Real-Time Monitoring and Glucose Control During Winter-Sport Exercise in Youth with Type 1 Diabetes: The AP Ski Camp Continued

TANDEM
DIABETES CARE

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Background and Rationale:

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

As described in the Background, this project is a result from a sequence of clinical trials that have tested extensively the control system in over 280,000 hours of outpatient human use and in several centers in the U.S. and overseas. The following 16 IDEs reflect this progress:

1. IDE #G110095: Feasibility study of closed loop control in type 1 diabetes using heart rate monitoring as an exercise marker, approved 10/08/2011;
2. IDE #G120032: Early feasibility (pilot) study of outpatient control-to-range; 3/2/2012;
3. IDE #G120210: Early feasibility study 2 of outpatient control-to-range; 10/12/2012;
4. IDE #G130118: DiAs control-to-range nocturnal closed-loop camp study; 6/19/2013;
5. IDE #G130121: Optimizing closed-loop control of type 1 diabetes mellitus in adolescents; 6/19/2013;
6. IDE# G130142: Closed loop control in adolescents using heart rate as exercise indicator; 7/16/13;
7. IDE #G130143: Early feasibility study of adaptive advisory/automated (AAA) control of type 1 diabetes; 7/19/2013;
8. IDE #G140066: Full day and night closed-loop with DiAs platform; 5/9/14.
9. IDE #G140068: Unified Safety System (USS) Virginia Closed Loop versus sensor augmented pump therapy overnight in type 1 diabetes; 5/14/2014;
10. IDE #G140089: Outpatient control-to-range: Safety and efficacy with day-and-night in-

home use; 6/6/2014;

11. IDE #G140169: Unified Safety System (USS) Virginia Closed-Loop versus Sensor Augmented Pump (SAP) therapy for hypoglycemia reduction in type 1 diabetes; 10/3/2014.
12. IDE #G150221: Reducing risks and improving glucose control during extended exercise in youth with T1DM: The AP Ski Camp; 11/09/2015;
13. IDE #G150240: Project Nightlight: Efficacy and system acceptance of dinner/night vs. 24 hr closed loop control; 11/12/2015;
14. IDE #G160047: Closed-loop in school-aged children 5-8 years old using DiAs platform; 03/29/2016;
15. IDE #G160097: Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed-Loop (iDCL) Trial/Research Site Training Protocol; 06/03/16.
16. IDE#G160181: PROTOCOL 1 for "Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed Loop (iDCL) Trial; 09/21/16

We reference pre-submission Q170885 and our discussion with FDA on July 18, 2017 regarding the structure of studies intended to test inControl implemented on t:slim X2. Based on the input provided by the Agency. This particular trial will add a stress situation during winter camp conditions that could eventually be used later for regulatory purposes.

- This trial will be initiated after the successful completion of the G170255 study. It will start with an adolescent phase ages 13-18 years old, and then involve school age children ages 6-12 years old. The school aged children phase (6-12 years old, see below) will only be initiated after the success of the adolescent (13-18 years old) phase. A DSMB will be created to evaluate the safety and feasibility of the adolescents' ski camp; the DSMB will evaluate, if any, AE, SAE and glucose control/technical aspects as follow: % time in closed-loop and any other relevant operational modes
- % time CGM data available to the controller
- Rate of relevant failure events and alarms per 24 hours
- % time spent above 250mg/dL while in closed loop
- % time spent below 70mg/dL while in closed loop

Purpose/Objective

The closed-loop system, also called Artificial Pancreas (AP), modulates insulin infusion according to computed real-time needs. It has proven to be successful in maintaining blood glucose in euglycemic ranges during the day and even more efficiently during overnight hours where it was shown that the system can keep glycemic values in the euglycemic range (70-180 mg/dL) for 75% to 80% of the time.

The biggest challenges for glycemic control during the day time involve meals and exercise variations, which are impacted by age, fitness level, duration, intensity and history of exercise. Meal variability has the benefit that meals are typically announced and quantified. Glucose control around exercise, on the other hand, is more complicated if the patient doesn't announce a change in activity level.

Over the last 5 years, our teams have developed and tested different version of closed-loop systems and remote monitoring systems conducting clinical trials in summer and winter camp settings demonstrating significantly improved glycemic control and hypoglycemia avoidance in young adult and pediatric patients with T1D.

There is a new wearable version of a closed-loop control system that is proposed to be tested in this clinical trial.

The Closed-Loop Control System contained in t:slim X2 with Control-IQ Technology that is described in Master File MAF-2032/A003. 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 (**Error! Reference source not found.**).

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

This proposal aims to demonstrate the superiority of the Closed-Loop Control (CLC), also known as Artificial Pancreas (AP) named t:slim X2 with Control-IQ Technology and assess usability in a supervised setting in a controlled environment compared with state-of-the-art Sensor-Augmented Pump (SAP)

therapy for the treatment of type 1 diabetes (T1D) in adolescents (13-18 years old) and school-aged children (6-12 years old). The CLC system has been shown to diminish hypoglycemic events by setting the alarms on the continuous glucose monitor (CGM) and taken action, such as performing SMBG and treating if it is confirmed to be low.

We propose to use the system in a winter/ski camp environment where muscle glycogen is systematically depleted, glucose uptake systematically increased, and meal sizes are naturally larger than normal: a 48 hours ski camp at moderate and high elevation altitude (~4000-14,000 feet), with the concomitant variable of oxygen consumption that this environment involves; during the winter, that will expose and challenge the different components of the system (pump and continuous glucose monitoring [CGM]) during cold temperatures, and with twice daily practice of physical activity designed to deplete glycogen reserves such as skiing. In addition, for the school-aged children phase, participants will use their assigned mode of therapy (SAP/AP per randomization) for another 72 hours at home under the parents' supervision.

Primary Specific Aims:

To gain experience using the proposed artificial pancreas system named t:slim X2 with Control-IQ Technology and assess usability in a supervised setting

Demonstrate the superiority of AP compared to the SAP in controlling blood glucose of adolescents & school-aged children with T1DM during extended exercise periods.

Test the AP components in altitude, cold, and during intense exercise.

Secondary Specific Aims:

1. Test the AP components (glucose sensors [Dexcom G6], insulin pump [Tandem t:slim X2] in high altitude, cold, and intense exercise conditions.

Assess the impact of strenuous exercise on this AP system performance

Assess the performance of the system 72 hours after finishing the ski camp by using the system at home under parental/caregiver supervision

Assess the impact of altitude on AP performance outpatient prospective randomized control clinical trial (RCT) of a single intervention (artificial pancreas) compared to SAP.

Study Design Overview

Subjects:

We will study up to 30 adolescents (13-18 years old) and 30 school-aged children (6-12 years old), with T1DM on an insulin pump at the University of Virginia, University of Colorado, and Stanford University during a ~48 hours diabetes ski camp. The study will be split in two sequential phases: (Phase 1) the adolescent camp, at the University of Virginia, with a simple RCT design, and (Phase 2) the school-aged children camps, at the University of Colorado and Stanford University. The school-aged children camps will also include the RCT design with 48 hours of ski camp, followed by an additional 72 hours at-home phase

under parental supervision. Study participants will be divided in two equal groups at each site, half using SAP, and half wearing the t:slim X2 with Control-IQ Technology.

Procedure:

The proposed study is an outpatient prospective, randomized control clinical trial comparing 2 groups: Group 1: the artificial pancreas system named t:slim X2 with Control-IQ Technology and an additional commercially available Dexcom G5 CGM and Group 2: SAP with their personal insulin pump and commercially available Dexcom CGM G5. Eligible subjects will be randomized to either experimental (AP) or control (SAP) group. The study will be randomized by block, enabling analysis of secondary effects such as altitude. In addition, groups will be matched by HbA1c and age.

Equipment for Experimental AP Group:

- Insulin pump: Tandem t:slim X2 with Control-IQ Technology (that works with Dexcom G6)
- Continuous Glucose Monitor: Dexcom CGM G5 with remote monitoring capability (commercially available "Dexcom Follow" App that will permit the study team to monitor CGM tracings)
- Glucometer: FDA approved glucose meter equal for both groups

Equipment for Control SAP Group:

- Insulin pump: Subject's personal insulin pump
- Continuous Glucose Monitor: Dexcom CGM G5 with remote monitoring capability (commercially available "Dexcom Follow" App that will permit the study team to monitor CGM tracings)
- Glucometer: FDA approved glucose meter equal for both groups

Visit 1: Screening Visit.

The families interested in participating in the clinical trial will be identified though camp registration or a clinical or therapeutic relationship with the investigative center An email or letter will be sent to all potential subjects interested in participating in the study. The study team will explain the study in detail with the interested subjects and their family members. The informed consent/assent form will be provided for the family for review. Once all the questions have answered by the study team, the study subject and their parent(s) may sign the consent/assent and return to us via fax, pdf, or as a scanned document. Parents may elect to sign the ICF upon arrival at the ski camp. The study team will explain the

study and obtain the necessary signatures. As this is Class III device trial, both parents will sign the consent form.

Visit 2: Diabetes Ski Camp.

Each participant will be randomized to the experimental Artificial Pancreas (AP) group or Sensor-Augmented Pump (SAP) group for up to 48 hours. The subjects (and their families for younger school-aged subjects) will report to the ski camp location by approximately 4PM on the first day of the ski camp. Once determined eligible, for the experimental group, the subject will be equipped with the study equipment. All participants will be fitted with a Dexcom CGM G5 continuous glucose monitor with Share™ capability. Control group participants will be wearing their personal insulin pump. Treatment group participants, and their families if in the school-aged phase, will then be trained in the use of the basic pump functionalities on the study AP t:slim X2 with Control IQ insulin pump. The subjects will continue to use the system for approximately 48h; for example, the system will be initiated at approximately 6 PM on the first evening of the camp and will be disconnected and returned to their own usual treatment on day 3 at approximately at 6 PM. During system use, subjects in both groups will be remotely monitored and with immediate access to medical personnel and technical personnel. Participants younger than 13 years of age may be accompanied by one parent/caregiver during camp if requested by the family. For all subjects <13 years old, a minimum of one parent/caregiver must participate in CGM & AP training sessions on the last day of camp to enable the subject to continue using the system at home for 72 hours.

For visit 2 (ski camp), the camp's recreational activities will be managed by '*Riding on Insulin*' with study staff supervision. '*Riding on Insulin'* (www.ridingoninsulin.org) is a non-profit organization specialized in engaging the pediatric T1DM population in skiing and snowboarding.

Visit 3: AP System at home (UColorado and Stanford only)

During the second phase (school-aged children ages 6-12 years old), subjects will continue the use their assigned treatment (SAP or AP) for another 72 hours at home under parental/caregiver supervision. The parent/caregiver trained during the ski camp will be the primary user/supervisor for the system. This additional testing period will **not** be included in the adolescent camp.

Activities at the ski camp will be as follows (times are approximations):

Phase 1 (ages 13-21)

- 4 – 6 PM: Check in
- 6 – 7 PM: Randomization and distribution of the equipment
- 7 – 8 PM: Dinner

- 8 – 11 PM: Evening activity
- 11 PM – 7 AM: Sleep
- 7 - 8 AM Breakfast
- 9 – 12 PM: Ski
- 12:30 – 2 PM: Lunch
- 2:30 – 5:30 PM: Ski
- 5:30 – 6:30 PM: Quiet time
- 6:30 – 8 PM: Dinner
- 8 – 11 PM: Evening activity
- 11 PM-7 AM: Sleep
- 7 – 8 AM: Breakfast
- 8:30– 11 AM: Ski
- 11:30 AM– 1 PM: Lunch
- 1:30 – 3:30: Ski
- 4– 6 PM: Dinner
- 6– 7 PM: Check out

Phase 2 (Ages 6-12)

- 3 – 5 PM: Check in
- 5 – 6 PM: Randomization and distribution of the equipment
- 6 – 7 PM: Dinner
- 7 – 9 PM: Evening activity
- 9 PM – 7 AM: Sleep
- 7 - 8 AM: Breakfast
- 9 – 11:30 PM: Ski
- 12 – 1:30 PM: Lunch
- 2 – 4 PM: Ski or other on-snow activity
- 4 – 5:30 PM: Quiet time
- 5:30 – 7 PM: Dinner
- 7 – 9 PM: Evening activity
- 9 PM-7 AM: Sleep
- 7 - 8 AM: Breakfast
- 8:30– 11:30 AM: Ski; Parents: Home-use AP and SAP training session
- 11:30 AM– 1 PM: Lunch

1:30 – 3:30: Ski4-6 PM: Check out

- 6pm Optional end of camp dinner
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Self-monitoring blood glucose (SMBG, also called fingerstick) will be obtained for the purpose of CGM calibration (i.e. pre-breakfast and pre-dinner) and before exercise and any other time that is deemed necessary by the study team following the glycemic guidelines.

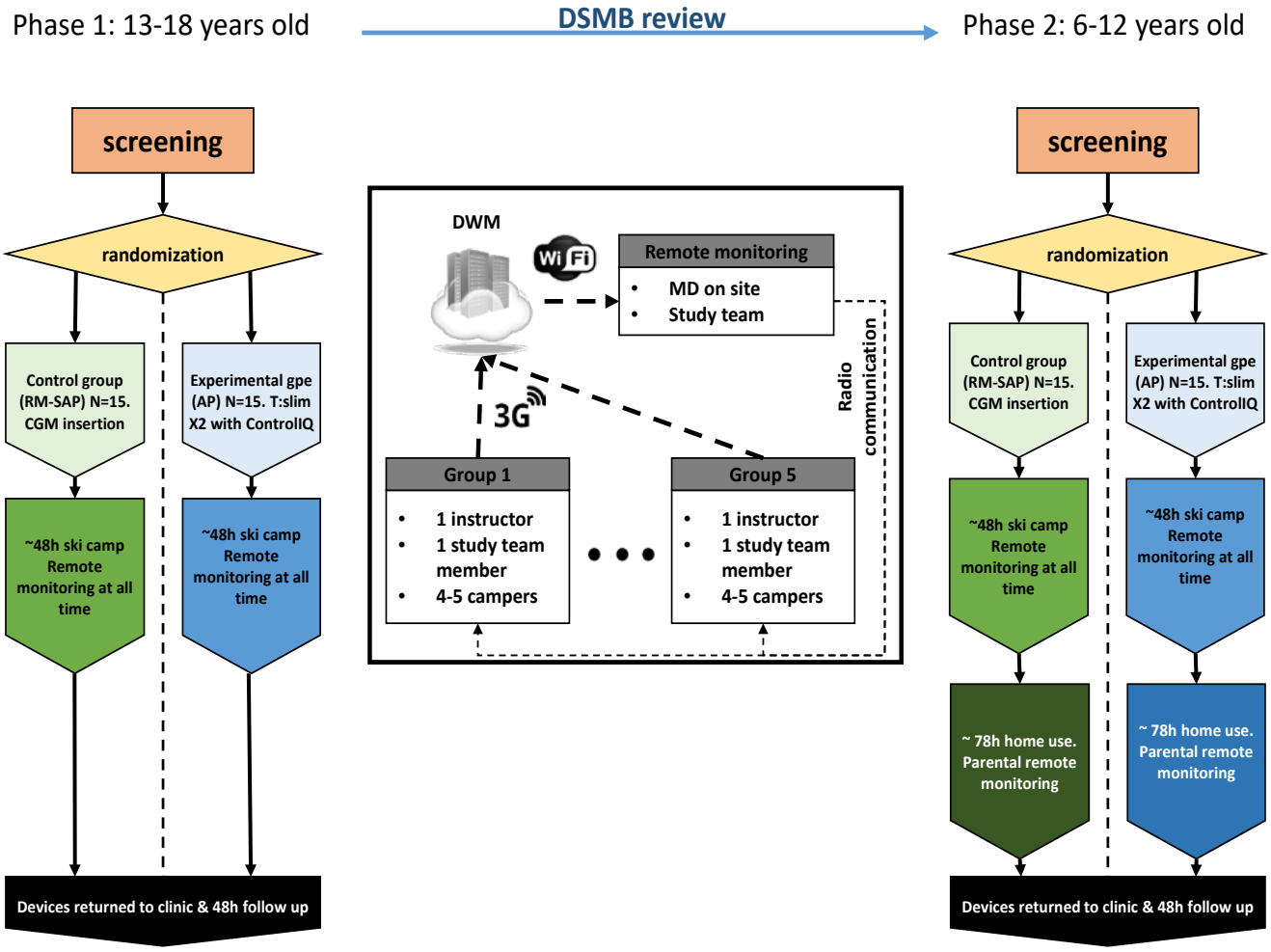

Figure 2: Study Diagram

Visit 4: Post-Study Follow up.

The study team will contact study participant families approximately 48 hours after the study to ask subjects about the occurrence of adverse events and to discuss any study-related questions or concerns.

Note: Study staff will be available 24/7 by phone to answer any questions or concern that the family may have or to help resolve any technical problem that may arise during the home use of the system.

Participants will discontinue use of the study devices at home with a check-in by site study staff. Devices will be returned by standard shipping (e.g. FedEx) provided by the research team.

Sample Size:

The studies will be conducted at the University of Virginia-Center for Diabetes Technology, the University of Colorado, and Stanford University. Up to 60 subjects (N=30 adolescents and N=30 school-aged children) with type 1 diabetes will be enrolled in the study. Based on our experience with similar studies, we estimate an expected 10-20% screen failures, dropouts, or withdrawals, thus we intend to set a recruiting target of 60 subjects to complete up to 50 participants for this trial.

Phase 1 is a pilot/feasibility study which purpose is to estimate the effect size of the t:slim X2 with Control IQ system versus remote monitoring. It is designed to achieve statistical significance.

Phase 2 is powered on the primary outcome (% time in desirable glycemic zone), with a medium effect size of 0.3 (based on previous trials of a similar algorithm) 80% power and a 2x2 within-between repeated measures ANOVA, with correlation of 0.5 between measures. Using G-power 3.1.9.2 (Universität Düsseldorf), this leads to a sample size of 24, leading to an enrollment of up to 30 with 20% expected drop-outs.

Investigational Sites:

The University of Virginia-Center for Diabetes Technology will perform the ski camp at:

Wintergreen Resort
Route 664
Wintergreen, VA 22958
(http://wintergreenresort.com)

Stanford University will perform the ski camp at:

Kirkwood Mountain Resort

1501 Kirkwood Meadows Dr,
Kirkwood, CA 95646,
(https://www.kirkwood.com)

The University of Colorado will perform the ski camp at:

Breckenridge Ski Resort
1599 Ski Hill Rd,
Breckenridge, CO 80424
(www.breckenridge.com/Breckenridge/Ski-Resort)

There will be at least one MD, registered nurse and/or other medical personnel who are specifically trained in diabetes management and trained technicians supervising the study during entire trial. There will be a team of at least 4 experienced study personnel in attendance during skiing activities. These staff members will be proficient with devices, the study protocol and its procedures, including the glycemic safety protocols. At least one study staff will be available during the overnight hours of 11PM-7AM monitoring the participants. Both the experimental (AP) and control (SAP) groups will have 24/7 remote monitoring; in case of remote monitoring failure CGM alarms will be activated at low=70 mg/dL and high=250 mg/dL for the study personnel to act if alarms are set off following glycemic treatment protocol. Medical personnel will be supervising on-site at all times and therefore are able to respond to emergencies during the camp phase. A study personnel, trained in the use and maintenance of the Tandem t:slim X2 with Control-IQ Technology, will be monitoring the system during the entire trial.

During Phase 2, the home portion of the trial for school age children, parents will set their remote monitoring alerts at 70 mg/dl and 250 mg/dl to mimic the monitoring during the ski study. Study staff will additionally set their remote monitoring alarms at low=>60 mg/dl for 15 minutes and high=>300 mg/dL for 1 hour, and will contact the family as needed for safety. The parents/caregivers will use their assigned technology treatment for up to 72 hours with their child. A phone line will be available 24/7 to answer any question or resolve any problem during this period. Upon study completion, subjects and parents may either visit the clinic or switch to their usual care during a videoconference session and ship the devices back to the study team.

During all phases of the trial, the duration of the Diabetes Ski Camp will be up to 60 hours total with up to 48 hours on the study devices.
Phase 2 (at home) will be up to 72 hours after the ski camp finished.

Inclusion and Exclusion Criteria

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

1. Criteria for documented hyperglycemia (at least 1 must be met):
    a. Clinical diagnosis of type 1 diabetes (C-peptide levels and antibody determinations are not required)
    b. The diagnosis of type 1 diabetes is based on the investigator's judgment
2. Criteria for requiring insulin at diagnosis (both criteria must be met):
    a. Daily insulin therapy for ≥ 6 months
    b. Insulin pump therapy for ≥ 3 months (note: must be willing to disable any glucose suspend, predictive suspend, or artificial pancreas functionality on insulin pump during study)
3. Age 6–18 years: 13-18 years old in Phase 1, 6-12 years old in Phase 2
4. Currently using no insulins other than one of the following rapid-acting insulins at the time of enrollment: insulin lispro (Humalog), insulin aspart (Novolog), or insulin glulisine (Apidra). Willingness to switch to lispro (Humalog) or aspart (Novolog) if using glulisine (Apidra).
5. Avoidance of acetaminophen-containing medications (i.e. Tylenol) while wearing the continuous glucose monitor.
6. Willingness to wear a continuous glucose sensor and physiological monitor for the duration of the study
7. Not being pregnant at the start of the trial. All female subjects of childbearing potential will be screened for pregnancy.
8. If the participant is less than 13 years of age and the parents or the study team request it, at least one parent commit to stay with the study subject at the camp site.,
9. A parent/caregiver is available for system training and will commit to be the main responsible person for the use of the AP system at home

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

10. Diabetic ketoacidosis in the past 6 months
11. Hypoglycemic seizure or loss of consciousness in the past 6 months
12. History of seizure disorder (except for hypoglycemic seizure)
13. History of any heart disease including coronary artery disease, heart failure, or arrhythmias

14. History of altitude sickness
15. Chronic pulmonary conditions that could impair oxygenation
16. Cystic fibrosis
17. Current use of oral glucocorticoids, beta-blockers or other medications, which in the judgment of the investigator would be a contraindication to participation in the study.
18. History of ongoing renal disease (other than microalbuminuria).
19. Subjects requiring intermediate or long-acting insulin (such as NPH, Detemir or Glargine).
20. Subjects requiring other anti-diabetic medications other than insulin (oral or injectable).
21. Pregnancy
22. Presence of a febrile illness within 24 hours of start ski camp or acetaminophen use while wearing the CGM. The camp study subject will not participate in the trial if these conditions are met.
23. Medical or psychiatric condition that in the judgment of the investigator might interfere with the completion of the protocol such as (for parent and/or child):
    - Inpatient psychiatric treatment in the past 6 months
    - Uncontrolled adrenal insufficiency
    - Alcohol abuse

STUDY TIMELINE

Visit 1: Screening / Enrollment Visit

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

24. Signed and dated informed consent by the parents
25. Signed child assent by the study subject
26. Demographics (date of birth, gender, race and ethnicity)
27. Medical history
28. Details of the diabetic history: duration of disease (number of years), diagnosis details, current insulin pump model, history of CGM use, current treatment (including basal rates,

carbohydrate ratios, insulin sensitivity factors, target glucose, average daily insulin, history of diabetic ketoacidosis, history of severe hypoglycemia, history of seizures or loss of consciousness, and average number of blood tests performed daily)

29. A targeted medical history will be obtained regarding medical conditions, current medications and drug allergies
30. Surgical history
31. Menstrual history (females)
32. Allergies
33. Medications and supplements
34. Social history including drinking, smoking, and drug habits (participants only in Phase 1, parent and participant in Phase 2)
35. Short Physical examination
36. Weight and height
37. Vital signs
38. Blood and Urine testing for screening labs:

    Hemoglobin HbA1c
    Pregnancy test: urine in women with childbearing potential

Parents may provide a recent physical exam if exam is within last 12 months and a recent Hemoglobin A1c if test result is ≤ 3months from the screening date. The study physician will have the discretion to repeat these tests as needed. Pregnancy tests will be done prior to initiating study equipment for females of childbearing potential. Once all results of the screening evaluations are available, a decision will be made to determine the subject's eligibility for the study or if one or more part of the screening will have to be repeated. If at the first screening or repeat screening an exclusionary condition is identified, the study subject will be excluded from participation with follow up and referred to their primary care physician as needed. Subjects may be re-screened at a later date if their clinical situation changes as determined by the study physician during an acceptable timeline. If the study subject is pregnant, the study subject will be excluded from participation. The subject will be asked to seek confirmation of the test and seek appropriate medical care.

All subjects (and families in Phase 2) will also be given instructions to avoid acetaminophen for the study subject during their study intervention as there is potential for interference with glucose oxidase systems for measuring glucose such as the CGM. These instructions will also advise the subject/families to contact

the study team in the event of a febrile illness within 24 hours of the start of the ski camp. All subjects will be given instructions to bring all of their current medications and pump supplies with them for use during the study.

Subjects will be coming from a large geographical area, and it may not be possible to meet with families in person for the consent process until they arrive at the ski lodge. In this event, subjects and parents will be consented over the phone, informed consent form/child assent will be sent by email or mail. Families will be asked to fax or scan/email the signed consent/assent forms to the study team prior to the start of the trial. Families will be also be given the opportunity to sign consent at the camp site should they meet inclusion/exclusion criteria. After receipt of the consent form, parents will be asked to complete the medical history form and again provide it to the research team prior to the start of the trial. The written informed consent will be obtained from the subject prior to performing any study-specific procedures. They will also be asked to bring the original consent/assent to the camp site.

Visit 2: Diabetes Ski Camp

Admission Procedures:

1. The consent/assent will be reviewed to check that appropriate signatures have been obtained.
2. Eligibility criteria will be reviewed.
3. A short targeted physical exam will be completed assessing for retinopathy, thyromegaly, skin conditions including any allergic conditions, and for acute and chronic changes at the insulin infusion sites. Height, weight and blood pressure will be reviewed from the one obtained at screening. Female subjects who have entered menarche will have a pregnancy test before devices are assigned.
4. The study team will confirm that the subject brought his/her insulin, insulin pump supplies, and regular medications. The study team will also confirm the absence of a febrile illness within 24 hours of admission.
5. During Phase 2 (for ages 6-12), the study team and subjects parents/caregivers will determine if any parent/caregiver needs to stay with the child at the camp site during camp. Study team will also confirm that one parent/caregiver will be available for device training and can serve as primary monitor during Phase 2.
6. The subject will be asked to perform a fingerstick (SMBG) using the study glucometer shortly after arrival.
7. The subject will be asked to perform a blood β-ketones after arrival. If ketones > 0.6 mmol/L, study staff should treat with oral hydration and, if needed, the Glycemic

Treatment Guidelines will be followed; BG and blood ketone levels will be re-checked in 1 hour. Subject will be able to start the clinical trial once a BG value between 80 – 300 mg/dL with blood β-ketones ≤ 0.6 mmol/L.

8. Data from subjects' insulin pumps will be reviewed and/or downloaded for a review of pump settings and average of daily insulin delivery.

9. All subjects will wear a commercially activity tracker (i.e. Fitbit) to collect additional information about movement and heart rate. The monitor can be removed during sleep and bathing.

10. The subject may take additional fingerstick readings as desired or instructed by study team.

11. All participating subjects will be within close proximity of the study team at all times. Subjects will only be in closed-loop mode whilst they are within the parameter of the ski resort (i.e. lodges, slopes)

12. The study team will assist the subjects with infusion site insertion. Insulin parameters will be reviewed by the camp medical team and adjustments may be made to address the increase in physical activity that will occur during the study. Reduction of total insulin dose may be changed 10% initially. If significant hypoglycemia is observed, further reduction of total insulin does may be made on the second day.

Randomization Procedures:

Using a randomized block design, the subjects will be assessed and put in blocks of two according to age and HbA1c, if identical match is not possible the closest in age and HbA1c value will be pair and then randomized. The members of each block are then randomly assigned, one to each of the two treatment groups.

Study Procedures:

39. CGM sensor/s will be inserted into the subjects with study team assistance for all participants. Subjects/families will be taught how to calibrate their CGM. The first sensor calibration will be entered at approximately 2 hours after sensor insertion. Sensors will be calibrated as per the manufacturer's recommendations.

40. Subjects' will be taught how to check fingerstick glucose levels with the study glucometer.

41. Experimental subjects will wear a CGM G6 with the Tandem t:slim X2. They will also wear a G5 sensor to permit remote monitoring of their CGM tracings.

42. Study team members trained in all protocol interventions (including the hypo & hypoglycemia safety protocols) will be skiing with the participants. Each study team

member on the slopes will be connected to up to 5 CGM sensors worn by the campers via the Dexcom G5 Share/Follow system and able to physically intervene as per defined in the protocol. In addition, a study member trained in all protocol and glycemic guidelines procedures will be available at a central location in the resort.

43. Monitoring of the G5 tracing will occur using an APP on the subjects' personal phone or a study phone during the trial.

44. During the overnight hours, study staff will be actively monitoring real-time CGM via the G5 Share/Follow system for all campers from a dedicated room in the ski resort with direct access to the campers (same building).

Procedures for Experimental Group:

a. The subject's insulin parameters will be programmed into their Tandem t:slim X2 with Control-IQ pump by two research staff. Subjects will then switch to the study insulin pump. The subject's personal pump and infusion site will be removed.

b. The subject will have an overview an instruction on how to operate the insulin pump although the interaction with the experimental equipment will be supervised by study stuff during the entire study.

c. During Phase 2, Parents will be trained on the use of the AP system in order for them to use the system confidently at home following the ski camp.

d. Tandem t:slim X2 with Control-IQ Technology will be initiated.

e. A Dexcom CGM G5 sensor will be inserted and initiated.

f. Subjects will be shown how to deliver boluses before meals with the system. Correction boluses can be given for hyperglycemia by using the correction bolus function.

g. Tandem t:slim X2 with Control-IQ Technology will be initiated in Closed Loop Control Mode once a CGM value is available. The meter glucose value needs to be between 80 – 300 mg/dL prior to initiation of Closed-Loop Control.

h. Subjects will be asked to respond to both hypoglycemia and hyperglycemia alarms. If they do not respond to the alarms within 10 minutes, study personnel will assist the subject as per the Glycemic Treatment Guidelines.

i. The subject will be primarily responsible for using the system at this time, with the study team serving as a back-up when needed. The subject will be re-educated as needed. Study staff will be available at all times to assure proper use of all study equipment.

j. Subjects will have all equipment with them at all times, including the personal cell

phone or study cell phone with the Dexcom Follow App.

k. Phase 2 study participants will continue to wear the CGM at home after the conclusion of the Winter Camp. All sensor changes during camp will be handled by the study team, but parents of subjects in Phase 2 will be trained on how to change sensors in case of sensor failure during the 72 hours home use.

Procedures for Control Group:

a. Subjects will wear their personal insulin pumps during the trial. Study staff will review proper use of insulin pump with the subjects.

b. A Dexcom CGM G5 will be inserted and initiated.

c. Subjects will calibrate the CGM per manufacturer instructions.

d. Subjects will have all equipment with them at all times, including the personal cell phone or study cell phone with the Dexcom Follow App.

Daily Routine during Camp Trial (up to 48 hours)

Recreational activities will be managed by '*Riding on Insulin*' with study staff supervision. The schedule is as follows (**times are approximate**):

45. A blood glucose value will be obtained, and a pre-meal bolus provided prior to breakfast. Breakfast will occur between 07:00 – 08:00h. The pre-breakfast meter glucose value will be used to calibrate the CGM if the rate of change is not greater than 2mg/dL/min.

46. A pre-activity blood glucose value will be obtained 30 minutes prior to the morning activity. The Glycemic Treatment Guidelines will be followed if SMBG ≤100 mg/dL.

47. Ski activity will occur between 09:00- 12:00h.

48. A blood glucose value will be obtained, and a pre-meal bolus provided prior to lunch. Lunch will occur between 11:30 – 14:00h.

49. A pre-activity blood glucose value will be obtained 30 minutes prior to the afternoon activity. (This SMBG value may also be used in treatment of the pre-meal snack.) The Glycemic Treatment Guidelines will be followed if SMBG ≤100 mg/dL.

50. Ski activity may occur between 14:00 – 17:00h (or 14:00 – 16:00 for younger children), alternative camp activities may replace skiing in the afternoon.

51. A blood glucose value will be obtained, and a pre-meal bolus provided prior to the afternoon snack. The afternoon snack will occur at approximately 16:00h.

52. A blood glucose value will be obtained, and a pre-meal bolus provided prior to dinner. Dinner will occur between 18:00 – 20:00h.

53. A blood glucose value will be obtained, and a pre-meal bolus is given prior to the bedtime snack. The snack is given at approximately 22:00h. The pre-bedtime meter glucose value will be used to calibrate the CGM if the rate of change is not greater than 2mg/dL/min.

54. An evening activity will occur from 20:30 – 23:00h (or 19:00 – 21:00 for younger children).

55. The subjects will be sleeping in assigned groups and supervised during overnight hours by study staff. All study personnel have been trained in glucose monitoring and diabetes treatments.

56. Overnight SMBG will be obtained if CGM lower than 70 mg/dL and arrow indicating down or higher than 300 mg/dL and arrow indicating up. If difference between SMBG and CGM is more than 20 %, CGM may be calibrated. If BG less than 70 mg/dL or more than 300 mg/dl, glycemic treatment protocol will be follow.

57. At the conclusion of the study, a brief questionnaire asking subjects about their experience with the t:slim X2 with Control-IQ Technology equipment will be provided to subjects.

Meals

58. Breakfast will occur approximately between 07:00 – 08:00h

59. Lunch will occur approximately between 11:30 - 1400h.

60. Dinner will occur approximately between 17:00 – 20:00h.

61. Snacks will be provided at approximately 15:00h and 22:00h.

62. During the 48 hours, all meal boluses will be supervised by research staff.

63. An insulin bolus is given before all meals and snacks, per the subject's parameters.

Equipment Specifications

64. All study equipment including the Tandem t:slim X2 with Control-IQ Technology, computers, and study CGMs as well as the personal insulin pumps will use international standard notation of 24-hour clock as a reference.

65. It will be a two-step remote monitoring as follow:

    A staff member assigned to each group will have access to follow on his/her cellphone up to 5 campers that can be monitored at the slopes.

    Additional monitoring will be conducted at a central location inside of the resort where a study stuff will be monitoring all the campers using transmission from each participant Dexcom CGM G5.

66. If needed, devices will be charged overnight while subjects are sleeping.

67. All subjects will wear a commercially activity tracker to collect additional information about movement and heart rate. The monitor can be removed during sleep and bathing.

Remote Monitoring

During camp (both Phase 1 and 2): Staff will remotely monitor the subjects using the Dexcom G5 capabilities provided by Dexcom® Inc. The research staff will be monitoring subjects in real-time. Notification will be set for CGM readings below 80mg/dl during the day and 70mg/dl at night or above 300mg/dl to alert study staff of the need treatment or SMBG confirmation. During Phase 2, considering the younger age of the participants, the upper threshold will be dropped to 250mg/dL.

During 72h home extension (Phase 2 only): Parents/caregivers will remotely monitor the subjects in real-time using the Dexcom G5 Share/Follow capabilities provided by Dexcom ® Inc. Alerts will be setup for values below 70mg/dL and above 250mg/dL.

In addition, the study staff will also remote monitor the subject but with alerts adapted to the existence of a first tier RM (the parents/caregivers) and the fact that they are not one site. Therefore the study staff (Tier 2) alerts will be <60mg/dL for more than 15min and >300mg/dL for more than 60min.

Self-Monitoring Blood Glucose Measurements Schedule (both Experimental & Control Groups)

Camp:
Once a fingerstick is obtained for any reason during the time that Tandem t:slim X2 with Control-IQ Technology is in use, Glycemic Treatment Guidelines (Appendix A-8) will be followed to determine timing of subsequent fingersticks.

- Scheduled times: SMBG levels will be measured to calibrate CGM as per manufacturer recommendations and when it deemed needed by the study stuff and before exercise periods. More detail is explained in the glycemic guidelines.

The SMBG collected prior to breakfast and dinner will be used to calibrate the CGM.

- A subject or a study personnel may request any additional fingersticks as desired
- CGM readings below 70mg/dl or above 300mg/dl during the study time.

Summary of subject's responsibilities who are randomized to t:slim X2 with Control-IQ Technology

Camp:

- Subjects will obtain at least 2 SMBGs values per day during the trial. SMBGs are collected before breakfast and before dinner for CGM calibration and before exercise.
- Subject will calibrate at least CGM twice daily.
- Use of a temp basal rate will be permitted.

AP Home Use:

- Families will be instructed during the ski camp portion of the study on how to use the AP system for 72 hours while at home
- Families will show proficiency of using the system before leaving for the home portion of the trial.
- Families will show proficiency on how to change CGM before leaving for the home use portion of the trial
- Subjects will obtain at least 2 SMBGs values per day during the trial. SMBGs are collected before breakfast and before dinner for CGM calibration.

Subject will calibrate the CGM at least twice daily per manufacturer recommendation.

Summary of subject's responsibilities who are randomized to SAP

Camp:

- Subjects will obtain at least 2 SMBGs per day values during the trial. SMBGs are collected prior to breakfast and dinner for CGM calibration and before exercise.
- Subjects will respond to CGM alarms as indicated, study staff will be closed by if subject does not attend to alarms. During the night, study staff will be alert at the remote monitoring provided by the Dexcom CGM G5 and provide hypo/hyperglycemia assistant to the participants if needed according to the glycemic guidelines (Appendix A-8).
- Use of a temp basal rate will be permitted.

AP Home Use:

- Families will be instructed during the ski camp portion of the study on how to use the AP system for 72 hours while at home
- Families will show proficiency of using the system before leaving for the home portion of the trial.
- Families will show proficiency on how to change CGM before leaving for the home use portion of the trial

- Subjects will obtain at least 2 SMBGs values per day during the trial. SMBGs are collected before breakfast and before dinner for CGM calibration.
- Subject will calibrate the CGM at least twice daily per manufacturer recommendation.

Safety Monitoring / Risk Analysis

Monitoring Procedures by Staff during Winter Camp:

1. CGM values are updated every 5 minutes.
2. Study staff will be constantly monitoring the CGM locally and in a central location inside of the resort as explained before. Field staff will be alerted when CGM <80 or >300 during exercise periods.
3. The Glycemic Treatment Guidelines will be applied during both the Experimental and Control groups.
4. If CGM < 80 mg/dL during the day, the patient will be treated until CGM reads >80 mg/dL.
5. If CGM < 70 mg/dL during the night. Hypoglycemia treatment will be provided until CGM reads > 80 mg/dL. SMBG may be performed if the MD on-call deemed is necessary.
6. An SMBG will be performed 30 minutes before exercise. SMBG must be > 100 mg/dL prior to the initiation of exercise. If SMBG ≤ 100 mg/dL, subject will be treated with oral glucose until BG is above 100 mg/dL.
7. If CGM >300 mg/dL, SMBG will be performed every 60 minutes. If SMBG >300 mg/dL,
8. The Glycemic Treatment Guidelines will be applied Experimental and Control Admissions.
9. All study staff will be trained on the use of study equipment and will monitor the system during the entire admission.
10. Medical personnel and emergency supplies will be available on site.

Monitoring Procedures by Staff during AP Home Use:

1. CGM values are updated every 5 minutes and parents will be able to see it on the pump and Dexcom Follow App.
2. CGM alarms on the parent controlled Dexcom Follow App will be set at 70 mg/dl and 250 mg/dl before leaving the camp and parents will be taught how to react to them.
3. The Glycemic Treatment Guidelines will be provided to the families in order to be applied at home should they be needed.
4. If CGM < 70 mg/dL during the night. Hypoglycemia treatment will be provided until CGM reads >

80 mg/dL. SMBG may be performed if the families wish it to do so.

5. If CGM >300 mg/dL, SMBG will be performed every 60 minutes. If SMBG >300 mg/dL, the Glycemic Treatment Guidelines will be applied.
6. Families will be provided with β ketones meter and strip to use at home if needed
7. All families will be trained on the use of study equipment and will monitor the system during the entire use at home.
8. A 24/7 phone line will be available for medical and technical support during the at home use of the system.

Insulin Pump Risk:
Tandem t:slim X2 with Control-IQ Technology described in Master File MAF-2032/A003. The system components include the t:slim X2 with Control-IQ Technology and the Dexcom CGM G6 (Figure 1). 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.

Glucose Monitoring Risk:
The study glucometers are single use devices. A FDA approved glucometer will be used.

Hypoglycemic / Hyperglycemic Risk:
Glycemic Treatment Guidelines (Appendix A-8) will be followed through the study.

Calibration of CGM Risk:
The CGM will be calibrated using fingerstick values per manufacturer's guidelines.

Sterilization Risk:
Study equipment cannot be sterilized in an autoclave. Cleaning instructions for study equipment provided to study the subject are provided below.

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

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

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

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.

Questionnaire
As part of the study, subjects will complete a Technology Acceptance Questionnaire which includes questions about their private attitudes, feelings and behavior related to t:slim X2 with Control-IQ. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

Misuse Risk

CGM Training:

Subjects will be introduced to the CGM by a qualified member of the study team. The subject will be instructed how the device is inserted, calibrated and removed. The subject will verbalize understanding of how the device is used, how to insert the device, how to calibrate the device and how to remove the device to the study team. The subject, with the guidance of the study team, will then insert the sensor and begin wearing the CGM. The study team will confirm that all questions have been answered and that the subject has understood the training.

Study Glucometer Training:
Subjects will be trained on study glucometer device. Study staff will demonstrate proper use of the meter as described in the user manual. The subject will then be required to demonstrate proficiency on the use of the device. The subject will be instructed to wash their skin with warm water and a clean towel prior to obtaining fingerstick values. If handwashing facilities are not readily accessible, an alcohol swab can be used. The subject will be instructed to obtain a fingerstick, avoiding alternative sites, when obtaining blood values. The first drop will be discarded. The second drop will be used to measure the glucose level. QC will be completed prior to subject receiving the study glucometer and when study glucometer results are suspect. The study team will confirm that all questions have been answered and that the subject has understood the training.

Tandem t:slim X2 with Control-IQ Technology:
The training with the study insulin pump is part of the training (below) and will occur with a qualified clinical member of the study team. All pump-related topics will be discussed, including but not limited to: temporary basal rates, bolus calculator function, insulin action duration, bolus increment, low reservoir warnings / alarms, auto off function, and changing the pump if needed. The study team will confirm that all questions have been answered and that the subject has understood the training.

Tandem t:slim X2 with Control-IQ Technology Training:
The t:slim X2 with Control-IQ Technology training will occur with a qualified clinical member of the study team, the subject will be instructed how to navigate the pump GUI. The subject's basal rates and pump parameters will be confirmed at this time. To minimize risk associated with the use of t:slim X2 with Control-IQ Technology:

- t:slim X2 with Control-IQ Technology will be pre-programmed with all the subject's individual pump settings by two research staff.
- The subject will be trained on the use of the t:slim X2 with Control-IQ Technology GUI.
- The subject will be instructed how to access the CGM trace from the primary CGM via the

  pump user interface.
- The subject will activate the meal screen of the system any time insulin will be given with a meal or any time additional correction insulin is desired.
- The subject will be assessed for understanding of the pump GUI and how to react to alarms. The subject will be re-educated as needed. The subject will be primarily responsible for using the system, with a medically qualified staff member and computer technician serving as back-up when needed.

Risks of Blood Sampling Collection, Contamination from Sampling Techniques

- Hand washing with either soap & water or waterless hand sanitizer will be used prior to caring for the study subject. Gloves will be worn during blood sample collection and processing. Medical personnel will continue to practice hygiene for the subject's protection (i.e. hand washing, changing gloves frequently, disposing needles properly). Gloves will be removed and hands washed prior to leaving and upon return to the subject's room. Soiled linen will be changed to minimize the transfer of pathogenic organisms.
- Study personnel with direct subject contact are required to complete Blood borne Pathogens and Infection Control training annually.

Medical Personnel Training:

Medical personnel will be oriented to the study protocol. All study personnel employed by the study are oriented to the care of the type 1 diabetes research subject. Certification of their skill level is supervised by the clinical site PI. Other medical personnel may be licensed Emergency Medical Technicians. All medical personnel who will have direct contact with the study subject have current certification in Basic Life Support including CPR and AED.

Camp Emergency Equipment:

The camp will be well equipped to handle diabetes emergencies and will have glucagon, fluids, blood ketone monitoring, ventilation and resuscitative equipment such as automated external defibrillators (AED).

Stopping Rules

Entire study

The study will be stopped if two distinct episodes of DKA or two distinct episodes of severe hypoglycemia occur that result in stopping the study for individual study subjects or if there are system communication failures, which may trigger revision of the system software. Additionally, the Principal Investigator, IRB-HSR may decide to stop the trial or part of the trial at any time. In this case, the Principal Investigator will promptly inform the subjects and assure appropriate therapy and follow-up. Additionally, the Principal Investigator will notify the IRB if the study is temporarily stopped. The pertinent regulatory authorities will be informed according to national regulations.

Early study stop will be documented and following information will be collected:

68. Date and cause of the ending

69. Description of any serious adverse event

70. A subject who does not complete the protocol may be replaced or rescheduled.

71. In the case of an unanticipated adverse device effects (UADE), the overall study may be suspended while the problem is diagnosed and the PI investigates the UADE. If the PI determines that the UADE poses an unreasonable risk to subjects, the study should be suspended until this UADE can be resolved. If it cannot be resolved, the study should be terminated. Termination should occur no later than 5 working days after PI makes the decision. The result of the investigation and the PI's decision to terminate the study shall be reported the site IRB, and the FDA per 21CFR 812.46(b) (2). The medical monitor must determine if the UADE presents an unreasonable risk to subjects. If so, the medical monitor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the medical monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

72. 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. The IRB will be notified if the study is stopped, and permission to resume will be obtained from the FDA and IRB prior to restarting.

Subject Withdrawal Criteria:

An individual subject can be stopped from study participation at subject, PI, study MD, or IRB request. The subject may request to be withdrawn from the study at any time for any/no reason (withdrawal of informed consent).

Criteria for stopping study in individual subject:

73. Malfunction of the system or controller that imposes upon the safety of the subject

74. Hypoglycemic seizure or coma

75. Abdominal pain, vomiting or decreased conscious state

76. Pregnancy

77. Loss of sensor data acquisition for more than 6 hours

78. Two consecutive hypoglycemic events below 50 mg/dL (an event is defined as confirmed SMBG, consecutive means more than 30 minutes and less than 60 minutes apart)

Definition of Hypoglycemic Event:
Hypoglycemic events are recorded as Adverse Events (severe hypoglycemic event) if the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma.

The subject may resume the study after the following problems are resolved:

79. Correction of a malfunction of the system or controller once the problem is clearly identified and the system has been repaired.

80. Resolution of two consecutive hypoglycemia values with meter glucose < 50 mg/dL as long as there was no seizure of loss of consciousness and the glucose after treatment is >80 mg/dL.

81. Correction of hyperglycemia. System may be resumed when ketones are ≤0.6 mmol/L and the meter glucose is between 80-250 mg/dL.

82. Loss of sensor data acquisition for more than four hours.

83. If remote monitoring cannot be restored within 180 minutes, closed-loop control may be suspended until remote monitoring is restored.

1. **Reason study stopped**	2. **Resume/repeat admission?**
3. Equipment failure or similar related issue	4. Can resume
5. Hyperglycemic event that did not result in serious adverse event	6. Can resume
7. Hypoglycemic event that did not result in serious adverse event	8. Can resume
9. PI initiated discontinuation of study due to subject or equipment concerns	10. Can resume
11. Serious unanticipated adverse event deemed related to the study	12. Do not resume

Table 1: Resume Trial Table

Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches

Definition of adverse events (AE) for this study

An adverse event is defined as unexpected, involves risk or harm, and related, or probably related, to research activities. Pregnancy during the trial will not be considered an adverse event.

Definition of serious adverse events

A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

Definition of an unanticipated problem

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

- not anticipated or foreseen (e.g., not described in the consent form);
- involves risk or harm to a research participant or others; and
- probably, definitely related to, or caused by, the research.

Definition of a protocol violation

A protocol violation is defined as an accidental or unintentional change to the IRB approved protocol that harmed participants or others or that indicates participants or others may be at increased risk of harm.

Definition of a Protocol Enrollment Exception

No enrollment exceptions will be permitted in this trial.

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.

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.

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 t:slim X2 with Control-IQ Technology 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 www.irb.virginia.edu/
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 www.irb.virginia.edu/
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 www.irb.virginia.edu/
Unanticipated Problems 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 www.irb.virginia.edu/
Protocol Violations/Noncompliance	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form.

The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by the sponsor **OR** **Enrollment Exceptions**			*http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
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 *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom*
Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- Police if breach includes items that are stolen: Stolen on UVA Grounds OR	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 time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 ITC: Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html UVa Police- Phone- (434) 924-7166

	Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI		
UVa PI HELD IDE			
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

CATASTROPHIC EVENT PLAN:

The Outpatient Emergency Plan (Table 3) will go into effect should a catastrophic event occur during Closed Loop Control. A catastrophic event is defined as any event that requires emergency treatment by medical professionals that exceed the expected parameters of the protocol.

Event	RN Response	Tech Response
Respiratory Arrest	1) Tell Tech to call 911 2) Begin Basic Life Support	Refer to Study Physician on-Site
Cardiac Arrest	1) Tell Tech to call 911 2) Begin Basic Life Support	Refer to Study Physician on-Site
Severe Hypoglycemic Event as defined by hypoglycemia accompanied by unconsciousness or seizure	1) Tell Tech to call 911 2) Administer glucagon IM or SQ 3) Remove study pump	Refer to Study Physician on-Site
Severe Hyperglycemic Event as defined by β-ketone level ≥3.0 mmol/L, or symptoms of nausea, vomiting and abdominal pain are present	1) Discuss correction dose of insulin to administer s.c. via syringe with study M.D. 2) Encourage p.o. water intake	Refer to Study Physician on-Site

Table 3: Outpatient Emergency Plan

In the unlikely event of a disruption in 911 phone service, the sites will contact their local non-emergency number.

If any emergent event occurs, the study staff will attend to it immediately by providing the necessary treatment. There will also be a portable rescue kit ready to treat the subjects who may need emergent treatment before he/she is moved to the medical cabin.

If required, the subject will be transferred to the nearest medical facility and will be accompanied by medical trained personnel involved in the clinical trial that will stay with the subject until is fully recovered or a parent/designated family member has arrived.

Endpoints

This study is an early feasibility study that will test the efficacy of t:slim X2 with Control-IQ Technology compared to sensor augmented therapy in an outpatient setting. These studies would generate up to 30 days of closed-loop data and 30 days of SAP data. This sample size allows for subject withdrawal.

Study Outcomes

Primary Outcome

Percent time spent in desirable glycemic zone (70-180mg/dl).

Secondary Outcomes

1. % time spent <70 mg/dl, <60mg/dl, and <54mg/dL
2. % time spent >180mg/dl, and >250mg/dl
3. % time spent between 70-150mg/dl overnight (11pm-7am)
4. % time spent between 70-180mg/dl during the day (7am-11pm)
5. Number of hypoglycemia below 70 mg/dL
6. Number of CHO treatments, as well as total amount of CHO treatments.

Success Criteria / Goal

As a general rule, a session will be considered useful for data analysis if the subject completes close to 80% of the active study protocol. Sessions are consider separate: (i) Ski camp=complete at least 38 hours of AP or SAP depending on the randomized group; (ii) at home use=complete at least 56 hours of either AP or SAP depending on the randomized group.

Phase 1 success criteria for enabling Phase 2:

- No device related severe AE
- No UADE
- Overall time spent in desirable glycemic zone in AP group no less than 5% below SAP group
- No significant (unpaired median test) increase in time below 70mg/dL in AP vs SAP group. Power analysis for a Wilcoxon signed-rank test was conducted in G*Power to determine a sufficient sample size using an alpha of 0.05, a power of 0.80, a medium effect size (dz = 0.5), and one tail. Based on the aforementioned assumptions, the desired sample size is 28.

Statistical Analysis Plan

Phase 1 will be analyzed by straight group comparison (i.e. unpaired t-test and Wilcoxon sign rank)

Phase 2 will be analyzed using Repeated measure ANOVA computing the outcomes on the 48h of camp and the last 48h of home use. Main outcome will be the within between group contrast, in addition within (camp vs home) and between (AP vs SAP) will be run.

Safety outcomes will also be assessed on the entirety of the home phase.