SCHOOL OF MEDICINE
Department of Psychiatry and Neurobehavioral Sciences
Center for Diabetes Technology

Reducing Risks and Improving Glucose Control during Extended Exercise in Youth with T1DM: The AP Ski Camp

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 is was shown that he system can keep glycemic values in the euglycemic range (70-180 mg/dL) for 75% to 80% of the time.

Over the last 5 years, our teams have developed and tested the first wearable AP system to date (called 'DiAs' for Diabetes Assistant), based on a specifically modified smart-phone; it enabled outpatient clinical trials demonstrating significantly improved glycemic control and hypoglycemia avoidance in adult and pediatric patients with T1D, in outpatient settings and at home. Furthermore, global control modules allowing remote monitoring/diagnosis and telemedicine are enabled using the communication functionalities of DiAs. Such a system could represent an optimal tool, with minimal burden thanks to its wearability, to reduce hypoglycemia at night in children both by the performance of the algorithms and the availability of remote monitoring.

As advancements in technology continue, we propose the use of the inControl Diabetes Management Platform during a research house admission. 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 and notifications for caregivers and family as well as retrospective analysis on data to identify areas of systemic risk or treatment inefficiencies. The data generated is stored at an inControl Cloud permitting the research team and support networks observe blood glucose values in real-time. The insulin dosing strategies used in this device are the same strategies currently used in DiAs. The purpose of this outpatient study is to assess inControl with the current strategies in a monitored setting. After a DSMB review, the Colorado site may elect to use the inControl platform or remain using the DiAs platform.

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.

Figure 1: inControl Diabetes Management Platform

The object of this study is to evaluate the UVa AP system in an environment where muscle glycogen is systematically depleted, glucose uptake systematically increased, and meal sizes are naturally larger than normal: a week of camp at high altitude, 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 during cold temperatures, and with twice daily practice of physical activity designed to deplete glycogen reserves such as skiing.

This proposal aims to demonstrate the superiority of the closed-loop control (CLC), also known as Artificial Pancreas (AP), compared to the state-of-the art system available on the market: Sensor-augmented pump (SAP). This system has shown to diminish hypoglycemic events by setting the alarms on the continues glucose monitor (CGM) and taken action, such as performing SMBG and treating if it is confirm to be low.

Primary Specific Aims:

1. Demonstrate the superiority of AP exercise module compared to the SAP in controlling blood glucose of adolescents and young adults with T1DM during extended exercise periods.
2. Test the AP components in altitude, cold, and during intense exercise.

Secondary Specific Aims:

1. Test the AP components (glucose sensors, insulin pumps, smart-phone controller) in high altitude, cold, and intense exercise conditions.
2. Collect regulatory data from the extreme testing of an exercise AP system and its components
3. Assess the impact of strenuous exercise on AP performance

4. 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 40 adolescents and young adults 10-25 years old, with T1DM on an insulin pump by two clinical research teams (University of Virginia and University of Colorado, Denver) during a weeklong diabetes ski camp (5 consecutive 24h periods under intervention). Study participants will be divided in two groups of 20 adolescents and young adults with T1DM using SAP, and another 20 adolescents and young adults with T1DM wearing the AP. All the efforts will be made to enrolled most of the participants between the ages of 10-18 year old. A study team may alternatively schedule a ski camp of a shorter duration to complete enrollment.

Procedure:

The proposed study is an outpatient prospective, randomized control clinical trial comparing the 2 groups. Group 1: the artificial pancreas with a control-to-range (CTR) algorithm. Group 2 SAP with their personal insulin pump. Eligible subjects will be randomized to either experimental (CTR) 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 age (below and above 15 years old), and HbA1c group (below 8.5 and above 8.5) across both camp.

Equipment for Experimental CTR Group:

- Insulin pump: Roche Accu-Chek Spirit Combo System or Tandem t:slim
- Continuous Glucose Monitor: Dexcom Continuous Glucose Monitor Gen 4 PLATINUM System with Share
- AP system: Diabetes Assistant (DiAs) with control-to-range algorithm or inControl with control-to-range algorithm Glucometer: Roche Accu-Chek Aviva Combo Blood Glucose Monitor or FDA approved glucose meter equal for both groups

Equipment for Control SAP Group:

- Insulin pump: Subject's personal insulin pump
- Continuous Glucose Monitor: Dexcom Continuous Glucose Monitor Gen 4 PLATINUM System with Share
- Glucometer: Roche Accu-Chek Aviva Combo Blood Glucose Monitor or FDA approved glucose meter equal for both groups
- The AP system will be used on sensor only mode in order to have access to 24 hours remote

monitoring on this group as well

Study Diagram

Visit 1: Screening Visit. 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 or as a scanned document. 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 closed-loop control (CLC) group or sensor-augmented pump (SAP) group for up to 5 days/6 nights. The subjects will report to the ski camp location by approximately 4pm on the first day of the ski camp. Once determined eligible, the subject will be equipped with the study equipment. Subjects will then be trained in the use of the basic pump functionalities on the study insulin pump. For the experimental group, the smart-phone controller will be programmed to run CTR algorithm. Communication between the sensor, the pump, and the smartphone platform will be established and the system will be activated. The subjects will continue to use the system for approximately 132h; for example, the system will be initiated at approximately 10 pm Sunday night with testing completed the following Saturday 10 am. During system use, subjects will be remotely monitored and with immediate access to medical personnel and technical personnel. The control (SAP) group will be fitted with a CGM equal to the experimental group, and the participants will be wearing their personal insulin pump The SAP control group will have a the AP system that will be used in sensor only mode to allow remote monitoring on this group as well.

The "camp" aspect of the trial will be handled by '*Ride On Insulin'* (www.rideoninsulin.org), a non-profit organization specialized in engaging the pediatric T1DM population in skiing and snowboarding. A typical day at the ski camp will be as follow (estimated times):

7 – 8 AM: Wake
8 – 9 AM: Breakfast
9 – 9:30 AM: Prepare to go outside
9:30 – 11:30 PM: Ski session
12 – 1 PM: Lunch
1 - 3 PM: Ski session
3 – 4 PM: Free Time
4 – 6 PM: Games/Activities
6 – 7 PM: Dinner
7:30 – 9:00 PM: Evening activity
9 – 10 PM: Prepare to sleep
11 – 7 AM: Sleep

SMBG will be obtained pre and two hours post meal, before and after exercise and any other time that is deemed necessary for CGM lower than 100 mg/dL during peri-exercise period or deemed needed by the study team following the glycemic guidelines.

Visit 3: Post-Study Follow up. The study team will contact study participants approximately 48 hours after the study to ask subjects about the occurrence of adverse events and to discuss any study-related questions or concerns.

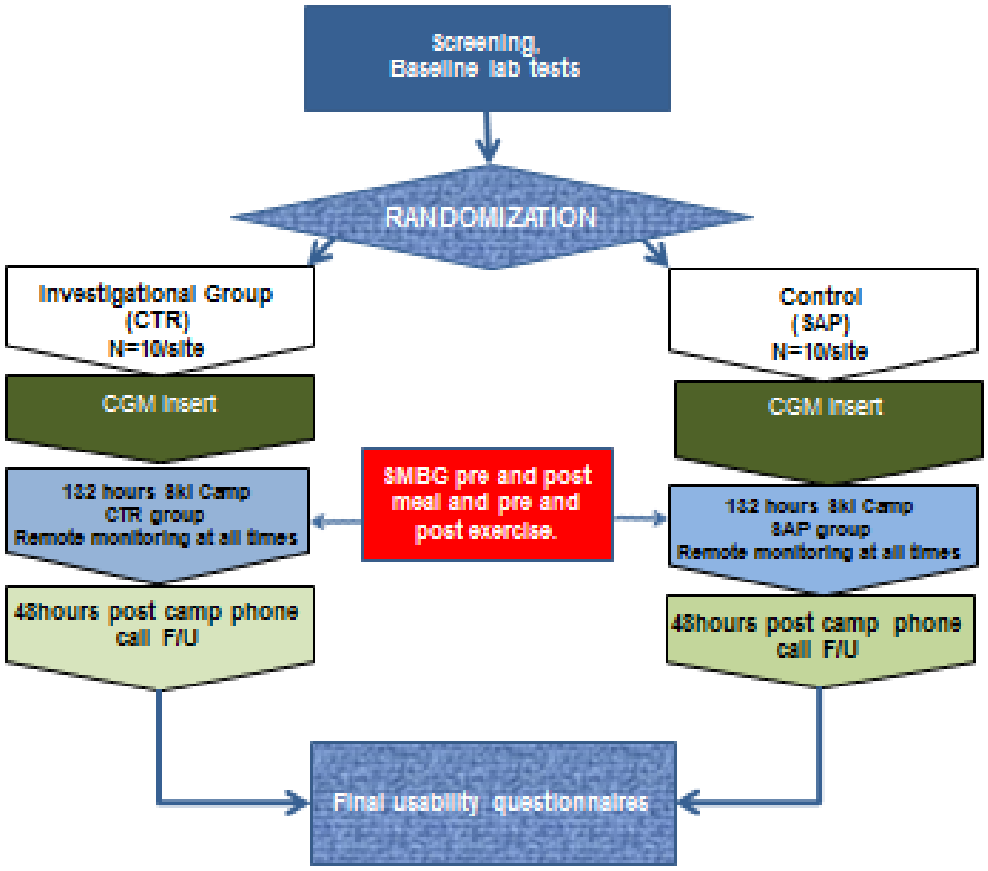

Figure 2: Study Diagram

Sample Size and Investigational Sites:

The studies will be conducted at the University of Virginia and at the University of Colorado, Barbara Davis Center for Childhood Diabetes. A total of forty subjects (N=20/site) with type 1 diabetes will be needed to complete at each investigational site. Based on our experience with similar studies, we estimate an expected

30% screen failures, dropouts, or withdrawals, thus we intend to set a recruiting target of 52 subjects for this trial at both sites. Screen dropouts at one clinical site may be replaced at the other clinical site.

Investigational Sites:

The University of Virginia will perform the ski camp at:
Wintergreen Resort
39 Mountain Inn Loop
Roseland, VA

University of Colorado, Barbara Davis Center will perform the ski camp at:
Breckenridge Ski Resort
1599 County Rd 3,
Breckenridge, CO 80424

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 1 study staff will be available during the overnight hours of 10PM-8AM monitoring the participants. Both the experimental (CTR) and control (SAP) groups will have 24/7 remote monitoring; in case of remote monitoring failure CGM receiver alarms will be activated at low=80 mg/dL and high=300 mg/dL for the study personnel to act if alarms are set off following glycemic treatment protocol. Medical personnel will be lodging at the same facility and therefore are able to respond to emergencies during the entire trial. A technician, trained in the use and maintenance of the AP system, will be monitoring the system during the entire trial.

Study Duration
The duration of the Diabetes Ski Camp will be up to 5 days/6 nights. An abbreviated camp may be less than 5 days/6 nights.

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):
    - Clinical diagnosis of type 1 diabetes (C-peptide levels and antibody determinations are not required)
    - 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):
   - Daily insulin therapy for ≥ 12 months
   - Insulin pump therapy for ≥ 3 months
3. Age 10 – 25 years
4. Avoidance of acetaminophen-containing medications (i.e. Tylenol) while wearing the continuous glucose monitor.
5. Willingness to wear a continuous glucose sensor and physiological monitor for the duration of the study
6. Female subjects who are sexually active must be on acceptable method of contraception (e.g. oral contraceptive pill, diaphragm, IUD)

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

1. Diabetic ketoacidosis in the past 6 months
2. Hypoglycemic seizure or loss of consciousness in the past 6 months
3. History of seizure disorder (except for hypoglycemic seizure)
4. History of any heart disease including coronary artery disease, heart failure, or arrhythmias
5. History of altitude sickness
6. Chronic pulmonary conditions that could impair oxygenation
7. Cystic fibrosis
8. 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.
9. History of ongoing renal disease (other than microalbuminuria).
10. Subjects requiring intermediate or long-acting insulin (such as NPH, Detemir or Glargine).
11. Subjects requiring other anti-diabetic medications other than insulin (oral or injectable).
12. Pregnancy
13. Sexually active females who do not practice acceptable contraceptive methods to prevent pregnancy.
14. 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.
15. Medical or psychiatric condition that in the judgment of the investigator might interfere with the completion of the protocol such as:
    - 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 / criteria will be checked and documented:

1. Signed and dated informed consent
2. Inclusion and exclusion criteria
3. Demographics (date of birth, gender, race and ethnicity)
4. Medical history
5. 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)
6. A targeted medical history will be obtained regarding medical conditions, current medications and drug allergies
7. Surgical history
8. Menstrual history (females) and sexual activity/contraception (females)
9. Allergies
10. Medications and supplements
11. Social history including drinking, smoking, and drug habits
12. Physical examination
13. Weight and height
14. Vital signs
15. Blood and Urine testing for screening labs:
    - Hemoglobin HbA1c
    - Pregnancy test**:** either urine or qualitative serum HCG in women with childbearing potential.

Parents may provide a recent physical exam if exam is within last 6 months and a recent Hemoglobin A1c if test result is < 30 days. The study physician will have the discretion to repeat these test as needed. Pregnancy tests will be repeated prior to initiating study equipment regardless of current screening result. 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 will also be given instructions to avoid acetaminophen 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 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 (i.e. insulin) 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 send 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. 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.

Participants will need to secure their own transportation to a Charlottesville hotel for the first night. The study team will arrange with a private charter for all subjects to be transported to the lodge the next morning. Parents will need to pick up the subject from Wintergreen Resort at the end of the ski camp. Parents will not stay with the subject during the ski camp.

Subjects will need to provide their own winter clothing (i.e. coats, gloves, hat, ski pants, hand warmers, etc…) for use during the activities. Skiing/snowboarding equipment may be obtained from the ski lodge.

Riding on Insulin will provide instructors to teach skiing/snowboarding. It is suggested that parents/subjects register at the ROI website after the study team has received their signed informed consent form. ROI will use this information to create the activities and bring gifts for the subjects. The website address is: https://www.eventbrite.com/e/riding-on-insulin-uva-clinical-trial-camp-tickets-19811437543.

A helmet must be worn during all skiing/snowboarding activities.

Lodging, food, study equipment, study supplies (i.e. rescue carbohydrates), ski lift tickets, and skiing/snowboarding equipment will be provided for by the study team.

Visit 2: Diabetes Ski Camp

Admission Procedures:

1. The study team ask that parents bring their child to a local Charlottesville hotel the first night of the study where the subjects will stay for one overnight. 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.
5. The study team will also confirm the absence of a febrile illness within 24 hours of admission. Subject will not be permitted to participate if fever was present within the past 24 hours.
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 physiological monitor such Fitbit or Bioharness, to collect additional information about movement and heart rate. The monitor can be removed during sleep and bathing.
10. The subject will be reminded that all treatment decisions should be based on fingerstick values and not on CGM values.
11. The subject may take additional fingerstick readings as desired or instructed by study team.
12. 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)
13. The study team will assist the subjects with infusion site insertion. The study insulin pump will be programmed with the subject's usual basal rates and pump parameters.

Procedures:

1. CGM sensor will be inserted into the subjects' abdomen for all participants. Subjects 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 twice daily as per the manufacturer's recommendations.
2. Subjects' will be taught how to check fingerstick glucose levels with the study glucometer.
3. All participants will be provided an AP system android phone to use during the trial.
4. **For experimental group:**
   a. The subject's insulin parameters will be programmed into their AP system 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.
   c. The AP system will be initiated in Pump Only Mode until the period of warming up the CGM is over,

about two hours. Pump Only Mode will administer the subject's usual basal rate. In order to allow the AP system to operate, the study pump will be programmed for a basal rate of 0 when Pump Only Mode is initiated. If there is any unforeseen delay of (approximately 15min or more) in initiating the AP system in Pump Only Mode, a basal rate will be entered into the study insulin pump until connection can be established.

d. Subjects will be shown how to deliver boluses before meals with the system by using the meal bolus function. Correction boluses can be given for hyperglycemia by using the correction bolus function.
e. The procedure for administering a snack or correction bolus using the AP system interface during Pump Only Mode is:
    i. subject enters carbohydrate estimation and fingerstick value
    ii. the AP system will recommend bolus treatment using subject's own parameters
    iii. subject may change the size of the bolus (or cancel it)
    iv. subject will confirm bolus amount in the AP system under study staff observation; after the subject confirms the bolus, the insulin will be injected.
f. The AP system 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.
g. Subjects will be asked to respond to both hypoglycemia and hyperglycemia red light alerts from the AP system. If they do not respond to the alarms within 10 minutes, study personnel will assist the subject as per the Glycemic Treatment Guidelines.
h. 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 and may be provided printed reminders/instructions as a reference. Study staff will be available at all times to assure proper use of the AP system.

5. **For control group:**
    a. Study staff will review proper use of insulin pump with the subjects.
    b. The AP system will be initiated in Sensor Mode Only. The control algorithms are not active in this mode. Sensor Mode Only Will allow the AP system to be used for remote monitor glucose readings only.
    c. Subjects will be use their own insulin pump to deliver insulin treatment.

Daily Routine during Camp Trial (5 days/6 nights)

First day only: After eating breakfast, study subjects will be transported to Wintergreen Resort in a shuttle contracted by the study team. Subjects will put their possessions in their room and then outfitted with equipment.

Recreational activities will be managed by '*Riding on Insulin*' with study staff supervision.

1. A blood glucose value will be obtained, and a pre-meal bolus provided prior to breakfast. Breakfast will occur between 08:00 – 09:00h. 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.
2. 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.
3. The activity will occur between 0930 - 11:30h.
4. A blood glucose value will be obtained, and a pre-meal bolus provided prior to lunch. Lunch will occur between 1200 - 1300h.
5. The activity will occur between 1300 - 1500h.
6. 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 1430h.
7. 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.
8.
9. A blood glucose value will be obtained, and a pre-meal bolus provided prior to dinner. Dinner will occur between 1700 - 1900h. 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 2100h. 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.
10. A blood glucose value will be obtained, and a pre-meal bolus is given prior to dinner. Dinner will occur between 1700 - 1900h.
11. An evening activity will occur from 1900 - 2100h.
12. 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 2100h. 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.
13. 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.
14. Overnight SMBG will be obtained if CGM lower than 70 mg/dL or higher than 300 mg/dL. If difference between SMBG and CGM is more than 20 %, CGM will be calibrated. If BG less than 80 mg/dL or more than 300 mg/dl, glycemic treatment protocol will be follow.
15. At the conclusion of the study, a brief questionnaire (Appendix A-11) asking subjects about their experience with the AP system equipment will be provided to subjects.

Meals

1. Breakfast will occur between 0800 - 0900h.
2. Lunch will occur between 1200 - 1300h.
3. Dinner will occur between 1700 - 1900h.
4. Snacks will be provided at approximately 1430h and 2100h.
5. For the first 24-48 hours, all meal boluses will be supervised by research staff as subjects become more familiar with the interface of the equipment.
6. An insulin bolus is given before all meals and snacks, per the subject's parameters.

Equipment Specifications

1. All study equipment including the android phones, computers, insulin pump, and CGM will use international standard notation of 24-hour clock as a reference.
2. Upon activation of the AP system, it assumes control of the pump during both Pump Only mode and Closed-loop control. The Roche Accu-Chek Aviva glucometer is paired to the insulin pump while the AP system is inactive: the Tandem t:slim is not paired to a glucometer while AP system is inactive.
3. The subject will be trained to use the AP system interface; the training will continue approximately an hour, or until all questions are answered.
4. If a lapse in server connectivity exceeding 30 minutes is detected by the study staff to any AP device, a team member will be assigned to this subject to manually check the subject's status via the smartphone at intervals not exceeding 30 minutes until such time as connectivity is restored.
5. Devices will be charged overnight while subjects are sleeping.
6. All subjects will wear a physiological monitor such Fitbit or Bioharness, to collect additional information about movement and heart rate. The monitor can be removed during sleep and bathing.

Remote Monitoring

Staff will remotely monitor the subjects using the remote monitoring website. The AP system will stream de-identified encrypted data via Wi-Fi or 3G to a secure server. The research staff will be monitoring subjects in real-time. DWM will give an audible and visual alert when CGM readings below 80mg/dl or above 300mg/dl to alert study staff of the need of SMBG if this alarms are set off. It will also trigger if CGM signal is lost for more than 20 minutes or if study pump becomes disconnected

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

Once a fingerstick is obtained for any reason during the time that the AP system is active, Glycemic Treatment Guidelines (Appendix A-13) will be followed to determine timing of subsequent fingersticks.

- Scheduled times: SMBG levels will be measured prior to meals and snacks, before and after exercise,

and at bedtime (~22:00).

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

- Hypoglycemia Red Light Alarm on the AP system
- Hyperglycemia Red Light Alarm on the AP system
- Prior to calibration of CGM
- A subject or a study personnel may request any additional fingersticks as desired
- CGM readings below 80mg/dl or above 300mg/dl during the day.
- CGM readings below 70mg/dl or above 300mg/dl during the overnight (11p-7a).

Summary of subject's responsibilities who are randomized to the experimental group

- Subjects will wear the AP throughout the study.
- Subjects will obtain at least 7 SMBGs values and import these values into the AP system during the trial. SMBGs are collected prior to meals and snacks, before and after exercise and at bedtime.
- Subject will calibrate at least CGM twice daily.
- Subject or study staff will inform the AP of hypoglycemia treatment by activating a hypoglycemia treatment button after the rescue glucose treatment is consumed. Use of a temp basal rate will be permitted.

Summary of subject's responsibilities who are randomized to the control group

- Subjects will obtain at least 7 SMBGs values and import these values into the AP system during the trial. SMBGs are collected prior to meals and snacks, before and after exercise and at bedtime.
- Subjects will respond to CGM alarms as indicated, study staff will be closed by if subject does not attend to alarms. During the night CGM receivers will be placed outside the rooms for study staff to respond to the alarms by performing fingerstick and executing glycemic treatment or calibration as needed.

Abbreviated Ski Camp

If a study team selects to run an abbreviated ski camp (less than 5 nights/6 days), the overnight lodging may be held an alternative site (i.e. hotel/research house) with the participants transported by shuttle to the ski lodge. All participants will wear the AP system during the entire trial. Ski instructors will be obtained from the lodge. If the ski camp is unavailable due to lack of snow, study subjects will participate in other sustained

activities (i.e. hiking). The study team will adhere to all other aspects of the clinical protocol. The DSMB will review data collected during this trial and will consider if it safe to use inControl at the Colorado ski camp. If the DSMB determines that inControl cannot be used at the Colorado ski camp, the team may revert to the previously approved DiAs platform to complete the trial.

Safety Monitoring / Risk Analysis

Safety Plan for Participants during Study:

- Study team members and Riding on Insulin staff will be present during the entire study, including skiing/snowboarding activities.
- Participants will be divided into groups based on skill level. Skiing/snowboarding instructors will be available during the entire week to provide you instructions on how to do these activities safely.
- Participants will wear ski equipment, including a helmet, during outdoor activities.
- Fingersticks will be performed before and after outdoor activities.
- There will be sporadic rest periods (i.e. ski lift) during the activity.
- The study team will be watching the screen remotely.
- The study doctor will be available for any clinical concerns.

Monitoring Procedures by Staff:

1. CGM values are updated onto the system every 5 minutes.
2. Study staff will be constantly monitoring the CGM and subject-entered SMBG values from the remote monitoring website. Field staff will be alerted when CGM <80 or >300 during exercise periods.
3. The Glycemic Treatment Guidelines (Appendix A-13) will be applied during both the Experimental and Control groups.
4. If CGM < 80 mg/dL during the day, SMBG will be performed every 15 minutes until above 100 mg/dL.
5. If CGM < 70 mg/dL during the overnight (11p – 7a), SMBG will be performed every 15 minutes until above 100 mg/dL.
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, the Glycemic Treatment Guidelines (Appendix A-13) will be applied Experimental and Control Admissions.
8. The AP trained technician will monitor the system during the entire admission.
9. Medical personnel and emergency supplies will be available on site.

Insulin Pump Risk:

Roche Accu-Chek Spirit Combo Insulin Pump is a FDA 510K Class II Medical Device (PMA Number K11135).

Tandem t:slim Insulin Pump is a FDA 510 Class II Medical Device (PMA Number K122361).

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

Accu-Chek Aviva Combo blood glucose monitor if Accu-Chek Spirit Combo Insulin Pump is used in trial.

Hypoglycemic / Hyperglycemic Risk:
Glycemic Treatment Guidelines (Appendix A-13) will be followed when throughout the clinical trial.

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 DexCom Continuous Glucose Monitor is labeled for single use only. The sensor (the component of the system that enters the skin) will be single use only. 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 subjects, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

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 subject 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's interface. The Accu-Chek Spirit Insulin Pump will be reused after cleaning adhering to hospital protocol as described below. All infusion set equipment will be single subject use only (infusion set insertion kits, tubing, cartridges etc.) The Tandem t:slim pump will also be cleaned per hospital protocol and reused between subjects. All infusion set equipment and glucometers will be single subject 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.

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. The subject will be given a contact sheet containing phone numbers for the study team to call with any questions 24 hours per day.

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.

Insulin Pump Training:
The training with the study insulin pump is part of the AP system training (below) and will occur with a qualified clinical member of the study team. While the AP is active, the subjects' interactions with the study pump will be carried out through the graphical user interface (GUI). Other pump-related topics that are not covered by the AP will be discussed, including but not limited to: temporary basal rates, bolus calculator function, administering extended bolus, insulin action duration, bolus increment, low reservoir warnings / alarms, auto off function, and changing the pump. The study team will confirm that all questions have been

answered and that the subject has understood the training.

AP System Training:

The AP system training will occur with a qualified clinical member of the study team. Working interactively with the AP, the subject will be instructed how to navigate the GUI. The subject's basal rates and pump parameters will be confirmed at this time. To minimize risk associated with the use of the AP system:

- The AP system 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 GUI.
- The subject will be instructed how to access the CGM trace from the primary CGM via the AP system 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 inform the system of hypoglycemia treatment by activating a hypoglycemia treatment button after each ~16 grams of glucose is consumed.
- The subject will be assessed for understanding of the GUI and how to react to the traffic lights and 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 three similar adverse events 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:

1. Date and cause of the ending
2. Description of any serious adverse event
3. A subject who does not complete the protocol may be replaced or rescheduled.
4. 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.
5. 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:

1. Malfunction of the system or controller that imposes upon the safety of the subject
2. Hypoglycemic seizure or coma
3. Abdominal pain, vomiting or decreased conscious state
4. Pregnancy
5. Loss of sensor data acquisition for more than 6 hours
6. Loss of remote monitoring for more than 2 hours
7. More than one hypoglycemic event <50 mg/dL

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

1. Correction of a malfunction of the system or controller once the problem is clearly identified and the system has been repaired.
2. Resolution of first hypoglycemia 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.
3. Correction of hyperglycemia. System may be resumed when ketones are <0.6 mmol/L and the meter glucose is between 80-250 mg/dL.
4. Loss of sensor data acquisition for more than two hours.
5. If remote monitoring cannot be restored within 180 minutes, closed-loop control will be suspended until remote monitoring is restored.

Reason study stopped	**Resume/repeat admission?**
Equipment failure or similar related issue	Can resume
Hyperglycemic event that did not result in serious adverse event	Can resume
Hypoglycemic event that did not result in serious adverse event	Can resume
PI initiated discontinuation of study due to subject or equipment concerns	Can resume
Serious unanticipated adverse event deemed related to the study	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.

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-9.

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 AP 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 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. *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 Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	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
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

The coordination for all emergencies in Nelson County, VA begins with the 911 Center in Lovingston, VA. 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 a medical trained personnel involved in the clinical trial that will stay with the subject until is fully recovered. Wintergreen participants would be transported to the nearest medical facility. . Medevac helicopter service from UVa provides medical air transport from to the UVa Medical Center. Subjects at Breckenridge Ski Resort are usually transported to St. Anthony Summit Medical Center (10 miles) or emergency clinics in Breckenridge and Keystone, CO. In the event of serious injury, ambulance personnel coordinate with St. Anthony Hospital Flight for Life to airlift patients to the Denver area hospitals.

Endpoints

This study is an early feasibility study that will test the efficacy of the AP system - a *smart-phone-based system* compared to sensor augmented therapy in an outpatient setting. These studies would generate up to 100 days of closed-loop data and 100 days of SAP data. This sample size allows for subject withdrawal.

Study Outcomes

Primary Outcome

Primary outcome will be the percent time spent in desirable glycemic zone (70-180mg/dl) during the entirety of the camp.

Secondary Outcomes

1. % time spent <70 mg/dl and <60mg/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 more than 80% of the active study protocol. Subjects completing less than 80% of the protocol may be rescheduled.

Statistical Analysis Plan

Based on past similar studies (summer and winter camp in 2013, 2014, and 2015), we expect the primary outcome effect size to be approximately 1.1 (corresponding in our past data to a shift from 45-50% to 60-65% in range, with a group SD of approximately 10%). Accepting a significance at 0.05 and power of 0.9, this leads to a sample size of 19 in each group (control and treatment). As we intend to run two identical camps, the sample size chosen is 20 in each group (10 in each group for each camp), for a total of 40 subjects. This should lead to an a posteriori power >0.92.

SUPPLEMENTARY DATA

Supplementary Table 1. Demographics by site and treatment group

	VA		CO	
	RM-SAP	**CLC**	**RM-SAP**	**CLC**
	N=8	N=8	N=8	N=8
Age [years]	12.9 ± 2	13.3 ± 1.8	13.4 ± 1.5	13.1 ± 1.7
Gender (% female)	50%	50%	50%	38%
Height [cm]	162.4 ± 9.7	162.6 ± 14	161.3 ± 10.2	160.9 ± 7.9
Weight [kg]	57.6 ± 10	55.1 ± 10.9	54 ± 17	50.1 ± 8.4
BMI [kg^2/cm]	21.6 ± 2.2	20.7 ± 1.4	20.7 ± 4.8	19.1 ± 2.5
HbA1c [%]	8.2 ± 1.8	8.9 ± 2	8 ± 1.2	8.9 ± 1.1
TDI [U]	63.8 ± 21.8	61.8 ± 12.1	48 ± 21.1	46.2 ± 13.6
TDI per weight [U/kg]	1.1 ± 0.3	1.1 ± 0.2	0.9 ± 0.2	0.9 ± 0.2
T1D duration [years]	6.5 ± 3.1	7.3 ± 4	6.5 ± 4.2	5.6 ± 3.1
Pump use [years]	5.1 ± 3.2	6.4 ± 3	5.3 ± 2.8	3.3 ± 2.7
ski experience (% of experienced skiers)	13%	13%	100%	75%