjects will be requested to use their personal glucometer or study glucometer for all fingersticks including CGM calibrations.
- Subjects will perform their usual activities and manage their diabetic regimen per their usual routine.
- Study staff will be available at any time for the study subject to contact.
- Staff will contact the subject once a month after the first month.

### **3.10 Study Procedures during USS + SAP(d) and USS + CLC(d)**

The subject will be wearing the study CGM, the study pump and utilizing the AP system for 8 weeks. Subject will be doing fingerstick testing using their personal glucometer or study provided glucometer.

For USS + SAP(d): The subject will be instructed to activate closed-loop operation each evening any time between just before eating dinner and prior to bedtime. The subject will be instructed to switch back to open-loop mode upon waking up in the morning.

For USS +CLC(d): The subject will be instructed to remain in closed-loop operation for 24 hours.

While using the closed loop system, the subject will be instructed to avoid deviating from his/her regular daily routine in regards to diet and exercise and to maintain his or her usual sleep schedule during the course of the study. The subject will specifically be asked to avoid consuming more than 3

alcoholic drinks in any one day. The subject will also be instructed to avoid use of closed-loop mode during periods of illness with an elevated temperature >101.5 degrees Fahrenheit, periods of significant illness, or during periods of use of medications such as epinephrine for the emergency treatment of a severe allergic reactions or asthma attack in addition to use of oral or injectable glucocorticoids. The subject will be asked to put the system in exercise mode when engaging in strenuous exertion.

The total duration during each of these phases will be 8 weeks of AP system use regardless of whether CLC was activated or not. If a subject was off the system entirely and unable to use the system (e.g. in Stopped Mode) on one or more days due to illness or other factors such as extended travel, the use period may be extended at investigator discretion to obtain 8 weeks of use.

### **3.11 Monitoring when the AP system is in Use during Visit 5, USS + SAP(d) and USS + CLC(d)**

Throughout the study, the study subject will be given contact information for study team members and can contact the study team at any time.

During the first use of the system at visit 5 and following completion of Visit 5 (second phase for Group A and first phase for Group B), the following procedures will be in place:

- The study team will contact the subject daily for the first week.
- The study team will review the Remote Monitoring System once daily for the first week (if using inControl).
- A subject will be assessed by the study team at the end of the first week on the following criteria:
  - The subject used the system appropriately including the following:
    - Responded to system alerts and treated hypo- and hyperglycemia appropriately
    - Avoided deviating from his/her regular daily routine in regard to diet and exercise and maintained his or her usual sleep schedule
    - Avoided consuming more than 3 alcoholic drinks in any one day
    - Performed a fingerstick BG at least 4 times daily (inControl subjects using Dexcom G5 only) and/or appropriate fingerstick BG testing by investigator discretion
    - Avoided use of closed-loop mode during periods of illness with an elevated temperature >101.5 degrees Fahrenheit, 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
  - Did not experience severe hypoglycemia or severe hyperglycemia/DKA (not associated with infusion set failure) as defined in Section 5.1
  - Did not develop >1.0 mmol/L ketones on 3 or more study days due to prolonged periods of inadequate insulin delivery
  - Study staff were able to contact the subject without difficulty and in a timely manner when the system was in use
  - Subject was able to communicate with the remote monitoring server without more than 3 prolonged periods of loss of connection during the time that the system use was active for

inControl. Subjects using Tandem-G6 will be asked to upload their pump to the t:connect website at least one time during this timeframe for the study team to ensure adequate data capture.

If the study subject did not meet these criteria, then an additional week of daily contact (all subjects) and daily remote monitoring (inControl subjects only) will be performed provided that the subject did not trigger any of the study stopping rules for individual subjects (as defined in Section 5.9).

Subject will be reeducated as appropriate and reassessed again at the end of the second week. Study staff will continue this weekly assessment per the staff's discretion in those subjects that are not meeting criteria.

When the subject meets all the criteria, then study staff will be contacting them (all subjects) and reviewing the remote monitoring data (inControl subjects only) once a week until the subjects complete their first 8 week time period using the AP system.

During the subsequent 8 week time periods of using the system, subjects will be contacted (all subjects) and remote monitoring data (inControl subjects only) reviewed every other week by the study staff.

Subjects using Tandem-G6 system will upload the study pump a minimum of once every 4 weeks and anytime the staff requests review of the data.

### 3.12 Duration of Study

Each study subject is expected to participate in the study for 44-50 weeks. The completion of the study (up to N=110 recruited) is expected to last approximately 42 months.

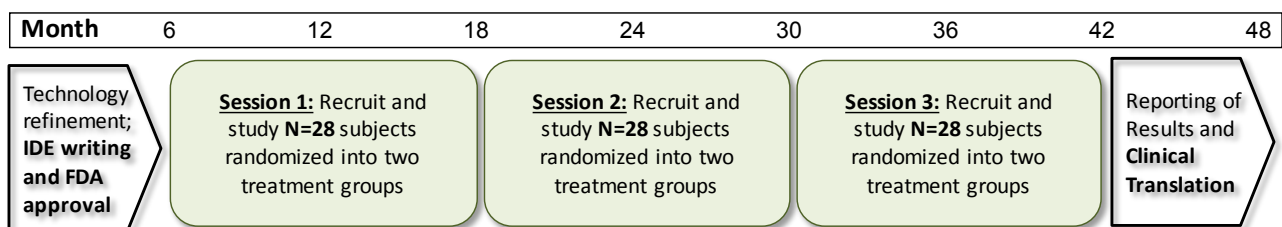


Figure 7. Timeline for recruitment

## Chapter 4 CLOSED-LOOP CONTROL SYSTEM OPERATION AND SAFETY

### 4.1 Algorithm Details

The control system consists of several modes with different functions adapted to different activities:

- Module 1 –Safety Supervision (SSM) responsible for prevention of hypoglycemia. This is a passive safety module that can only attenuate insulin delivery.
- Module 2 -- Basal Rate (BRM) responsible for augmentation of basal rate up to a total of 3X basal, to compensate for changes in insulin sensitivity (e.g. dawn phenomenon).
- Module 3 – Range Control (RCM) is responsible for postprandial correction insulin administered as needed.

In addition, the system includes a sophisticated meal bolus calculator that takes into account the current glucose state of the subject and available insulin to make a recommendation for a pre-meal bolus. The recommendation must be confirmed before delivery; if not confirmed, pre-meal insulin is not delivered automatically. The bolus calculator is activated on demand by the user, prior to meals.

### 4.2 System Details

The study system will function in different operational modes in the proposed study: Stopped, Pump, and Closed-Loop. Pump mode will be referred to throughout this protocol and consistently means the delivery of preprogrammed basal rates (Open-Loop) regardless of the system being used. In Closed-Loop mode, basal delivery can be attenuated or increased by the control algorithms.

For inControl system only: If the system malfunctions but the system can still communicate with the pump, the system will fail safe to Pump mode so that the user will continue to receive basal insulin under the direction of the system. If there is a malfunction in which the system cannot communicate with the pump, the system will fail safe to Stopped mode. If the system is in Stopped mode and the Roche pump is being used, the user will begin receiving basal insulin from the pump without any direction from the AP system within a short period of time.

The table below summarizes the system modes for inControl and some of the functionality available in each mode:

Mode	Overview	CGM data?	Basal Insulin delivered via AP?	Bolus Insulin delivered via AP?	Hypo-/Hyper Glycemia Alerts?	Data Transfer to Remote Server to allow monitoring?
<b>“Stopped”</b>	System comes online in Stopped mode and awaits user action. User may switch the system into Stopped mode at any time.	No	No	No	No	No
<b>“Pump”</b>	Emulates traditional insulin pump behavior of open-loop basal insulin delivery according to preprogrammed pattern; used instead of Closed-Loop mode when replacing CGM sensor	Yes, if available	Yes, identical to preprogrammed pattern	Yes, but only user-requested manual boluses; no automated boluses	Yes	Yes
<b>“Closed Loop”</b>	Control algorithm determines appropriate automated insulin delivery. Can only activate if CGM data is available.	Yes	Yes, according to algorithm based on preprogrammed pattern attenuated or increased when needed	Yes, automated boluses if algorithms are active, and user-requested manual boluses at any time	Yes	Yes

Table 1: Basic functionality of system in each operational mode

### 4.3 Setup and Operation of the Closed-loop Control System

Prior to closed-loop use, the AP system is initialized with each subject’s individual parameters, including carbohydrate ratio, correction factor, and basal rate pattern.

## 4.4 Safety Measures

### 4.4.1 *Safety Measures of Insulin Dosing*

In Closed-Loop mode, all dosing is supervised by a dedicated safety supervision system module and insulin correction for meal boluses must be manually confirmed. In Pump and Closed-Loop mode:

- Bolus size is checked by the algorithm to ensure it is smaller than the maximum bolus that the pump can handle;
- For inControl, switching to “Stopped” mode includes a ‘cancel all’ delivery message to the pump so that any active but incomplete bolus is cancelled with the Roche Accu-Chek pump.
- All insulin requests are made in the form of boluses or temporary basal rate changes; this ensures that in case of a system crash or pump disconnection, no request has permanence;
- Users will be able to monitor delivered insulin in the plots menu on the phone which is available from the main screen in any operating mode. The remote monitoring displays the delivered insulin and total insulin delivered during the past 4 hours via the web interface;
- It is important to note that IOB constraint is an internal safety feature of the closed-loop system. It is not read from the pump or any other external source. The IOB in the system is computed by the system using a model of the transport and clearance of insulin from the subcutaneous infusion site to the circulation, and is intended to prevent insulin overdose.

### 4.4.2 *Hypoglycemia Safety Guidelines*

If the subject receives a hypoglycemia alert from the study system, the subject will be instructed to perform a fingerstick test with the blood glucose meter. The hypoglycemia alerts will be active in Pump and Closed-loop modes. If the subject’s BG result is  $\leq 80$  mg/dL, the subject will be instructed to treat with ~8-16 grams of oral glucose and for inControl users indicate treatment was given on the system by activating the hypoglycemia treatment button. Further details will be included in a Subject User Guide regarding retesting, retreatment, and criteria for glucagon treatment, stopping the system, contacting the study physician, and contacting emergency responders.

### 4.4.3 *CGM Calibration*

Throughout the study, the subject will be instructed to calibrate the CGM at least twice a day (Dexcom G4) and any time there is a calibration request from the CGM itself, provided that the fingerstick glucose is between 40-400 mg/dL and the CGM arrow is flat (horizontal), indicating that the sensor glucose value is not changing rapidly.

### 4.4.4 *Hyperglycemia Safety Guidelines*

If the subject receives a hyperglycemia alert from the study system, the subject will be instructed to perform a fingerstick test with the blood glucose meter. The hyperglycemia alerts will be active in Pump and Closed-loop modes. If the subject’s BG result is  $\geq 300$  mg/dL for over 1 hour, or over  $\geq 400$  mg/dL at any point, the subject will be instructed to perform a blood ketone measurement with the study ketone meter. Further details will be included in a Subject User Guide regarding criteria for stopping the system, administering correction boluses, retesting, retreatment, infusion set replacement, contacting the study physician, and contacting emergency responders.



#### **4.4.5 CGM Sensor Failure**

If the CGM signal becomes unavailable for an extended period of time during Closed-Loop mode, the system will revert to Pump mode.

#### **4.4.6 Pump Failure**

For inControl, If the insulin pump stops communicating for >10 minutes, the system will generate an alert on the phone and will eventually switch to Stopped mode if the communication problem persists. If loss of pump communication persists, the Roche pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the controller (within 15-45 minutes from time of failure of communication based on estimated glucose at the time of loss of communication).

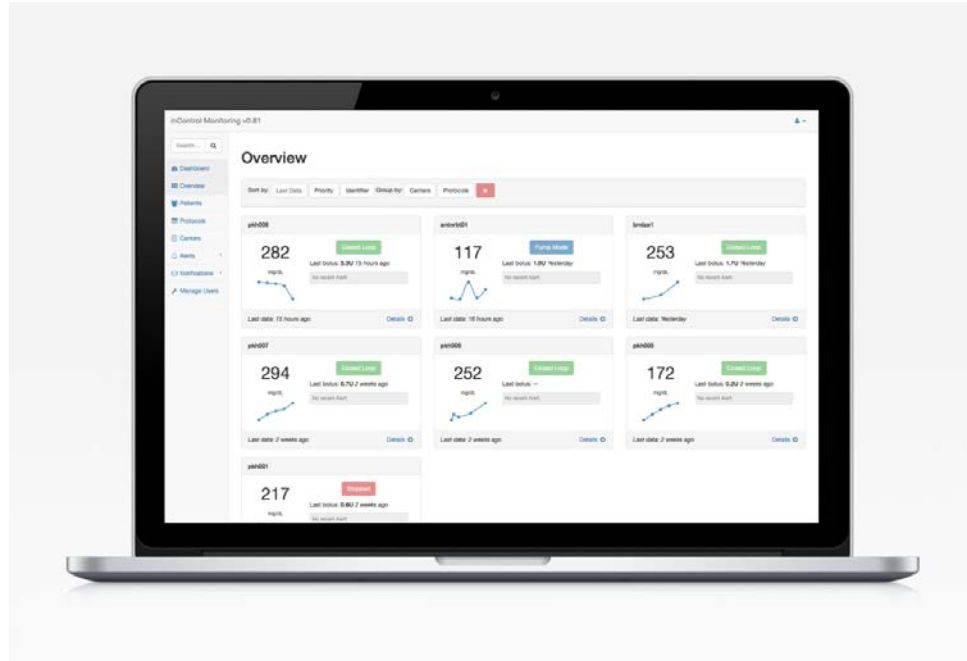
#### **4.4.7 Study System Failure**

For inControl, If the study system stops working, the Roche pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the controller (within 15-45 minutes from time of failure of communication based on estimated glucose at the time of loss of communication).

For Tandem-G6 system, if the t:slim X2 detects a system error that does not allow the pump to operate, the Malfunction Alarm will display and the subject will be instructed to contact the study team.

#### **4.4.8 Remote Monitoring for inControl**

**REMOTE MONITORING SERVER** – The TypeZero Technologies inControl-Cloud data collection and monitoring application is a cloud-based system that stores de-identified user data received from the inControl-AP artificial pancreas smartphone application over a secure SSL link. Access to inControl-Cloud is password protected and access is restricted by account to members of the study team and to TypeZero authorized personnel. inControl Cloud may run on systems from one of a number of vendors such as Amazon Web Services. The system offers the possibility to track many patients at the same time, with automated alarms and alerts (Figure 6).



**Figure 6: Remote Monitoring Interface**

During the Closed-Loop Training visit, the subject will be supervised using the monitoring system in order to verify that the system cell phone, data link and server are all functioning properly. The subject will be shown how to verify that the data link to the server is working and what to do if the system indicates link failure. The subject will also have a chance to ask questions and discuss with study staff where they may travel during the trial such that continuous monitoring of the system is possible. Subjects will be provided a Subject User Manual containing glycemic guidelines and the AP system manual.

## Chapter 5 ADVERSE EVENT REPORTING AND PROTOCOL MONITORING

### 5.1 Definition

A reportable adverse event is any untoward medical occurrence or any unexpected medical occurrence in a study subject.

Hypoglycemic events are recorded as Adverse Events if the event required assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat him or herself, was unable to verbalize his or 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.

Hyperglycemic events are recorded as Adverse Events if evaluation or treatment was obtained from a health care provider or if the event involved diabetic ketoacidosis (DKA), as defined by the Diabetes Control and Complications Trial (DCCT), and had all of the following:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones 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

### 5.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the subject at each visit and complete all adverse event forms online.

The 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 or study procedures.

The intensity of adverse events 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.

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.

Definitions of relationship and intensity are listed on the website data entry form.

Documentation of adverse events will discontinue at the completion of Visit 9 Washout Period.

### **5.3 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 recorded on a CRF but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than manufacturer recommended use
- 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

### **5.4 Definition of a Protocol Enrollment Exception**

No enrollment exceptions will be permitted in this trial.

### **5.5 Definition of a Data Breach**

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

### **5.6 Data Collection**

Endpoint data be collected/recorded in the form of source documents and will be stored on a database on a Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA.

At UVa, safety data oversight will be completed by a member the UVa Clinical Trials Office. An example of the Monitoring Form is presented in Appendix A-13.

The PI will conduct an aggregate review of the following data:

- All adverse events
- Unanticipated Problems
- Protocol violations
- Audit results
- Early withdrawals
- Data processing review

IRB-HSR will be updated annually on the IRB-HSR continuation status form. This annual report will address:

- Brief summary of research progress
- Whether adverse event rates are consistent with pre-study assumptions
- Enrollment status
- Reason for dropouts from the study
- Whether continuation of the study is justified
- Conditions whereby the study might be terminated prematurely

The relevant device regulation for reporting adverse events to the FDA will also be followed. Data from each subject will be reviewed by the PI after completion of participation to determine whether the system was working properly and whether there were safety concerns.

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation (Note: An internal event is one that occurs in a subject enrolled in a UVa protocol.)	IRB-HSR	Within 24 hours	IRB Online and phone call <a href="http://www.irb.virginia.edu/">www.irb.virginia.edu/</a>
Internal, Serious, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time, the study team received knowledge of the event. Timeline includes submission of signed hardcopy of AE form.	IRB Online <a href="http://www.irb.virginia.edu/">www.irb.virginia.edu/</a>

For Device Studies: Unanticipated adverse device effects (internal)	IRB-HSR	Within 10 day calendar days of the study team receiving knowledge of the event	IRB Online <a href="http://www.irb.virginia.edu/">www.irb.virginia.edu/</a>
<b>Unanticipated Problems</b> that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 10 day calendar days of the study team receiving knowledge of the event	IRB Online <a href="http://www.irb.virginia.edu/">www.irb.virginia.edu/</a>
Protocol Violations/Noncompliance The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by the sponsor  OR Enrollment Exceptions	IRB-HSR	Within 7 calendar days from the time, the study team received knowledge of the event.	Unanticipated Problem report form.  <a href="http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc">http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc</a> )
Data Breach	IRB-HSR	Within 7 calendar days from the time, the study team received knowledge of the event.	Protocol Violation, Noncompliance and Enrollment Exception Reporting Form  <a href="http://www.virginia.edu/vprgs/irb/hsr_forms.html">http://www.virginia.edu/vprgs/irb/hsr_forms.html</a> Go to 3 <sup>rd</sup> bullet from the bottom
Data Breach	The UVA Corporate Compliance and Privacy Office, a  ITC: if breach involves electronic data-	As soon as possible and no later than 24 hours from the time, the incident is identified.  As soon as possible and no later than 24 hours from the	UVa Corporate Compliance and Privacy Office- Phone 924-9741  ITC: Information Security Incident Reporting procedure, <a href="http://www.itc.virginia.edu/security/reporting.html">http://www.itc.virginia.edu/security/reporting.html</a>

	<p>Police if breach includes items that are stolen:</p> <p>Stolen on UVA Grounds</p> <p>OR</p> <p>Stolen off UVA Grounds- contact police department of jurisdiction of last known location of PHI</p>	<p>time, the incident is identified.</p> <p>IMMEDIATELY.</p>	<p>UVa Police- Phone- (434) 924-7166</p>
<b>UVa PI HELD IDE</b>			
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
Unanticipated adverse device effects (internal or external)	FDA	Within 10 working days of the study team receiving knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IDE annual report

**Table 2: Reporting Table**

### 5.7 Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward 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 significant disability/incapacity
- Is a congenital anomaly/birth defect

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of the nature, severity or frequency given the research procedures that are described in the protocol –related documents AND in the characteristics of the population under study.
- Is related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research places the subject or others at greater risk of harm (physical, psychological, economic or social) than was previously known or recognized OR results in actual harm of the subject or others. An unanticipated problem generally required a change in policy or procedure, warrants consideration of substantive changes to the protocol/consent or other immediate corrective actions in order to reduce the risk or eliminate immediate hazard.

As noted in the table above, the study team will notify the FDA of any adverse event that is serious, unexpected, and related or possibly related. Notification will be made within 15 days after the study team becomes aware of the event.

The principal investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB.

### 5.8 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (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.

We will implement a system to oversee and monitor our randomized clinical trial to ensure the safety of participants, as well as the validity and integrity of the data. We will establish a data safety monitoring board, ensuring that the DSMB's responsibilities are commensurate with the risks, complexity, and nature of our studies. We will define the role of the DSMB prior to initiating the clinical trial and clearly delineate the operating procedures and policies of the board, including "stopping rules" for the study.



**Membership:** Our DSMB will be comprised of experts in diverse scientific disciplines to ensure participant safety and help interpret the data in our studies.

**Meetings:** Prior to implementation of the study, the DSMB will meet to review the consent and protocol, making recommendations for any needed changes. For this meeting, study investigators will be on hand to answer any specific questions. After the initial meeting, the DSMB will plan to meet in-person or by conference call once yearly. DSMB members will have the ability to request more frequent reviews or meetings at any time during the study if they determine such reviews could help ensure patient safety or data integrity. The DSMB may meet in "closed session," and they may periodically ask study investigators to attend a meeting to provide additional details on the implementation or conduct of the trial or other pertinent information. After its initial meeting, the DSMB will review the implementation and progress of the study, evaluating study data in both individual and aggregate form to detect evidence of significant benefit or harm for participant while the trial is in progress. This latter review, beyond that provided by the IRB, serves as a means of additional human subject protection. It does not supplant the regulatory requirement for the principal investigator to report serious and unanticipated adverse events to the local IRB or relevant regulatory bodies.

**Summary of DSMB duties:** The DSMB will perform the following activities: 1) Review of the research protocol and plans for data and safety monitoring; 2) Evaluate the progress of the intervention trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that could potentially affect study outcome; 3) Protect the confidentiality of the trial data and the results of monitoring; and 4) Make recommendations to the investigators concerning continuation, modification, or termination of the trials. The DSMB also has the right to make independent representation to the regulatory bodies (NIH, IRB) if there has been any failure in reporting by the principal investigator. The DSMB can also instruct the principal investigator to pause or terminate pursuance of research if there is a breach in regulatory guidelines or good clinical practices. If the DSMB notes serious and unexpected adverse events, or unanticipated problems involving risks to participants or others, which are related to the study, the PI will be notified immediately in writing.

To assist the DSMB in their duties, the investigators will prepare a report prior to each DSMB meeting, including issues related to participant recruitment (consent, enrollment, dropout), data collection (e.g., quality, timeliness, completeness, security), outcome analyses, and all serious and unexpected adverse experiences. The investigators will also notify the DSMB of any significant study modifications, emphasizing any changes made in response to adverse events (see definition below)

After the DSMB meeting, the DSMB will issue a report summarizing their findings. More specifically, they will provide commentary on participant recruitment, consent, and drop out; the quality, timeliness, and completeness of data collection; outcome analyses that help determine whether a study should continue; and all serious and unexpected adverse experiences. In each area (e.g., participants consent), they will recommend any necessary changes in study policies or

protocol and explain how the changes will help ensure participant safety or data integrity. These reports will be kept by the PI, who will file them with the local IRB.

This application includes a trial that requires registration in ClinicalTrials.gov.

## **5.9 Potential Risks and Side Effects**

### **5.9.1 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.

### **5.9.2 Fingertick Risks**

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

### **5.9.3 Subcutaneous Catheter Risks (Continuous Glucose Sensor)**

Subjects using the continuous glucose sensor will be at low risk for developing a local skin infection at the site of the sensor needle placement. There may be bleeding where the catheter is put in and bleeding under the skin causing a bruise (1 in 10 risk).

Study staff should verbally alert the subject that on rare occasions, the continuous glucose sensor 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.

### **5.9.4 Risk of Hypoglycemia**

As with any person having insulin-dependent diabetes, 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 patients may not be as aware of symptoms of low blood sugar.

### **5.9.5 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 sensor which was functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery.

### **5.9.6 Risk of Device Reuse**

The Dexcom CGM 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 will be reused after cleaning as described below. The transmitter is attached to the sensor but does not enter the skin and the receiver is a hand held device. The transmitter and receiver will be cleaned adhering to hospital protocol as described below. Subjects will be informed that the FDA has 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 Accu-Chek Combo System and Tandem t:slim X2 insulin pump are labeled for single-patient use. The Accu-Chek Combo system is comprised of the Accu-Chek Spirit Insulin Pump and the Aviva Combo Device. The Aviva Combo device when used as a glucometer will be single patient use at all times. The Accu-Chek Spirit Insulin Pump itself is handheld and is not a glucometer. The subject interactions are primarily with the AP system interface and the Aviva Combo device, not with the Accu-Chek Spirit Insulin Pump menu interface itself. The Accu-Chek Spirit Insulin Pump handheld device and the Tandem t:slim X2 insulin pump will be reused after cleaning adhering to hospital protocol as described below. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.)

Cleaning Procedure: Equipment that touches intact skin will be cleaned with ethyl or isopropyl alcohol (70-90%), quaternary ammonium germicidal detergent (i.e. CaviCide) or household bleach. The contact time on the surface depends on the method used to clean the equipment. CaviCide requires three minutes on the surface. Clorox Germicidal Bleach Wipes require two minutes on the equipment. The surface should remain wet (i.e. slightly damp) with the disinfectant to be considered effective though not wet enough to leave drops of liquid. Equipment will be stored in a clean zipped bag.

Hb1Ac Risk: The University of Virginia central labs have College of American Pathologist (CAP) and the Clinical Laboratory Improvement Amendments (CLIA) certifications. While the central lab is not NGSP certified, the calibrators for the HbA1c assay are traceable to NGSP. The equipment (Tosoh G7) is NGSP certified. An NGSP Point of Care analyzer (i.e. DCA Vantage Analyzer) may also be utilized at the research site to obtain the subject's HbA1c level.

### **5.9.7 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 CSII. 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 a sensor is used for

longer than manufacturer recommendations. Therefore, participants will be carefully instructed about proper use of the sensor.

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

Loss of confidentiality is a potential risk; however, data are handled to minimize this risk.

## **5.10 Study Stopping Criteria**

### **5.10.1 Criteria for Individual Subjects**

Rules for stopping the study for an individual subject are as follows:

1. System or controller malfunctions that impose on the safety of the subject, unless the problem can be clearly identified and the system definitively repaired
2. Two distinct episodes of severe hypoglycemia or hyperglycemia/DKA (not associated with infusion set failure) as defined in section 5.1 related to automated insulin delivery during closed loop use
3. The subject requests the study be stopped
4. Subject pregnancy
5. Use of oral or injectable glucocorticoids during closed-loop system operation (subject may resume study procedures once effects of glucocorticoids are no longer present)
6. Study staff are persistently unable to contact the subject in a timely manner during the course of the study
7. Persistent subject non-adherence to safety-related procedures such as frequency of fingersticks or hypoglycemia, hyperglycemia and ketone treatment instructions
8. Ketones  $\geq 3$  mmol/L or with symptoms requiring action regardless of blood sugar or ketones (i.e. abdominal pain, vomiting illness, unable to eat or drink, fever  $\geq 101.5$ , clinical need for Tylenol/acetaminophen, significant illness, use of epinephrine). Subject may resume study procedures once conditions or symptoms are no longer present.

### **5.10.2 Criteria for Suspending/Stopping Overall Study**

In case of a recurring system malfunction or a severe hypoglycemia event or severe hyperglycemia event during closed loop control (as defined in Section 5.1) that is thought to be device-related (either due to excess insulin administration or suspension due to system malfunction) that occurs in more than two (2) subjects, the overall study will be suspended while the problem is diagnosed. The study 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.

An instance of severe hypoglycemia or hyperglycemia as defined in section 5.1 will result in DSMB review of the data to determine whether the event was triggered by the system or not and whether it is safe to proceed. The currently-enrolled subjects will continue use of the system during this time unless the DSMB determines it is unsafe for them to do so.

## Chapter 6 STATISTICAL CONSIDERATIONS

### 6.1 Analysis Plan

**Statistical Analysis:** The overall analysis will follow Intention-to-treat approach and will use Generalized Linear Mixed Models (e.g. those available in IBM SPSS) including fixed factors following the factorial designs presented in study figure for the specific aims listed below, and random effects reflecting patients' attrition rate.

Metrics:

- (i) Five HbA1c determinations approximately 10 weeks apart;
- (ii) Eight-week sequences of CGM data accompanied by BG self-monitoring readings and recording of the timing of events such as meals and exercise through the GUI
- (iii) Psychometric questionnaires administered concurrently with HbA1c, and
- (iv) Individual structured interview and qualitative/quantitative technology acceptance assessments. CGM data will be used to compute established metrics of risk for hypoglycemia, e.g. the Low BG Index (LBGI), glucose variability, and BG dynamics, as presented in our review of statistical tools for CGM data analysis.

#### *Primary Hypothesis by Specific Aims of the Study*

**Specific Aim 1:** *Overnight CLC achieved by USS+SAP(d) will be superior to SAP alone in terms of: (1) Improved HbA1c without increasing the risk for hypoglycemia; (2) Reduced incidence and risk for hypoglycemia overnight, and (3) Reduced fear of hypoglycemia and improved diabetes quality of life scores.*

**Specific Aim 2:** *CLC during the day achieved by USS+CLC(d) will preserve the benefits of USS+SAP(d) and will be superior to USS+SAP(d) in terms of: (1) Increased time within target range of 70-180mg/dl during the day; (2) Reduced risk for hypoglycemia during and after exercise, and (3) Reduced postprandial glucose variability.*

**Specific Aim 3:** *CLC system acceptance evaluated by an individual structured and technology acceptance scores will be: (1) Superior, for USS+SAP(d) compared to SAP alone, i.e. adding USS overnight will increase patients' acceptance of CLC, and (2) Marginally inferior, for USS+CLC(d) compared to USS+SAP(d); i.e. some patients would prefer SAP alone during the day due to perceived increased system complexity.*

#### *Primary Outcomes*

**Specific Aim 1:** *The primary outcome is improvement in diabetes control on USS+SAP(d) vs. SAP alone as defined by reduced risk for hypoglycemia (Time <70 mg/dL by CGM) without increase in HbA1c. Repeated Measures ANOVA with covariate will assess this effect. Inversely, comparing HbA1c with covariate overnight Time <70 mg/dL by CGM will address SA1-2, while comparing the psychometric questionnaire scores pre-post treatment will address SA1-3.*

**Specific Aim 2:** *The primary outcome is improved time within the target range of 70-180mg/dl during the day on USS+ CLC(d) vs. USS+SAP(d). Repeated Measures ANOVA following the study design outlined will assess this effect. SA2-2 will be addressed*

*comparing frequency of hypoglycemia within the post-exercise periods recorded by the system; SA2-3 will be addressed using Variability-Grid Analysis, and SA-4 will be addressed by a sub-analysis limited to those who did not achieve HBA1c $\leq$ 7.5% during the first 3 months of the study.*

**Specific Aim 3:** *will be addressed by comparing structured interviews and technology acceptance scores along the two sequences of treatment modalities specified in the study design: treatment escalation for Group A and de-escalation for Group B. Analyzing the random effect of patient attrition will shed additional light on system acceptance.*

## 6.2 Sample Size

Sample Size Determination is based on our pilot studies of overnight CLC. We conservatively estimate that the effect size of USS+SAP(d) vs. SAP will be  $f \geq 0.2$ . Power calculations (G\*Power 3) assuming  $\alpha=0.01$ , 90% power, correlation of 0.4 between the repeated measures, and attrition of up to 31% yield a sample size of **N=110** subjects to be randomized at baseline, with N=76 subjects completing the study. For SA2 using USS+CLC(d), our pilot data with this same system during the day indicate a larger effect size  $f=0.3$ . For SA-3, the expected effect size is  $f=0.35-0.4$  based on our previous interviews. Thus, a sample size that is adequate for SA-1 will have adequate power to address SA-2 and SA-3 as well.

## Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name \_\_\_\_\_

**Principal Investigator:** Sue Brown, M.D.  
University of Virginia  
Department of Endocrinology & Metabolism  
Center for Diabetes Technology  
Box 400888 Charlottesville, VA 22903

**Sponsor:** National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK-NIH)

### What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a signed copy of this form.

### Who is funding this study?

This study is paid for by a grant from the National Institute of Health (NIH). If using the inControl study equipment, TypeZero Technologies will provide the inControl Diabetes Management Platform. With this platform, the Roche insulin pump will be provided in agreement with the Jaeb Center for Healthcare Research, Inc. (Tampa, FL). If you use the Tandem insulin pump in this trial, the equipment will be obtained by the study team from the manufacturer. The Dexcom G6 Continuous Glucose Monitors will be provided by Dexcom, Inc. The Dexcom G4 Continuous Glucose Monitors will be purchased with grant funding. The glucometer supplies may be purchased with grant funding.

### Why is this research being done?

The purpose of this study is to gain experience using an experimental insulin management system ("study system") before starting a larger study. This Artificial Pancreas (AP) system is designed to help control blood sugar in people with type 1 diabetes mellitus who are on insulin pump therapy and can successfully be used and supervised in a non-hospital (research house) setting. This study will test an insulin pump and continuous glucose monitoring (CGM) to automatically give insulin and control blood sugar.

The study systems are experimental devices that has not been proven to be safe or helpful. These devices are not approved by the U.S. Food and Drug Administration (FDA). The t-slim X2 with Control-IQ Technology is new research and has been tested in 17 people living with type 1 diabetes before this study. However, the algorithm (the complex mathematical formula that calculates your insulin dosage) has been tested in more than 299,000 patient hours using laptops and cell phones.



You are being asked to be in this study because you live with type 1 diabetes and are using an insulin pump.

You are being asked to be in this study because:

- You are at least 18 and less than 70 years of age
- You have had Type 1 Diabetes Mellitus for at least 1 year
- You have been using an insulin pump to treat your diabetes for at least 6 months

Up to 110 people will be in this study at UVA.

### **Is there a possible conflict of interest?**

When a person or an organization has a financial or other interest large enough to seem as if it could affect their judgment, it is called a conflict of interest. Members of this study team have a conflict of interest with TypeZero Technologies, Inc. University of Virginia (UVa) faculty members invented some of the technology upon which this trial is based. If this technology leads to marketable products, UVa may receive compensation. UVa has a financial interest in the outcome of this study.

### **How long will this study take?**

Your participation in this study will require up to 9 study visits over 11 months. The first visit will be a screening visit at the Clinical Research Unit that will last about 2 hours. Visit 2, 3, and 4 will be equipment training sessions at the Center for Diabetes Technology Clinical Research Unit (CRU). Visit 5 will involve using the AP system. The occurrence of the visits will be dependent upon your randomization to Group A or Group B. Visits will involve using the AP system with the USS algorithm at night and Sensor-Augmented Therapy during the day. At another point in the trial, you will use the AP system with the USS Algorithm and Closed-Loop Control during the day.

### **Study Figure Definitions:**

**CGM** = Continuous Glucose Monitor

**(d)** = day

**AP system**= Artificial Pancreas system used in this trial is the inControl Diabetes Management Platform or the Tandem t:slim X2 with Control-IQ and Dexcom G6 system.

**SAP** = Sensor augmented pump therapy: You will be on the study CGM and your personal insulin pump. There are no predictive or control algorithms. You will administer your basal and bolus insulin using the usual home insulin parameters.

**USS** = Unified Safety System (USS Virginia): The closed loop control algorithm used during this trial.

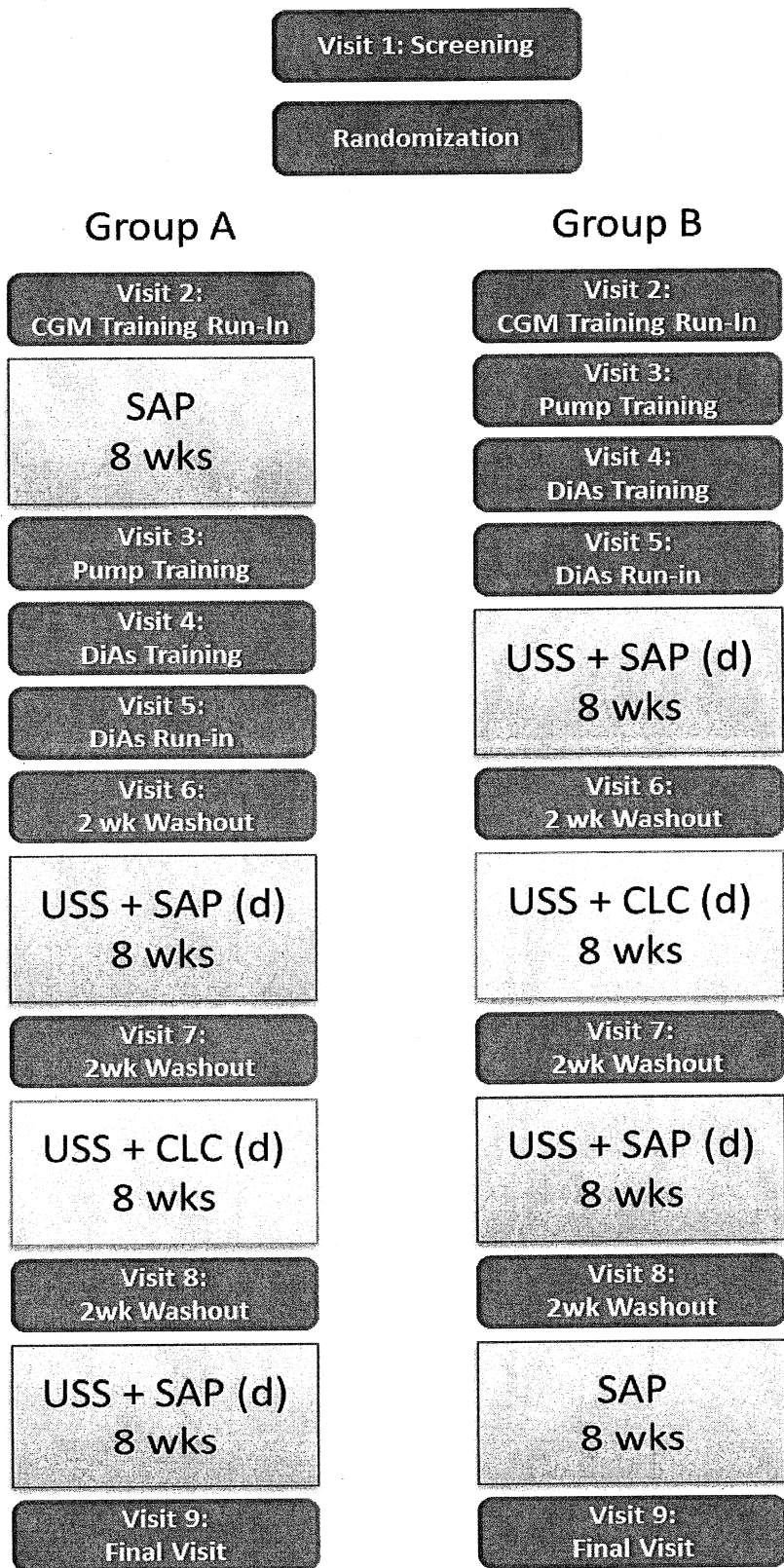
**USS+SAP (d)** = USS Virginia plus SAP during the day (d). You will be using the study pump and CGM with the AP system in Pump mode (open loop only, no closed loop algorithms running). You will activate the USS Virginia Closed-Loop Control (CLC) as early as pre-dinner but are expected to activate CLC by bedtime. You will



continue in CLC until the time of awakening in the morning. The USS will monitor CGM and insulin-on-board data to predict your risk of hypoglycemia and adjust insulin delivery accordingly.

**USS+CLC (d)** = USS Virginia and CLC over 24 hours. This will test a fully-integrated closed-loop control (CLC) system. When hypoglycemia is predicted, the USS issues an alert and reduces basal rate insulin to prevent hypoglycemia, or issues an alert that signals that carbohydrates are required to treat hypoglycemia. The USS also generates alerts about correction bolus requests that are considered potentially dangerous, or meal bolus requests that require user approval prior to delivery.

**Washout** = up to two weeks without using study equipment



## What will happen if you are in the study?

*All procedures outlined in this consent form are being done for research purposes only.*

### **Visit 1 (Day 1): SCREENING (will take about 2 hours to complete)**

If you agree to be in this study, you will sign this consent form before any study related procedures take place. Before you can start in the study, there will be a screening period. You will have tests and procedures during this time to make sure you are eligible and it is safe for you to participate.

These tests and procedures include the following:

- You will be asked to fill out a medical history form. You will be asked about your diabetes history, past and current medical conditions, surgical history, menstrual history (females), allergies, medications and supplements, social history (including drinking, smoking and drug habits), and whether or not you have various symptoms. You will also be asked about your pump settings and average daily insulin use over the past 7 days.
- Physical exam and vital signs (blood pressure, heart rate)
- Height and weight
- Standard blood tests (2 teaspoons of blood) to check certain salts, blood sugar, kidney function, liver function, blood counts, HbA1c (your blood glucose average over 8-12 weeks), Hematocrit (percentage of red blood cells in your blood), and thyroid levels (TSH). This will also include a pregnancy test if you are a woman who can become pregnant. The pregnancy test must be negative in order to participate.
- The HbA1c may be collected on a Point of Care machine or at a certified laboratory. The value must have been obtained within 4 weeks of randomization.
- You may have these blood tests performed locally with any participating LabCorp facility
- You will be asked not to take medications containing acetaminophen (like Tylenol) 24 hours prior to wearing the continuous glucose monitor sensor and while you are wearing the sensor.
- If female and sexually active, you must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative pregnancy test will be required for all premenopausal women who are not surgically sterile prior to putting on study equipment. If you become pregnant during the trial, you will be discontinued from the study.
- You will be asked to confirm that you have an emergency glucagon kit available at your home per usual care guidelines.
- You will complete a questionnaire to assess the impact of artificial pancreas systems on diabetes-relevant psychosocial measures such as fear of hypoglycemia and hyperglycemia scales. In addition, you will complete structured questions related to system performance and usability surveys on the Artificial Pancreas. These questionnaires will be administered after enrollment and after visits 6, 7, 8 and 9. Completion of these questionnaires will take about 30 minutes. The study team will review your medications and supplements to determine if you are eligible. If you are on beta blockers or nutraceuticals (e.g. cinnamon extract, chromium picolinate) that are intended to lower blood glucose at the time of enrollment, you may be at higher risk for low blood sugars. You may also be at risk for not being aware when you have a low blood sugar.

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If the screening tests show you are eligible, you will return to the clinic within 8 weeks to begin study procedures.

### **RANDOMIZATION**

You will be randomly assigned (like the flip of a coin) to 1 of 2 study treatment groups – Group A or Group B. You have an equal chance of being assigned to any one of the groups. Neither you nor your doctor can choose which treatment you are assigned.

**Group A** will start SAP within four weeks of completing Visit 2 and Visit 3 and Visit 4 will occur following completion of SAP.

**Group B** will proceed directly to Visit 2, Visit 3 and 4.

**Visit 2 - CGM Training Run-in (Day 2-16/up to 14 days)**. If you don't have prior Dexcom CGM experience, you will complete a maximum 2 week run-in phase using the CGM. If you do use the Dexcom CGM, your CGM may be downloaded to evaluate the data.

If you are randomized to Group A, you will begin SAP using your home pump and the study CGM for 8 weeks after you complete the CGM Training Run-In. We may request obtaining CGM data from your personal equipment if there are issues with the study CGM. Test strips are not provided during the SAP phase of the study.

You will be asked to check your fingerstick SMBG measurements at least 4 times daily (before meals, and at bedtime) throughout the study. Please use the same glucometer for all finger sticks and calibrations. Do not use alternate site testing.

**Visit 3 - Pump Training (Day 17-31/up to 14 days)**. You will have a run-in period on the study pump of up to two weeks duration. If you have prior experience with the study pump, this may be a shorter run-in period. Study staff will review your pump parameters manually and/or download your personal insulin pump.

**Visit 4 – AP System Training (Day 32/~5-10 hours)**. You will be trained to use the system to control the study pump, including meal announcement, meal bolusing, exercise, and switching back and forth between Pump (open-loop) mode and Stopped mode. You may be asked to view study materials at home (e.g. user guides and study videos on the use of the AP system) prior to coming to Visit 4. If you are premenopausal women who are not surgically sterile, you will have a urine or blood pregnancy test prior to the start of this visit. You will be instructed not to drive if your blood glucose is equal to or less than 70 mg/dL.

Visit 3 and 4 may occur during the same visit for inControl users. For subjects starting on the Tandem system, Visit 3 and 4 will be held at the same time.

**Visit 5 - AP System Run-In (Day 33-97/up to 2 weeks).** If you have not used the system recently, you will complete up to a 2-week home use period with the full system in pump only (open loop) configuration where no closed loop algorithms are activated. If you have prior experience with the system as defined by the study, you will not be required to do Visit 5.

If you are randomized to Group B, you will begin USS + SAP (d) for the next 8 weeks after you have completed the AP System Run-In.

At the completion of the each phase (visit 5 – 8) of the study, you will have up to a two week “washout” prior to proceeding to the next phase. During this time, you may continue on the study pump if Visit 4 (AP system Training) has been completed or switch to you own personal pump. You will either come to the study site or complete the following locally: HgbA1c and questionnaires.

Data will be downloaded from study equipment, personal glucometer and personal pump (during SAP) by one of several methods: (a) you will download the equipment and send the files to study staff, or (b) at the study site by study staff.

**Visit 6 – 2 Week Washout (Day 98-169).**

Group A: USS + SAP (d) for 8 weeks

Group B: USS + CLC (d) for 8 weeks; Individual Structured Interview

**Visit 7 – 2 Week Washout (Day 170-241).**

Group A: USS + CLC (d) for 8 weeks; Individual Structured Interview

Group B: USS + SAP (d) for 8 weeks; Individual Structured Interview

**Visit 8 – 2 Week Washout (Day 242-313).**

Group A: USS + SAP (d) for 8 weeks; Individual Structured Interview

Group B: SAP for 8 weeks; Individual Structured Interview

**Visit 9 – Final Visit (Day 314).** You will either come to the CRU or complete the following closer to home: HgbA1c, and questionnaires. Group A only will complete the structured interview. Data will be downloaded from study equipment, personal glucometer and personal pump (during SAP) by one of several methods: (a) you will download the equipment and send the files to study staff, (b) at the CRU by study staff; or (c) equipment mailed to the study team for downloading.

**Individual Structured Interview [Optional] (approximately 1 hour):** You will be asked to participate in an individual structured interview after using the AP system (Group A= after visit 7, 8, 9; Group B=after visit 6, 7, 8). You will be asked by a study team member about the negative and positive opinions of the AP system. This interview will be recorded to assist staff with documenting your responses. We will not refer to you by name

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during the audio recording. The recording of the session will be identified using your study subject ID number. The recording will be saved with all study documents.

You and your family members may use the cell phone apps to monitor the CGM values

### STUDY SCHEDULE

Study Procedures	Screening	CGM Training	Pump Training	AP system Training	AP system Run-In	AP system Use	AP system Use	AP system Use	Final Visit
Visit	1	2	3	4	5	6	7	8	9
Days for Group A	1	2-73	74-88	89	90-97	98-169	170-241	242-313	314
Duration	~2 Hours	Up to 10 weeks	Up to 2 week	About 10 hours	Up to 2 weeks	10 weeks	10 weeks	10 weeks	~2 Hours
Days for Group B	1	2-16	17-31	32	33-97	98-169	170-241	242-313	314
Duration	~2 Hours	Up to 2 weeks	Up to 2 week	About 10 hours	10 weeks	10 weeks	10 weeks	10 weeks	~2 Hours
Location	CRU	OPTX	OPTX	CRU	OPTX	OPTX	OPTX	OPTX	OPTX
Informed Consent	X								
Clinical exam & medical history	X								
Inclusion/Exclusion Criteria	X								
Screening Labs	X								
Randomization	X								
pregnancy test for premenopausal women not surgically sterile	X	X	X	X					
Wear study equipment		X	X	X	X	X	X	X	
Equipment Downloads		X	X	X	X	X	X	X	X
Washout (2 weeks)					X	X	X	X	
Questionnaires	X					X	X	X	X
Hemoglobin A1c	X					X	X	X	X
Structured Interview						X	X	X	X

~ = approximately

OPTX = Outpatient

CRU = Clinical Research Unit

### What Are Your Responsibilities In The Study?

You have certain responsibilities to help ensure your safety. These responsibilities are listed below:

- You must attend each study visit as advised by the study staff.
- You must be completely truthful about your health history.
- Follow all instructions given.
- You should tell the study doctor or study staff about any changes in your health or the way you feel.
- Answer all of the study-related questions completely.
- Inform the study doctor or study staff as soon as possible if you have to take any new medications, including anything prescribed by a doctor or those that you can buy without a prescription (over-the-counter), including herbal supplements and vitamins. The study doctor will let you know if you can take these medications.

- You must not use acetaminophen (like Tylenol) 24 hours prior to wearing the continuous glucose monitor sensor and while you are wearing the sensor.

### **Blood Testing**

We will take (or “draw”) up to 2 tablespoons of blood during the screening visit. The blood we taken at the screening appointment will be tested to measure your diabetes control, your thyroid function, how well your kidneys/liver work, the amount of certain salts and sugars, and to see if you are pregnant (females). When these tests are done, any remaining sample will be thrown away. It will not be stored for any future testing.

You will take fingersticks during the trial to measure your blood glucose levels. The physician may ask that you take more fingersticks to help monitor your glucose levels. An additional HbA1c will be taken at the end visit 6, 7, 8 and 9. Less than a teaspoon of blood is necessary for each of these samples. Please note that if you access LabCorp, more blood will be taken than the UVa laboratory. No other blood sampling will be completed during the trial.

When these tests are done any left-over sample will be thrown away or they will be de-identified. This means there is no information that could be used by anyone to determine who the sample came from.

### **If you want to know about the results before the study is done:**

During the study you are having an investigational test done. The purpose of the test is NOT to diagnose any disease or abnormality you may have. Because the test is investigational, there is no way for the study leader to understand if the results are “normal” or “abnormal”. However, IF any test results are concerning, your study leader will let you know.

In addition, as the research moves forward, your study leader will keep you informed of any new findings about the research itself that may be important for your health or may help you decide if you want to continue in the study. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time, you can ask for more information about the study results.

### **What are the risks of being in this study?**

Possible side effects that may occur during this study include:

#### **Risks related to treating type 1 diabetes (with or without using AP system):**

- Risk of possible mild to moderate low blood sugar and possible symptoms of low blood sugar, such as sweating, trembling, difficulty thinking, dizziness, and feeling uncoordinated.
- Risk of possible mild to moderate high blood sugars and possible symptoms of high blood sugars such as thirst and frequent urination

#### **Rare but serious**

- Risk of severe temporary low blood sugar (hypoglycemia) that can lead to unconsciousness, hypoglycemic seizure, hospitalization or even death.
- Risk of prolonged high blood sugar leading to diabetic ketoacidosis, hospitalization, and even death.

### **Fingerstick Risks**

#### **Likely:**

- Pain at site of lancet (finger-pricking needle) use
- Bleeding at site of lancet use

#### **Less Likely:**

- Incorrect information from a false low or false high fingerstick value

#### **Rarely:**

- Infection at site of lancet use

### **Risks associated with continuous glucose monitor insertion:**

#### **Likely:**

- Failure or lack of sensitivity of the continuous glucose monitor sensor that requires replacement / insertion of new sensor
- Fingerstick for calibration of the continuous glucose monitor
- Discomfort from insertion of sensor

#### **Less Likely:**

- Bruising less than ½ inch
- Bleeding less than ¼ teaspoon
- Sensitivity to adhesives with use of continuous glucose monitor resulting in skin irritation, redness, blistering, scarring, systemic allergic reaction or secondary skin infection

#### **Rarely:**

- Swelling or redness at insertion site
- Breakage of the continuous glucose monitor sensor under the skin with possible symptoms of skin irritation and inflammation. If a sensor breaks and no portion of it is visible above the skin, do not attempt to remove it. Please call the study team or seek immediate medical assistance. Seek professional medical help if you have symptoms of infection or inflammation – redness, swelling or pain – at the insertion site.

### **Risk of symptoms related to the insulin pump site insertion:**

#### **Rarely:**

- Sensitivities to adhesives associated with insulin catheter resulting in skin irritation, swelling, redness, blistering, scarring, nodular reactions, systemic allergic reaction or secondary skin infection
- Bruising greater than ¼ inch
- Bleeding greater than 1/8 teaspoon of blood

### **Risks and side effects related to blood glucose collection via fingerstick:**

#### **Likely:**



- Pain at site of lancet (finger-pricking needle) use
- Bleeding at site of lancet use

**Less Likely:**

- Incorrect information from a false low or false high fingerstick value

**Rarely:**

- Infection at site of lancet use

**Risks associated with performing a serum (blood) or urine pregnancy tests (women who are able to become pregnant):**

**Less Likely:**

- False positive or false negative results

**Risk of sharing the Continuous Glucose Monitor**

We will use the continuous glucose monitor equipment with other study subjects. The sensors will not be shared. The transmitter wirelessly sends your glucose information from the sensor to the receiver. The transmitter, which snaps into the sensor, will be cleaned thoroughly with a diluted mixture of bleach or another appropriate cleaner after use per hospital guidelines. The FDA approved the continuous glucose monitor as a 'single use device'. This means that they recommend that only one person use this device as there is a rare risk that a bloodborne pathogen, such as Hepatitis B, may be spread if used with multiple patients.

**Risk of sharing the Insulin Pump:**

The FDA approved the insulin pump for 'single-patient use'. This means that they recommend that only one person use this device as there is a rare risk that a bloodborne pathogen, such as Hepatitis B, may be spread if used with multiple patients. The insulin pump handheld device may be reused after cleaning thoroughly with a diluted mixture of bleach or another appropriate cleaner after use per hospital guidelines.

**Risks of having your blood drawn:**

Having blood drawn may cause:

- ✓ pain (common),
- ✓ a bruise (sometimes),
- ✓ fainting or passing out (not very often), and
- ✓ infection (rare).

If the people doing the study are exposed to your blood or body fluids in a way that could give them a disease, your blood may be tested. The tests might check for:

- ✓ hepatitis,
- ✓ HIV (Human Immunodeficiency Virus), or
- ✓ other infections.

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You and the person exposed would be told the test results. However, your name would be kept private. If your test is positive for hepatitis or HIV, we will tell you the results and help you understand what the results mean for you.

**Risks of Videotaping/Audiotaping:**

The structured interview will be audiotaped. We will not refer to you by name in the audiotape and the taped record will be stored and labeled with a unique study ID.

With your permission, we may photograph or videotape your participation in this trial. Photographs and videotapes will be used in presentations at conferences, potential study subjects, and potential research donors. Your willingness to have photos taken is independent of your participation in this trial. Your photo or videotape will not be used without your consent. Your identity can remain anonymous.

- I agree to be photographed/videotaped during this trial.  
\_\_\_\_\_  
Initials
- I agree to be photographed/videotaped during this trial but would like to remain anonymous.  
\_\_\_\_\_  
Initials
- I do **NOT CONSENT** to being photographed/videotaped during this trial.  
\_\_\_\_\_  
Initials

**Risks for women:**

You must use an approved form of birth control during this study. You will be told to ask your doctor for more details about the proper birth control method. If you become pregnant during this study, you are told to inform your study doctor right away. Your study doctor will discuss her treatment and the effect of the study on your pregnancy.

**Other unexpected risks:**

You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems.

**Could you be helped by being in this study?**

You will not benefit from being in this study. However, the information researchers get from this study may help others in the future.

**What are your other choices if you do not join this study?**

You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment even if you choose not to be in this study. The usual treatment would include continuing your home insulin regimen.

If you are a patient at UVA, your usual care will not be affected if you decide not to participate in this study. If you are an employee of UVA, your job will not be affected if you decide not to participate in this study.

### **Will you be paid for being in this study?**

You will be paid \$500 when you complete the study as well as the diabetes supplies noted below. **You will receive payment after the study equipment and data has been returned to the study team.** You should get your payment by check about 4 weeks after finishing the study. The income may be reported to the IRS as income.

- Completion of Visit 3 - \$50
- Completion of Visit 5 – \$100
- Completion of Visit 7 – \$150
- Completion of Visit 9 (including structured interviews) – \$200

The study will provide you with the following to use during the study:

- Study equipment and their associated supplies (e.g. infusion sets, CGM sensors, etc....)
- Blood Ketone Meter and Test Strips
- You will use your own insulin
- You will use your own blood glucose meter and tests strips. A study glucometer will only be provided if your personal glucose meter cannot be downloaded.

Should you withdraw from the study, you will be paid for the visits that you have completed. If the study leader says you cannot continue, you will be paid for the visits that you have completed.

If you owe money to any Virginia state agency, the state can use the money you earn in this study to pay those debts. These state agencies include the UVa Medical Center, VCU Medical Center or a college or university. The money may be withheld to pay back debt for such things as unpaid medical bills, taxes, fines, child support. Even if this happens, the money you earn may be reported to the IRS as taxable income.

### **Will being in this study cost you any money?**

Being in this study will not cost you any money. Your insurance company will also not be billed.

You and/or your insurance company must pay for any tests or care given beyond what is required in this study. In addition, you and/or your health insurance may also have to pay for other drugs or treatments that are given to help you control any side effects. You will have to pay for any costs not covered by your health plan. You may be responsible for any co-payments or deductibles. You may wish to ask for an estimate of your financial costs. You may also wish to check with your insurance company before the study starts. Ask what they will cover and if they require you to get their permission before you decide to be in the study.

You will be responsible for the cost of travel to come to any study visit and for any parking costs. All of the research facilities have an appropriate parking lot where free parking is available.

### **What if you are hurt in this study?**

If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your

insurance. You will be responsible for any amount your insurance does not cover. You do not give up any legal rights, such as seeking compensation for injury, by signing this form.

### **What happens if you leave the study early?**

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include

- a) Your study physician is concerned about your health
- b) Your disease gets worse
- c) The side effects of the treatment are too dangerous for you
- d) New information shows the treatment will not work or is not safe for you
- e) You do not follow your doctor's instructions

If you decide to stop being in the study and you are wearing the study insulin pump or continuous glucose monitor, we will ask you to return it to the Center for Diabetes Technology. The insulin pump and continuous glucose monitors remain property of the study sponsor and will need to be returned. If you decide to stop being in the study and are not wearing the study insulin pump or continuous glucose monitors, we ask that you notify the research team so any admissions scheduled may be cancelled.

### **How will your personal information be shared?**

The UVA researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

### **If you sign this form, we may collect any or all of the following information about you:**

- Personal information such as name, address and date of birth
- Social Security number ONLY IF you are being paid to be in this study
- Your health information if required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers. This may include mental health care records, substance abuse records, and/or HIV/AIDS records.

### **Who will see your private information?**

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your participation in the study
- Tax reporting offices (if you are paid for being in the study)

- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.
- Researchers from outside of UVA may be present during your study visits. They will be observing to learn how to conduct this study and to train on the use of the equipment in order to conduct the trial at their own sites in the future.
- If using the inControl Platform, TypeZero personnel may review the remote monitoring upon the request of the study physician or a designee to observe how their device, inControl is performing and for the purpose of troubleshooting. This information is de-identified. Viewing this data will remain within the limits established in the UVA and TypeZero agreement.

Some of the people outside of UVA who will see your information may not have to follow the same privacy laws that we follow. They may release your information to others, and it may no longer be protected by those laws.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

**What if you sign the form but then decide you don't want your private information shared?**

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

A copy of this consent form will be put in your medical record. (This is not the same as the record of this research study.) This means that everyone who is allowed to see your medical records will be able to find out that you are in this study. This is done so your regular doctors will know what you receive as part of this study. If you have other health problems during the study, they will be able to treat you properly.

**Please contact the researchers listed below to:**

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Sue Brown, M.D.

University of Virginia

Department of Endocrinology & Metabolism

Box 400888 Charlottesville, VA 22908

Phone: 434-982-0602

**What if you have a concern about this study?**

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research  
PO Box 800483  
Charlottesville, Virginia 22908 Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

**Signatures**

**What does your signature mean?**

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form, it means that you agree to join the study. You will receive a copy of this signed document.

**Consent from Adult**

_____	_____	_____
PARTICIPANT	PARTICIPANT	DATE
(SIGNATURE)	(PRINT)	

**To be completed by participant if 18 years of age or older.**

**Person Obtaining Consent**

By signing below, you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT	PERSON OBTAINING CONSENT	DATE
(SIGNATURE)	(PRINT)	