PROTOCOL TITLE: A randomized, four-way, cross-over outpatient study to assess the efficacy of a dual-hormone versus insulin alone closed-loop system with exercise detection vs a predictive low glucose suspend system vs current care

STUDY SITE: Oregon Health & Science University
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FUNDING: National Institute of Health

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Background:

The risk of hypoglycemia in type 1 diabetes increases considerably during exercise. This risk stems from increased glucose utilization during exercise as well as increased insulin sensitivity both during and after exercise. As a result, hypoglycemia is a potential barrier to an active lifestyle for individuals with type 1 diabetes.

Closed-loop systems are an emerging technology that automate hormone delivery. They are quickly paving the way to revolutionize the treatment of type 1 diabetes. Several categories have emerged: dual-hormone (insulin and glucagon) closed-loop systems and closed-loop systems with insulin only, one variety of which is the low glucose suspend safety feature now available from Medtronic (MiniMed 530G with Enlite®). Already, the benefit of improved glycemic control compared to current open-loop pump therapy has been demonstrated in several trials. Our group has shown that a dual-hormone system effectively manages blood glucose in a clinic setting with great progress using glucagon to reduce hypoglycemic episodes (1-3). Clinical home studies using insulin only closed-loop systems have demonstrated improved overall glucose control without increasing the risk of hypoglycemia when compared to standard open-loop therapy (4, 5). Haidar recently completed a clinical study comparing bi- and single-hormone closed-loop systems and standard open-loop therapy. Their group found no difference in the proportion of time spent in the target glucose range with single vs double hormone closed-loop systems, however the number of hypoglycemic events was reduced using a dual-hormone approach to manage blood glucose (6). Danne has shown that sensor-augmented pump therapy with low glucose suspend reduces the frequency of hypoglycemia without compromising safety (7). The purpose of this study will be to further delineate the most effective approach towards engineering closed-loop systems.

Our most recent inpatient study, under review for publication, shows that adjusting insulin and glucagon delivery during closed-loop treatment after exercise announcement effectively reduces mean time glucose is below 70 mg/dl when compared to closed-loop control without adjustments. In order to prepare for a future home study, the ability to detect and grade physical activity to appropriately adjust system parameters is vital in helping to prevent exercise-induced hypoglycemia in the home setting.

The study described within this protocol is designed to test the efficacy of a new closed-loop algorithm for managing blood glucose in people with type 1 diabetes before and after exercise. The new algorithm will have 3 modes: a single hormone insulin only mode, a dual-hormone insulin and glucagon mode and an insulin only mode with predictive low glucose suspend. The first two of these modes use a Fading Memory Proportional Derivative (FMPD) model for dosing either insulin only or insulin and glucagon within an automated closed-loop system with insulin and glucagon delivery adjusting every 5 minutes based on sensor glucose data. The last mode delivers insulin using the subject's own basal profile(s) with a predictive low glucose suspend feature. The FMPD closed-loop algorithms include an exercise detection component that includes a reduction in insulin delivery upon exercise detection, with the dual-hormone system also increasing glucagon delivery upon detection. 3-axis accelerometry data as well as heart rate data will be collected using the Zephyrlife BioPatch. This data will be used in both FMPD systems to detect exercise and automatically trigger algorithm adjustments to reduce exercise-related hypoglycemia during and after exercise in individuals with type 1 diabetes. A Zephyr BioPatch will transmit heart rate and accelerometry values to the APC for the purposes of exercise detection while in the predictive low glucose suspend mode, but exercise detection will not trigger any hormone delivery changes while in this mode.

Specific Objectives:

Primary Objectives:

- To determine whether a dual hormone AP with an exercise detection algorithm out-peforms a single hormone AP using exercise detection, a low glucose suspend algorithm and current care as measured by frequency of hypoglycemia across all four arms in free-living conditions.
- To determine whether a dual hormone AP with an exercise detection algorithm out-peforms a single hormone AP using exercise detection, a low glucose suspend algorithm and current care as measured by percent of time with sensed glucose between 70 – 180 mg/dl across all four arms.

Secondary Objective:

- To determine whether a dual hormone AP with an exercise detection algorithm out-peforms a single hormone AP using exercise detection, a low glucose suspend algorithm and current care as measured by other glucose metrics across all four arms.

Study Hypothesis:

Our hypothesis is that use of a dual-hormone artificial pancreas that automatically detects exercise and adjusts dosing based on the exercise will reduce exercise-induced hypoglycemia compared with an insulin-only AP, a low-glucose suspend AP and current care.

Endpoints

Primary Endpoints:

1. Percent of time in hypoglycemia (CGM <70 mg/dL): across four arms
    - Period: entire study
    - Period: start of exercise in clinic until next meal

2. Percent of time in euglycemia (CGM 70-180 mg/dL): across four arms
    - Period: entire study
    - Period: start of exercise in clinic until next meal

Secondary Endpoints: (Time duration: Entire study)

1. Mean sensed glucose
2. Number of carbohydrate treatments
3. Percent of time with sensed glucose <50 mg/dl
4. Percent of time with sensed glucose >180 mg/dl
5. Number of events with capillary blood glucose (CBG) <70 mg/dl
6. Number of events with capillary blood glucose (CBG) <50 mg/dl
7. Total amount of insulin delivered (in units/kg)
8. Total amount of glucagon delivered (in mcg/kg)

Study Type

This is a single center, randomized, four treatment, crossover trial designed to compare the glucose control resulting from the use of (1) a dual-hormone closed-loop system with an exercise detection algorithm that adjusts insulin and glucagon dosing, (2) a single-hormone closed-loop system with an exercise detection algorithm that adjusts insulin dosing, (3) a predictive low glucose suspend system and (4) current care using the subject's own pump.

Study Population

Study population will be adults with type 1 diabetes, ages 21 – 45 years of age. Older subjects are excluded due to higher risk of unrecognized coronary artery disease. Younger subjects are excluded as it is appropriate to assess safety first in the adult population. Twenty one subjects will be recruited to participate in studies.

Power Analysis

We estimate that 21 subjects will allow us to detect an approximately 60% reduction from a mean of 11% of time in hypoglycemia during the four hours between onset of exercise and the next meal. We simulated data for three treatment conditions in two steps: First, we used a

random draw from a binomial distribution for the probability of having any hypoglycemic event; then, given that the event occurred, we generated total time in hypoglycemia with uniform probability from a minimum of five to a maximum of 90 minutes in multiples of five, which mimics the continuous glucose monitoring measurements. These simulated numbers allowed us to model time in hypoglycemia as a proportion of the total four hours of observation using a generalized linear model with a normal distribution and log link to constrain the estimates between 0 and 1. We used generalized estimating equations (GEE) with an exchangeable correlation structure and robust variance estimators to model the repeated observations on the same individual; we did not specify a correlation in the data generating phase, but partially randomized the data to induce a mild positive correlation. The assumptions for probability of any hypoglycemic event, minutes in hypoglycemia, percent of time in hypoglycemia, and correlation between repeated observations were informed by our previous study as well as other published work(6, 8). We repeated this simulation 500 times. We found a significant reduction in 80% of simulations at the 0.05 level of significance.

Protocol Summary:

Subjects will undergo four approximately 84 hour studies. The first day of each study will be an approximately 12 hour inpatient visit to include activities of daily living and an exercise period with 2 days spent as an outpatient. The subject will come back to the research center on the fourth day to complete another approximately 12 hour inpatient visit to include activities of daily living and an exercise period followed by removal of all devices. In randomized order, subjects will have glucose controlled using the following systems: 1) dual-hormone closed-loop system, 2) insulin only closed-loop system, 3) predictive low glucose suspend system and 4) a current care arm. Both of the closed-loop system algorithms have an exercise detection algorithm that uses inputs from a heart rate monitor and accelerometer, the Zephyrlife BioPatch. After exercise detection, insulin is turned off for the first 30 minutes, the total insulin infusion rate is adjusted by an exercise multiplier, and for the dual-hormone system, the target glucose for glucagon is increased along with the maximum dose of glucagon allowed. The predictive low glucose suspend system will utilize the patient's optimized basal rates, correction factor, and carb ratio. The patient will bolus for meals and hyperglycemia as usual under PLGS, but will have the additional safety net of the pump suspending insulin when it predicts a hypoglycemic event. The Dexcom CGM system will be used for all four arms. The Tandem t:slim pumps will be used for three of the intervention visits, the dual and single hormone arms and the predictive low glucose suspend arm. For the current care arm, subjects will use their own insulin and insulin pump.

Subjects will arrive at the CTRC at ~7am at the start of intervention visits. Subjects will eat breakfast, lunch and dinner in the research center. Subjects will eat breakfast at ~8:30am. After breakfast, subjects will complete activities of daily living (sitting on a chair, lying on a bed, washing dishes, sweeping the floor, etc.). Subjects will eat lunch at ~12pm. Subjects will exercise for ~45 minutes on a treadmill around 2pm. Subjects will eat dinner at ~6pm and be discharged. See **Figure 1** below. The subject will then go home for Day 2 and Day 3 and return on Day 4 to complete another 12 hour inpatient visit with the schedule of activities identical to Day 1.

Figure 1: Schematic of Inpatient Study Flow

During each study, the subject will wear one subcutaneous Dexcom™ G4 Share or G5 continuous glucose monitoring (CGM) system. (For the current care visit, the subject will use a blinded Dexcom G4 Share receiver or G5). The CGM system will provide sensed glucose data every 5 minutes. The accuracy of the sensed data will be obtained by reference measurements of capillary blood glucose. Sensed glucose data will be wirelessly transmitted from the Dexcom Share sensor receiver or G5 transmitter to the Nexus 5 master controller every five minutes. The controller for the dual and single hormone and predictive low glucose suspend modes is a Google Nexus 5 phone. The Dexcom Share sensor receiver or G5 transmitter and smart phone will communicate wirelessly via Bluetooth Low Energy (BTLE). The smart phone will wirelessly communicate via BTLE to either a single t:slim pump for insulin delivery or two t:slim pumps, one used for automated insulin delivery and one for automated glucagon delivery.

A study investigator or nurse practitioner will be present for study start-up, be on campus and immediately available via page during both exercise periods completed at OHSU. At all other times, the study investigator will be on call. Other personnel on site during the inpatient portion of the intervention visits will be a registered nurse and a study coordinator. The study investigators also retain the authority to modify any aspects of the protocol at his/her discretion if he/she believes the subject's safety is a concern.

Subject Criteria

Inclusion Criteria:

1. Diagnosis of type 1 diabetes mellitus for at least 1 year.
2. Male or female subjects 21 to 45 years of age.
3. Physically willing and able to perform 45 min of exercise (as determined by the investigator after reviewing the subjects activity level)
4. Current use of an insulin pump.
5. Lives with another person age 18 or older who will be present while subject exercises at home and that can attend the training on using the system with subject.

6. Lives within 20 miles of OHSU.
7. A1C<10%
8. Willingness to follow all study procedures, including attending all clinic visits.
9. Willingness to sign informed consent and HIPAA documents.

Exclusion Criteria:

1. Female of childbearing potential who is pregnant or intending to become pregnant or breast-feeding, or is not using adequate contraceptive methods. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence.
2. Any cardiovascular disease, defined as a clinically significant EKG abnormality at the time of screening or any history of: stroke, heart failure, myocardial infarction, angina pectoris, or coronary arterial bypass graft or angioplasty. Diagnosis of 2nd or 3rd degree heart block or any non-physiological arrhythmia judged by the investigator to be exclusionary.
3. Renal insufficiency (GFR < 60 ml/min, using the MDRD equation as report by the OHSU laboratory).
4. Liver failure, cirrhosis, or any other liver disease that compromises liver function as determined by the investigator.
5. Hematocrit of less than or equal to 34%.
6. Hypertensive subjects with systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg despite treatment or who have treatment-refractory hypertension (e.g. requiring four or more medications).
7. History of severe hypoglycemia during the past 12 months prior to screening visit or hypoglycemia unawareness as judged by the investigator. Subjects will complete a hypoglycemia awareness questionnaire (included in Appendix). Subjects will be excluded for four or more R responses.
8. Adrenal insufficiency.
9. Any active infection.
10. Known or suspected abuse of alcohol, narcotics, or illicit drugs.
11. Seizure disorder.
12. Active foot ulceration.
13. Severe peripheral arterial disease characterized by ischemic rest pain or severe claudication.
14. Major surgical operation within 30 days prior to screening.
15. Use of an investigational drug within 30 days prior to screening.
16. Chronic usage of any immunosuppressive medication (such as cyclosporine, azathioprine, sirolimus, or tacrolimus).
17. Bleeding disorder, treatment with warfarin, or platelet count below 50,000.
18. Allergy to aspart insulin.
19. Allergy to glucagon.
20. Insulin resistance requiring more than 200 units per day.

21. Need for uninterrupted treatment of acetaminophen.
22. Current administration of oral or parenteral corticosteroids.
23. Any life threatening disease, including malignant neoplasms and medical history of malignant neoplasms within the past 5 years prior to screening (except basal and squamous cell skin cancer).
24. Beta blockers or non-dihydropyridine calcium channel blockers.
25. Current use of any medication intended to lower glucose other than insulin (ex. use of liraglutide).
26. Diagnosis of pheochromocytoma, insulinoma, or glucagonoma, personal or family history of multiple endocrine neoplasia (MEN) 2A, MEN 2B, neurofibromatosis or von Hippel-Lindau disease.
27. History of severe hypersensitivity to milk protein.
28. Current use of any medication with strong anticholinergic properties, such as antihistamines, sleep aids, and antidiarrheal medications.
29. Current use of indomethacin.
30. Conditions that may result in low levels of releasable glucose in the liver and an inadequate reversal of hypoglycemia by glucagon such as prolonged fasting, starvation or chronic hypoglycemia as determined by the investigator.
31. A positive response to any of the questions from the Physical Activity Readiness Questionnaire with one exception: subject will not be excluded if he/she takes a single blood pressure medication that doesn't impact heart rate and blood pressure is controlled on the medication (blood pressure is less than 140/90 mmHg). See Appendix B.
32. Any chest discomfort with physical activity, including pain or pressure, or other types of discomfort.
33. Any clinically significant disease or disorder which in the opinion of the Investigator may jeopardize the subject's safety or compliance with the protocol.

Subject Recruiting:

Subjects will be recruited from OHSU clinics, from flyers to be posted in approved places at OHSU or posted on the web to the clinical trials page for the OHSU Schnitzer Diabetes Clinic, to the Clinic's facebook group, electronic newletter or from the OHSU Subject Recruitment website. Handouts will also be made available to the Juvenile Diabetes Research Foundation staff based in Portland and faculty at Providence and Legacy to pass along to patients/participants who show interest in the study. Records from OHSU Schnitzer Diabetes Clinic patients may be screened to find potential subjects. Subjects will also be recruited from a list of subjects who participated in past OHSU studies who have agreed to be contacted regarding future studies involving Drs. Castle or El Youssef, from the OHSU diabetes research registry and/or www.clinicaltrials.gov. Non-english speaking subjects will not be recruited since this protocol would require the use of medical devices and mobile software that do not have non-english versions available.

Up to 50 subjects may be screened in this study. Goal enrollment is 21 subjects. Up to four subjects will be replaced if needed, with a total enrollment of up to 25 subjects.

Withdrawal Criteria

The subject may withdraw at will at any time or at the discretion of the Investigator.

A subject must be withdrawn if the following applies:

1. Hypoglycemia during the treatment period posing a safety problem as judged by the investigator.
2. Hyperglycemia during the treatment period posing a safety problem as judged by the investigator.
3. Protocol deviation that is related to patient safety as judged by the investigator.
4. Substantial and repeated non-compliance with trial procedures.
5. Pregnancy.
6. Intention of becoming pregnant.
7. Persistent nausea and/or vomiting thought to be secondary to glucagon.
8. Seizure or unconsciousness associated with hypoglycemia.

Visit Procedures

Screening (Visit 1)

Screening will take place within 12 weeks prior to the 2 week run-in period (Visit 2). All screening visits will take place at OHSU's Oregon Clinical Translational Research Institute (OCTRI) outpatient clinic or at the Harold Schnitzer Diabetes Health Center. VO_{2max} testing will take place at the Human Performance Lab, which is located within OHSU and is attached to the main hospital. A code cart is on site within the Human Performance Lab and a code team is available by page at all times. Subjects will be asked to fast before the screening visit for 3 hours. Upon arrival and prior to any procedures, the consent form will be signed. A copy of the consent/authorization form will be given to the subject. The original will be kept for the source document. A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter and recorded after consenting. Prior to measurement of any blood samples, the meter will undergo quality control testing with two different glucose levels, one high and one low, and both values must fall within the accepted range for a meter to be used. After the CBG is obtained, the study investigator may adjust the subject's basal insulin rate as necessary in preparation for VO_{2max} testing to avoid hypoglycemia.

Study personnel will review medical history, and medications. Height, weight, pulse, and blood pressure will be obtained. A study investigator will perform a physical examination, excluding breast and pelvic exams. Females of child-bearing potential will take a urine pregnancy test, which must be negative to participate. A venous blood sample will be taken for the following tests: hemoglobin A1C, complete blood count, complete metabolic set (including creatinine, liver set, and electrolytes). In addition, for subjects with signs and symptoms suggestive of pheochromocytoma, fractionated plasma metanephrines will be measured. An EKG will be performed. A study investigator will assess inclusion/exclusion criteria and review the subject's medical record for clarification as needed. A three-digit subject ID number will be assigned to the subject. Subjects will undergo VO_{2max} testing at the end of the screening visit if all inclusion criteria are met, and no exclusion criteria are met, with the exception of blood test results which

will not be immediately available. A study investigator will be present for the entire VO_{2max} testing procedure. Additional CBG samples will be taken immediately before and after completion of the VO_{2max} test. Subjects will be given juice and the VO_{2max} test will be delayed by approximately 1 hour for CBG values of <80 mg/dL. Subjects will be given 15-20 grams of carbohydrates for CBG values of <70 mg/dL at any point during the screening visit. CBG values will be reviewed by an investigator and subjects will be provided with a snack after VO_{2max} testing as needed to avoid post-testing hypoglycemia. Subjects that screen fail by meeting any of the exclusion criteria prior to proceeding to the VO_{2max} test will not complete the VO_{2max} test.

Two Week Run-in Period (Visit 2)

The two week run-in period will take place within 6 weeks prior to the first 84 hour treatment visit (Visit 3). After arrival at the OHSU OCTRI outpatient clinic or Harold Schnitzer Diabetes Health Center clinic, women of childbearing potential will receive a urine pregnancy test. This test must be negative before further participation is allowed. Subjects will receive training during this visit on the following: the t:slim pump and the Dexcom G4 or G5 CGM system.

A certified t:slim pump trainer will instruct each subject on how to use the Tandem t:slim insulin pump, adjust their basal, give meal boluses and corrections and change out the cartridges and infusion sets. Subjects will also be shown how to connect the t:slim pump to the Nexus 5 smart phone via Bluetooth. The time required for this training will vary, depending on the experience of each subject, but will be sufficient to help him/her become comfortable using the t:slim pump and changing out the infusion set. If the subject experiences difficulties using the t:slim pump during this two week run in period, study staff will be available to educate and support this transition by phone. Subjects will switch back to using his/her own insulin pump at the end of the two week run in period. Subjects may be asked to bring back devices after the two week run-in period is complete.

Subjects will receive training on how to use and calibrate the Dexcom G4 Share or G5 CGM system including changing out the sensor every 7 days. The wire glucose sensor is sterile and commercially available from Dexcom™ and will be used for single use only as directed by the manufacturer. Subjects will be trained to insert the sensor into the subcutaneous tissue of the abdomen or flank after appropriate preparation of the abdominal skin as per the manufacturer's directions. The Dexcom G4 Share or G5 CGM system will be calibrated at home according to the manufacturer's directions. Subjects will be clearly instructed to use capillary glucose levels, not sensed glucose values, for the purpose of managing their diabetes at home. Subjects will be given a Dexcom G4 Share receiver and transmitter or G5 transmitter and sensors to insert the day before each treatment visit along with a Contour Next meter for measuring their capillary blood glucose in order to calibrate the Dexcom Share sensor receiver or G5. Subjects will be instructed to completely avoid acetaminophen for all periods when wearing the Dexcom CGM system. Additionally, subjects may be asked to wear an ActiGraph wGT3X-BT or ActiGraph GT9X activity watch.

84 hour Treatment Visits (Visits 3-6)

The subject will be asked to check his/her CBG before driving to the clinic and to bring a snack in the car in case hypoglycemia does occur (in which case, the subject must park and treat the

hypoglycemia). After the first treatment visit, the washout period will be 7 to 45 days calculated from the day of admission to the research center until the start of the next admission. Subjects will be asked to avoid vigorous activity within the 24 hours prior to all treatment visits. The subject will arrive at the research center at approximately 7am.

A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter and recorded. A new meter will be used for each subject. When they arrive, subjects will be given 15-20 grams of oral carbohydrate if the CBG reading is less than 70 mg/dl. CBG values > 300 mg/dl will be managed at the discretion of the investigator with a correction bolus. Serum ketones will also be checked. If serum ketones are ≥ 0.6 mM, the study will be rescheduled and insulin therapy will be guided by the onsite investigator.

During each treatment visit, glucose will be controlled using either: 1) the single hormone insulin only mode 2) the dual-hormone insulin and glucagon mode, 3) the insulin only mode with predictive low glucose suspend or 4) current care using subject's own insulin pump. The first 12 hours of the visit will be conducted in the OCTRI inpatient research unit, the Harold Schnitzer Diabetes Health Center or the Medicine Specialties clinic. The subjects will then go home for the remainder of the intervention period, returning on the fourth day to one of these locations for the last 12 hours of the visit. A code cart is on site at all locations and a code team is available by page at all times. .

Inpatient Visit on Day 1 (12 hours)

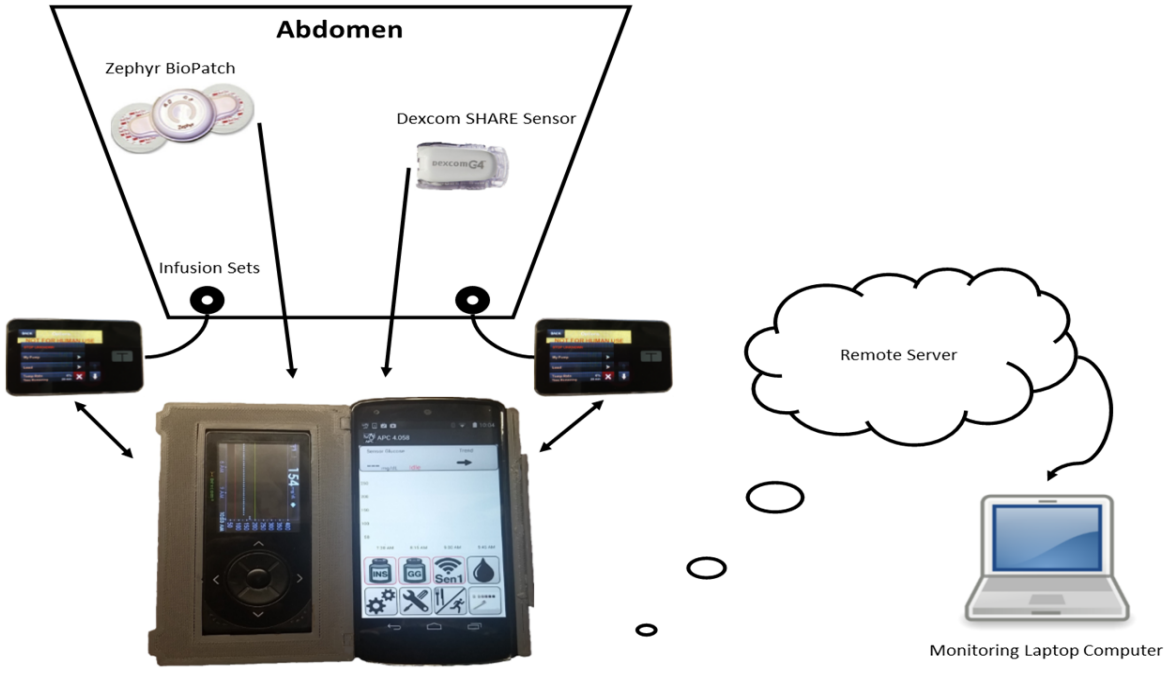
IV placement for dual-hormone insulin and glucagon mode study visit only

An 18-22 gauge IV catheter will be placed for the inpatient portion of one closed-loop intervention visit (dual-hormone closed-loop studies). The IV cathether will be placed at least one hour before noon. Starting at noon, blood samples for pharmacokinetic analysis of insulin and glucagon levels will be collected every 15 minutes until discharge from the unit at 7pm. Normal saline will be infused at a rate of ~25 ml/hr to keep the IV catheter patent. It is possible that the IV catheter will not remain patent for the entire 7 hours, it which case another will be placed. In a blood-sparing technique, venous blood will be withdrawn from the IV catheter using a double stop-cock method. One side of the stop-cock is used to pull ~ 5 mL of saline-blood admixture. The other side of the stop-cock is used to pull approximately 2 ml for collection with the saline-blood admixture re-infused after collection. Heat will be applied to an IV catheter site as needed to facilitate blood withdrawal. There will be up to 28 samples drawn during the course of the study with approximately 2 mL per draw, for a total of ~56 ml of blood per study. The visit requiring an IV will occur at the OCTRI inpatient research unit.

A t:slim infusion pump (Tandem® Diabetes Care) will be filled with aspart insulin for three of the four studies (excluding the current care arm), but the dual-hormone study will also have a t:slim pump filled with glucagon. The subjects will be instructed to remove his/her own infusion set/pump once study insulin is being delivered. Each pump will be labeled with a sticker indicating either "insulin" or "glucagon" for clear identification. A glucagon hypokit (GlucaGen, Novo-Nordisk) will be reconstituted with sterile water to a concentration of 1.0 mg/mL. The pumps will be primed and infusion sets inserted into the skin of the subject's abdomen or flank as directed by the manufacturer. Glucagon will be replaced every 24 hours. The subject will also

wear a Zephyr heart rate monitor and accelerometer. For male subjects, two small areas may be shaved on either side of the sternum to allow proper placement of the Zephyr. Additionally, subjects may be asked to wear an ActiGraph wGT3X-BT or ActiGraph GT9X activity watch. The ActiGraph will be used in addition to the Zephyr to collect heart rate and activity data. The Actigraph will not be connected to the APC system. See **Figure 2** below for a diagram of the system design.

Figure 2: Closed-loop Study Design



Google Nexus 5 controller running APC with Dexcom SHARE Receiver, Zephyr Biopatch, and Tandem t:slim insulin and glucagon pumps

The research staff will initialize the system and begin the closed-loop study. With the oversight of study staff, the subject will perform a CBG measurement and use this measurement to calibrate the glucose sensor at the start of the closed-loop study. The subject will be given an ample supply of Contour Next BG strips as well as supplies to change the insulin and/or glucagon reservoir. The study investigator will then depart the subject's room at the research center but remain on call.

During the 12 hour inpatient visit, study staff will complete a training with each subject and his/her companion on using the Zephyr BioPatch heart rate and accelerometer and how to use the Nexus 5 controller user interface which includes: entering meals, carb treatments, blood glucose values and ketone levels, addressing alarms, troubleshooting the devices connection to the phone via Bluetooth, and pausing the study. The subject will need to demonstrate competency in operating the system as well as having emergency contact numbers available before study staff leave the room. Subjects will also complete training on the proper reconstitution of the GlucaGen hypokit.

A study coordinator will be available at all times for the dual and single hormone and predictive low glucose suspend visits with the ability to monitor the APC remotely via a cloud system via the web in the event of any issues. The APC will generate alarms on the smartphone as required. If the subject does not appropriately respond to the alarm in the alotted timeframe, the coordinator will be alerted (see Appendix D). At that time, the coordinator will pull up the web-based monitoring system. An investigator will be assigned to serve as a back-up to the coordinator, and will also be available on call at all times during these three visits. The study investigator and technician may intervene with a telephone call or a personal visit at any time. For example, staff will call to remind the subject to calibrate the sensor.

During the dual and single hormone and predictive low glucose suspend visits, sensed glucose data will be wirelessly transmitted via BTLE from the Dexcom Share sensor receiver or G5 transmitter to the Google Nexus 5 phone every five minutes. The algorithm will run on the Google Nexus 5 phone (predictive low glucose suspend, insulin only closed-loop or insulin and glucagon closed-loop). The smart phone will wirelessly communicate via BTLE to a t:slim pump to drive insulin delivery, and in the case of the dual-hormone closed-loop system, will also communicate with a second t:slim pump for automated glucagon delivery.

During normal operation, the sensor will be calibrated approximately every 12 hours. If at any time that the study staff determines that a sensor can no longer be used, a new sensor will be inserted, which will be calibrated after two hours and then used to run the closed-loop system.

In order to ensure safety and to assess sensor accuracy, the subject will be asked to check their blood glucose four times during the day (typically before meals and at bedtime). The subject will be able to check his/her capillary blood glucose more than 4 times a day if they feel they need to. Subjects will also be asked to check capillary blood glucose immediately before exercise and when exercise is completed. If the subject's blood glucose is < 70 mg/dl or is experiencing symptoms of hypoglycemia, he/she will be instructed to treat with 15-20 grams of carbohydrates and repeatedly check blood glucose every 15 minutes until greater than 70 mg/dl. Fruit juice and glucose tablets will be available for rescue treatment. The study investigator retains the authority to check blood glucose at more frequent time points at his/her discretion.

All alarms, including if sensor glucose is <70 mg/dL without exercise detection, will be populated on the smartphone. If the subject does not appropriately respond to the alarm in the alotted timeframe, the coordinator will be alerted (see Appendix D). At that time, the coordinator will pull up the web-based monitoring system. A study coordinator will be available at all times for the entire duration the subject is on the closed-loop system. An investigator will be assigned to serve as a back-up to the coordinator, and will also be available on call at all times during the closed-loop intervention visits. The study investigator and technician may intervene with a telephone call or a personal visit at any time. If the subject cannot be reached and sensor glucose is below 50 mg/dl, the emergency contacts provided by the subject will be contacted. If the alert is still unserviced and study staff are unable to reach the subject or either of the emergency contacts, emergency medical services will be contacted. To facilitate this, the Nexus 5 phone will

track the subject's location and push GPS coordinates to the cloud server every 10 minutes. Cloud coordinates will be pushed with a known, fixed offset to allow for scrambling.

Subjects will eat a normal breakfast at ~8:30am after admission. Subjects will complete activities of daily living. These activities may include:

1) sitting on a chair or lying on a bed,
2) washing dishes or folding laundry,
3) sweeping the floor or vacuuming,
4) organizing a room or adjusting furniture in a room,
5) scrubbing the carpet or the walls and/or
6) going up and down flights of stairs.

Each activity will be performed between 5-15 minutes. Subjects will perform the activities in the OCTRI inpatient unit, Harold Schnitzer Diabetes Health Center or Medicine Specialities clinic or at the Point of Care Lab in the Biomedical Engineering department at the CHH.

Subjects will eat lunch at ~12pm. Subjects will warm-up for 5 minutes then exercise for approximately 45 minutes on a treadmill at ~2pm. Subjects will exercise at the CTRC. A code cart is on site within the unit and a code team is immediately available by page at all times. For subject safety, capillary blood glucose must be 80 mg/dl or higher to begin exercise. Subjects will exercise at a fixed intensity level to a target heart rate (±10%) based on the heart rate achieved at 60% of their VO_{2max} determined at screening. This protocol will allow the exercise to be graded according to each participant's relative capacity. The speed and grade of the treadmill will be adjusted by trained research personnel with a goal of keeping participants within their target heart rate range for the entire 45 minutes.

During the exercise period, there will be defined rules for stopping exercise, including:

1) If the subject feels unwell,
2) If the subject develops hypoglycemic symptoms, such as excessive sweating, shaking/tremors, palpitations, feelings of dread or panic, light-headedness, nausea, difficulty concentrating or the like,
3) If the subject develops chest pain/pressure,
4) If the subject develops undue shortness of breath (SOB),
5) Signs of poor perfusion: light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin
6) If the maximum heart rate of the subject (MHR) is exceeded,
7) For patient preference.

If the exercise is stopped prematurely, the duration of exercise will be noted by the study staff and if the subject is deemed safe to participate in future studies, the exercise will be stopped after that same time duration for subsequent studies. For subject safety, if capillary blood glucose is < 70 mg/dl at any point during the exercise period, the subject will consume 15 g of carbohydrates and delay completion of exercise until blood glucose raises above 80 mg/dl. Since insulin will be turned off briefly, exercise will be delayed for subjects with ketones above 0.6 mM to minimize hyperglycemia until levels drop below this threshold.

Subjects will eat dinner at around 6pm. After dinner, the subject will be discharged from the inpatient unit to continue the study at home.

During normal operation, the sensor will be calibrated approximately every 12 hours. The sensor will also be recalibrated if the sensor becomes inaccurate. An inaccurate sensor is defined as either (1) a sensor whose value is 35% or more different than a CBG when the CBG is greater than or equal to 75 mg/dl or (2) when a sensor is more than 30 mg/dl different than a CBG when the CBG is less than 75 mg/dl. Subjects will be advised not to calibrate if his/her glucose is rising or falling rapidly (greater than 2 mg/dl/min) or after administering oral carbohydrates. Additional calibrations may be ordered at the discretion of the investigator on call.

For subject safety, if a sensor value is not available or communication with the insulin pump is lost for more than 20 minutes, the insulin t:slim pump will begin insulin delivery according to a pre-set basal profile(s) inputted for the subject at study start. When this occurs for a lost sensor, the APC system will also activate the predictive low glucose suspend feature if the last known sensor value was within the range of 70-140 mg/dl and predicted to fall below 90 mg/dl within thirty minutes or if the sensor glucose is less than 70 mg/dl. Maximum suspension time is 2 hours. Prediction of sensor glucose is based on linear regression of the prior ten minutes of sensor glucose data. When communication with the pump or sensor is restored, system will automatically resume, updating the IOB accordingly.

We are aware that there is a risk of true hypoglycemia occurring in the periods of time between blood glucose checks. For this reason, if the sensed glucose values fall below 70 mg/dl, the system will prompt the subject to obtain a capillary blood glucose sample. Daytime glucose target is 115 mg/dl (nominal) with nighttime target increased to 140 mg/dl (nominal) to account for sensor drift.

Meals will be announced to the controller. For each meal during the inpatient study, food items will be self-selected from the hospital menu. The number of grams of carbohydrates will be counted by the subject and entered in the controller. Immediately before eating, each subject will receive approximately 60% (nominal) of his/her typical pre-meal insulin dose based on their insulin to carbohydrate ratio. The same self-selected meal will be offered on subsequent inpatient visits, and in the event a particular food item is not available, a different item with a similar amount of carbohydrate will be provided.

Subjects will wear a Zephyrlife BioPatch monitoring device for collecting heart rate and accelerometry data. The Zephyr transmits this data to the Nexus 5 master controller via Bluetooth. The APC system will convert the heart rate and accelerometry data into an estimated energy expenditure to determine if the subject is exercising. Energy expenditure (EE) is estimated every minute using a time series approach. This time series model uses the inputs of heart rate (HR) and physical activity (PA). The EE estimation is further personalized by incorporating anthropometric characteristics of the individual. If the communication is not

working between the Zephyr and the Nexus 5 at the time of exercise during a visit, exercise may be delayed until communication is restored.

The exercise threshold will be set to 4 METs/min for every subject at the start of the study. If the corrected MET value is greater than 4 METs for a period of 5 consecutive minutes during the first exercise period, exercise is considered to be ongoing. An exercise dosing adjustment algorithm will be used when exercise is detected that has been previously tested and published (9) When exercise is detected while in single or dual-hormone mode, and the subject confirms he/she is exercising, insulin will be turned off for 30 minutes (nominal) immediately after detection of exercise. Subsequently, the insulin infusion rate will be reduced to 50% (nominal) for a period of 1 hour (nominal). During use of the dual-hormone closed-loop system, the glucagon set point during exercise will also be set higher to 110 mg/dl (nominal). This will result in glucagon being called for at an earlier point with an increase in the amount of glucagon delivered. Also, the maximum amount of glucagon allowed to be delivered in a 50 minute time period will be increased by double, which will allow for more glucagon to be delivered during and immediately after exercise if glucose levels are dropping rapidly. The maximal amount of glucagon that can be delivered in a 24 hour period will remain unchanged. These adjustments will continue during the same period of time that insulin adjustments are being made (nominal 1.5 hours) after exercise. After the initial adjustment in glucagon target, the investigator will evaluate the subject's response to glucagon during exercise and may change the target further, within the range of nominal values, based on whether the subject still went hypoglycemic (< 70 mg/dl) or hyperglycemic (>180 mg/dl) within 3 hours from the start of exercise.

With regards to the daytime and nighttime glucose target, % of premeal insulin bolus and exercise insulin and glucagon adjustment parameters: these are current nominal values that may be adjusted within the FDA approved minimum and maximum range for each adjustable parameter.

During predictive low glucose suspend mode, a Zephyr BioPatch will transmit heart rate and accelerometry values to the APC for the purposes of exercise detection, but exercise detection will not trigger any changes in insulin delivery while in this mode.

We are aware that there is a risk of hyperglycemia if the subject stops exercising after a short time with continued adjustments to insulin or insulin/glucagon. Therefore, an exercise cancellation option is available on the user interface for up to 30 minutes after the start of exercise that will revert insulin and glucagon parameters to their nominal values. If exercise is not detected by the algorithm when the subject is actually exercising, an exercise announcement button on the APC user interface will be used.

The exercise detection algorithm will prompt the participant if exercise is occurring prior to adjusting dosing. For example, if the participant's METs exceed a threshold of 4 METs, the AP will detect this and ask the participant if they are excercising. If the participant acknowledges this and says "Yes", the AP will adjust the dosing. If the participant says "No", this is considered a false alarm because the algorithm has detected exercise, but the participant was not actually exercising. Because these false alarms can be annoying to the participants, the AP

includes an adjustable exercise detection threshold. The adjustable exercise detection threshold works as follows:

- At the start of the study, the participants' exercise detection threshold will be set to 4 METs.
- On the first day of the study, when the participant exercises at the hospital, the AP records the participants' METs during exercise and also records the participants' METs during activities of daily living and other non-exercise events.
- Based on data from this controlled setting, a "lower bound MET" for that subject will be calculated based on a lower-bound confidence interval set around their METs recorded during exercise.
- If that participants' lower bound MET during exercise is greater than 4, their maximum allowable exercise threshold value (MAETV) will be set to the lower bound MET. Otherwise, the MAETV will remain at 4.
- Every time a false alarm occurs for detecting exercise, the participants' exercise detection threshold will increase by 0.25 MET. However, the exercise detection threshold will never exceed the MAETV described above.

The Fading Memory Proportional Derivative (FMPD) algorithm will determine the insulin and (when applicable) glucagon delivery rates for the closed-loop studies. The FMPD algorithm determines insulin and glucagon delivery rates based on proportional error, defined as the difference between the current glucose level and the target level, and the derivative error, defined as the rate of change of the glucose. Each of these errors is calculated over a time interval. The "fading memory" designation refers to weighting recent errors more heavily than remote errors. This weighting provides an adaptive component to the algorithm. In simple terms, the insulin rate is increased for high or rising glucose levels and glucagon is given for low or falling glucose levels (at times of impending hypoglycemia). Gain factors determine the degree to which proportional or derivative errors lead to changes in hormone delivery rates. There are separate gain factors for proportional and derivative error for both insulin and glucagon. Positive proportional errors (glucose level above target) and positive derivative errors (rising glucose level) call for an increase in the insulin delivery rate.

When in predictive low glucose suspend mode, the system will deliver insulin based on the basal profile(s) entered for each subject. The subjects will manually enter in boluses for meals and corrections into the APC user interface. Using this system, the subjects will manage their blood glucose as they normally would. The advantage is that the system is integrated with a glucose sensor to give advanced diabetes control.

The predictive suspend feature will activate when the participants' glucose levels are in the range of 70-140 mg/dl and if sensor glucose is predicted to fall below 90 mg/dl within thirty minutes. The predictive suspend feature will deactivate within the range of 70-140 mg/dl if sensor glucose is predicted to rise above 120 mg/dl within thirty minutes. If sensor glucose falls below 70 mg/dl, insulin delivery will remain suspended. As long as sensor glucose is above 140 mg/dl, the predictive suspend feature will not activate. Prediction of sensor glucose is based on linear regression of the prior ten minutes of sensor glucose data. During the hours of 7am-11pm

(daytime), maximum time of suspension is 120 minutes within any 150 minute window. During the hours of 11pm-7am (nighttime), a maximum of 180 minutes of suspension time is allowed. During the predictive suspend mode arm of the study, subjects will not be allowed to change their insulin dosing prior to the start of the exercise. This is being done to allow for equal comparison of dosing and subsequent glucose control across the four arms.

The algorithm will push data up to a cloud server for that can be monitored remotely every 5 minutes for three visits, dual and single hormone and predictive low glucose suspend.

Current Care Arm Visit (1 Visit)
The study procedures for this visit are exactly the same as stated in the above protocol with the following exceptions: 1) the closed-loop system will not be used to manage blood glucose, 2) subjects will use their own insulin pump and insulin, 3) subjects will use his/her own sensor, if they typically use one, 4) subjects will wear a Dexcom G4 Share provided by the study with a blinded receiver or G5 with blinded glucose values, and 5) studies will not be remote monitored. The subject will continue to sample capillary blood glucose as stated above, but they will be able to check at other times if they feel they need to. The subject's blood glucose will be managed using insulin pump therapy on the subject's own insulin pump, contacting his/her provider with any questions or concerns. Subjects will wear the Zephyr Biopatch heart rate monitor for the duration of the study which will be transmitting data to the Nexus 5 smart phone controller. The subject's insulin pump will be downloaded after the current care arm visit. Subjects will be given a glucose and hypoglycemia reporting diary to complete during the visit. For subjects randomized to complete the current care arm as his/her last visit, the subject will be asked to come in to the Diabetes Health center for one additional visit in order to download the full data set from his/her pump.

Discharge from inpatient unit
At the completion of the inpatient visit, subjects will be discharged from the unit. Capillary blood glucose will be measured with two consecutive blood glucose measurements at least 15 minutes apart prior to discharge. Subjects will be given enough supplies to continue running the study while at home for 2 days. All IV catheters will be removed before discharge. Subjects will be given an exercise diary to record the specifics of his/her exercise on Day 3 at home. After the subject is discharged on Day 1, he/she will return home for Day 2 and Day 3 and return to OHSU on Day 4.

We are aware that there is a risk of severe hypoglycemia while the subjects are at home. The system will alarm if the sensed glucose values fall below 70 mg/dl without exercise detection and below 85 mg/dl with exercise detection,, prompting the subject to obtain a capillary blood glucose sample. Subjects will be required to live with at least one other person age 18 or older and live within 20 miles of OHSU. All subjects will provide two emergency contacts to study staff and will be given an emergency glucagon hypokit if they don't already have one.

In case of a system error that cannot be corrected immediately with the subject off campus, the subject will be able to to pause the APC system. Pausing will allow the tslim pump filled with insulin to begin basal insulin delivery for a pre-set basal profile(s) inputted for the subject at the

study start. If there is a pending meal bolus in the insulin back log, the pause mode will be delayed to allow the bolus to finish delivering. Subjects will be able to give meal boluses and corrections through the tslim insulin pump while in pause mode. When the error is resolved, the participant can exit pause mode and the closed loop system can be resumed. For subject safety, when the system resumes normal insulin delivery after being in pause mode, the system will not allow any boluses to be entered into the phone controller for 15 minutes so the APC can get the bolus history from the t:slim insulin pump. If the subject pauses the system, this will be visible on the cloud server and may prompt a telephone call from study staff to determine the issue and the best way to resolve it.

Subjects will be given sufficient blood glucose testing supplies, ketone testing supplies and infusion sets/cartridges for 2 days of closed-loop treatment at home as well as back up supplies. Subjects will continue to change out the glucagon every 24 hours. Whenever possible, subjects will be asked to have a second person verify the identity of the insulin or glucagon pump before changing out the cartridge/infusion set. Study staff will check in with the subject each morning. The subject may contact study staff at any time during the outpatient portion of the visit. Subjects will be asked to perform 45 minutes of an aerobic exercise of his/her choice (excluding swimming) on Day 3 while at home. Subjects will be reminded to check their blood glucose before and after exercise. For subject safety, capillary blood glucose must be 100 mg/dl or higher to begin exercise while subject is at home. Subjects will be required to have a person age 18 or older who attended a training session on the system present while the subject exercises at home. The companion will stay after the exercise until the subject's CBG is > 100 mg/dl or for 60 minutes after exercise is completed-whichever is longer.

Inpatient Visit on Day 4 (12 hours)

On the fourth day, subjects will return to the OCTRI inpatient clinic, the Harold Schnitzer Diabetes Health Center or the Medicine Specialties clinic at 7am. The procedures for the second inpatient visit on Day 4 are exactly the same as those on Day 1 with two exceptions: 1) the closed loop system will already be in progress, and 2) there will not be an IV placed during the dual-hormone closed loop study.

After completion of the visit, the single or dual-hormone closed-loop, predictive low glucose suspend system will be terminated and the subject's own insulin pump will be restarted. The study investigator will consult with the subject regarding appropriate insulin dosing for the remainder of the day. The HR monitors, infusion sets and Dexcom sensor will be removed from the subject. The infusion sites and sensor site will be inspected for signs of irritation or infection. In addition, the sensor will be inspected for the possibility of breakage or fracture. If there is any evidence of sensor breakage, it will be recorded. If an area of inflammation of 1 cm or greater exists around the point of insertion, a de-identified photograph will be taken of the area and the subject will return 1-3 days later for a follow-up visit. A capillary blood glucose value will be taken immediately prior to discharging the subject. Subjects will be given oral carbohydrate for values below 85 mg/dl, and will be given an insulin bolus if deemed appropriate by the study investigator for values above 150 mg/dl.

If a study visit is stopped prematurely, such as due to technical problems, the subject will be asked if they can repeat the study visit that was terminated early with additional compensation provided. Repeating the study visit will be optional.

If multiple subjects have inpatient visits on the same day, the times for admission, meals, exercise, daily activities and discharge will be moved ahead approximately one hour for the second subject. The timing of all procedures will remain consistent for all four visits for each subject.

Hypoglycemia Treatment Guidelines

- **CBG < 70 mg/dl**
  - Give 15 grams of oral carbohydrate.
  - Verify that insulin pump is turned off.
  - Repeat treatment every 15 minutes as needed to raise blood glucose ≥70 mg/dl.
- **Presence of STUPOR, LOSS OF CONSCIOUSNESS, or SEIZURE**
  - Give 1 mg glucagon SC.
  - Verify that insulin pump is turned off.
  - Further management per bedside study investigator.

Hyperglycemia Treatment Guidelines

If the sensed glucose is ≥ 300 mg/dl, the subject will be instructed to check their blood glucose and to check the insulin pump for malfunction. This would include checking for insulin leaks, making sure infusion site is securely adhered to skin, and for closed-loop studies, making sure there are no error messages on the phone running the algorithm.

If either the sensor or capillary blood glucose value is over 300 mg/dl for more than 2 hours or is ≥ 400 mg/dl at any time, the subject will be instructed to check serum ketones using the Abbott Precision Xtra meter and to change out the infusion set. If serum ketones are over 0.6 mM for two hours, the on call study investigator will instruct the subject to administer a correction insulin dosage by injection. In addition, the subject will be encouraged to drink sugar-free liquids. If serum ketones are above 1.5 mM at any time, the study will be stopped and insulin will be administered as directed by the on call investigator.

Cleaning and Disinfecting

All devices will be cleaned and disinfected between subjects. The smart phone, Dexcom G4 Share receiver and transmitter or G5 transmitter, heart rate monitors and t:slim pumps are cleaned by study staff. Technicians who are disinfecting units will wash hands thoroughly and wear gloves. All items will undergo intermediate-level disinfection using SANI-CLOTH AF3 Germicidal disposable wipes. The disinfectant will be applied and allowed to air dry. Technicians will dispose of gloves as biohazard waste and wash their hands immediately after completing disinfection. After disinfection, when the units are completely dry, they will be placed in a sealed bag labeled with the cleaning method, date and initials of technician that performed the disinfection.

Stopping Rules

The closed-loop study will be stopped and open-loop control will be resumed under the guidance of the on call study investigator if any of the following occur after the first 4 hours of the study: 1) capillary blood glucose falls to < 40 mg/dl at any time point, 2) capillary blood glucose exceeds 400 mg/dl on two occasions (60 min or more apart within a 4 hour window), 3) capillary blood glucose exceeds 400 mg/dl on two occasions more than 60 minutes apart but outside of the 4 hour window and during that time, the capillary blood glucose has not fallen below 250 mg/dl, or 4) serum ketones are above 1.5 mM at any time.

Statistical methods

Primary endpoint

The primary study endpoints are percent of time with sensed glucose < 70 mg/dl and percent of time with glucose sensor in target range of 70-180 mg/dl. The hypothesis to be tested is the dual-hormone closed-loop system with exercise detection reduces hypoglycemia and increases time spent in target range as compared to an insulin only closed-loop system, a predictive low glucose suspend system or current care. Data will be analyzed using generalized estimating equations, which takes into account correlated data and repeated measures.

Secondary endpoints

Secondary endpoints will be analyzed using generalized estimating equations. A Bonferroni-Holmes correction for multiple comparisons will be applied only to the secondary endpoint analyses.

Confidentiality and Protection of Human Subjects

RISKS and BENEFITS

Risks: The risks of the protocol procedures are considered minor. Nonetheless, since pumps and sensors used within automated glucose control systems are imperfect, there is a risk for hyperglycemia and hypoglycemia The single and dual-hormone mode studies will issue alerts and will be remote monitored during each visit with unserviced alerts being pushed to the study coordinator and investigator. If sensed glucose goes below 70 mg/dl or above 300 mg/dl for these studies, a capillary blood glucose check will be required A study investigator will be on call at all times. Though glucagon has been shown to be effective in avoiding hypoglycemia, it can sometimes cause nausea or vomiting when given in high doses, but is unlikely in the low doses that will be delivered under this protocol.

Risks from exercise include falls, sprains, bruises, very low risk of bone fractures and head trauma. The likelihood of significant harm is quite low.

Rarely, there can be allergic responses to insulin or glucagon, such as skin redness, hives, itching of the skin, swelling of the mouth, or breathing difficulties. These reactions are considered very unlikely.

There is a small risk of sensor fracture, and in such a case, a piece of the sensor could be left in the tissue after sensor removal. For this reason, the study investigator will inspect each removed sensor for the possibility of breakage or fracture. Any evidence of sensor breakage will be recorded and reported to FDA and the sensor company.

Benefits: The subject may not directly benefit from being in this study; however, their participation may help to advance automated insulin and glucagon delivery technology.

COSTS:
Subjects will receive $900 for completion of all study visits. If subjects withdraw early from the study, compensation will be given as follows: $60 for visit 2 and $210 each for visits 3, 4, 5 and 6. There is no compensation for the screening visit. If a subject is asked to repeat a study due to technical problems, yhe/she will receive an additional $210.

Monitoring Entity:

This investigation will be monitored by the principal investigators, Jessica Castle, MD and Peter Jacobs, PhD. Drs. Jacobs and Castle have no commercial interest in any of the companies which manufacture any of the devices used in this study. Dr. Castle is an inventor on patents regarding the algorithms.

Data Collection:

Subject privacy will be protected by using a three-digit identifying number to code study documents. Study staff will record data required by the protocol onto the Case Report Forms (CRF). Case report forms (CRF) for this study will be entered into REDCAP, a clinical research electronic data application designed to support traditional case report form data capture for research studies housed at Oregon Health Science University and administered by the Oregon Clinical and Translation Research Institute (OCTRI). Investigators and research coordinator will verify that the procedures are conducted according to the approved protocol. All paper source documents will be kept in a locked cabinet for a minimum of five years. Original, completed CRF's will be kept with the PI in a designated repository. All data from CRF's will subsequently be entered into the authorized electronic REDCAP database.

Recording of Data:

Investigators and staff will record data collected during the clinical trial on the CRF's. Case report forms (CRF) for this study will be entered into REDCAP, a clinical research electronic data repository housed at Oregon Health Science University and administered by the Oregon Clinical and Translation Research Institute (OCTRI). The REDCAP CRFs will include:

Screening form
Two Hour Run-in and Training Visit
APC Verification form

Day 1 Inpatient Dual-hormone Closed-loop Study Visit
Day 1 Inpatient Insulin Only Closed-loop Study Visit
Day 1 Inpatient Predictive low glucose suspend Study visit
Day 1 Inpatient Current Care Visit
Notes on Outpatient Visits
Day 4 Inpatient Dual-hormone Closed-loop Study Visit
Day 4 Inpatient Insulin Only Closed-loop Study Visit
Day 4 Inpatient Predictive low glucose suspend Study visit
Day 4 Inpatient Current Care Visit
Phone Update Form
Adverse Event form
Serious Adverse Event form
Concomitant Medications

The Principal Investigators may authorize other personnel to make entries in the CRF.

Monitoring Procedures:

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and amendments and clarifications adopted by the 29th (Tokyo, 1975), 35th (Venice, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, South Africa, 1996), 52nd (Edinburgh, 2000), 53rd (Washington, 2002), 55th (Tokyo, 2004), 59th (Seoul, 2008), and 64th (Brazil, 2013) General Assemblies. The investigator will ensure that the study described in this protocol is conducted in full conformance with those principles, the protocol, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IEC requirements relative to clinical studies.

Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual subject. The investigator will also ensure thorough familiarity with the appropriate use and potential risks of use of the study device, as described in this protocol, prior to the initiation of the study.

Unanticipated problems will be detected by reviewing descriptions of known or foreseeable adverse events and risks in the IRB-approved research protocol and the current IRB approved consent form, any underlying disease or conditions of the subject experiencing the adverse event, a careful assessment of whether the adverse event is related or possibly related to the subject's participation in the study.

Triggers for reporting unanticipated problems are seizure, hospitalization, death or any other occurrence considered serious by the PI. If ongoing monitoring of the closed-loop studies reveals studies repeatedly being terminated because of unresponsive hyperglycemia or repeated serious hypoglycemia (resulting in altered mental status, loss of consciousness, or seizure) believed not amenable to revisions in control system parameter tuning, then the study will be discontinued immediately. If studies in two subjects are stopped for severe hypoglycemia or severe hyperglycemia, then the entire study will be halted. In addition, if there is any unexpected event

such as death or patient hospitalization, the studies will be stopped until the root cause is evaluated.

Any adverse event (AE) and/or unanticipated problem (UP) will be reported to the investigator monitor immediately by one of the investigators. Hypo- and hyperglycemia will not be considered AEs unless subject has positive ketones or displays symptoms of hypoglycemia such as: loss of consciousness, slurred speech, hospitalization or EMS services called. One of the investigators will always be on-call during the closed-loop studies and will write up a description of the adverse event/unanticipated problem. All reportable new information (RNI) will be reported to the IRB within five calendar days after the PI learns of the event. RNI is any information that might meet the regulatory definition of an unanticipated problem involving risks to subjects or others or serious or continuing noncompliance that might impact the criteria for IRB approval. The report will be submitted to the IRB by the principal investigator or study coordinator. A summary of all UP's and adverse events, including those that do not meet the requirement for RNI, will be submitted with the continuing review. The FDA will be notified of any unanticipated adverse event related to the use of the study device. Notification will be made within 10 days after the Principal Investigator becomes aware of the event.

Confidentiality Procedures:

To protect confidentiality, standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures. Upon enrollment, subjects will be assigned with a three-digit code that will be used instead of their name, medical record number or other personally identifying information. The key associating the code and the subjects personnal identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive in a limited access folder.

Electronic files for data analysis will contain only the subject code. Access to data or blood samples is restricted to study personnel and requires OHSU ID/password authentication. Paper files will be stored in locked filing cabinets in restricted access offices at OHSU. Electronic data is stored on restricted drives on the OHSU network or stored on encrypted computers as well as on the web-accessible REDCap database housed on an OHSU secure server. User passwords will be changed every 3 months and a firewall will be enabled at all times. After the study, source documents will be maintained at the participating clinical center (or offsite record storage facilities) 2 years after a marketing application is approved for our group's artificial pancreas/decision support device or discontinuance of pursuit of marketing approval. At the end of the study, an electronic copy of the database will be provided on a CD for long-term storage under lock.

Appendix A: Physical Activity Readiness Questionnaire

Physical Activity Readiness Questionnaire (PAR-Q) and You

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly:

YES	NO		
☐	☐	1.	Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
☐	☐	2.	Do you feel pain in your chest when you do physical activity?
☐	☐	3.	In the past month, have you had chest pain when you were not doing physical activity?
☐	☐	4.	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5.	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	6.	Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
☐	☐	7.	Do you know of any other reason why you should not do physical activity?

If you answered:

YES to one or more questions

Talk to your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want – as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- Start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- Take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.

Delay becoming much more active:

- If you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- If you are or may be pregnant – talk to your doctor before you start becoming more active.

Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed use of the PAR-Q: Reprinted from ACSM's Health/Fitness Facility Standards and Guidelines, 1997 by American College of Sports Medicine

Appendix B: Devices

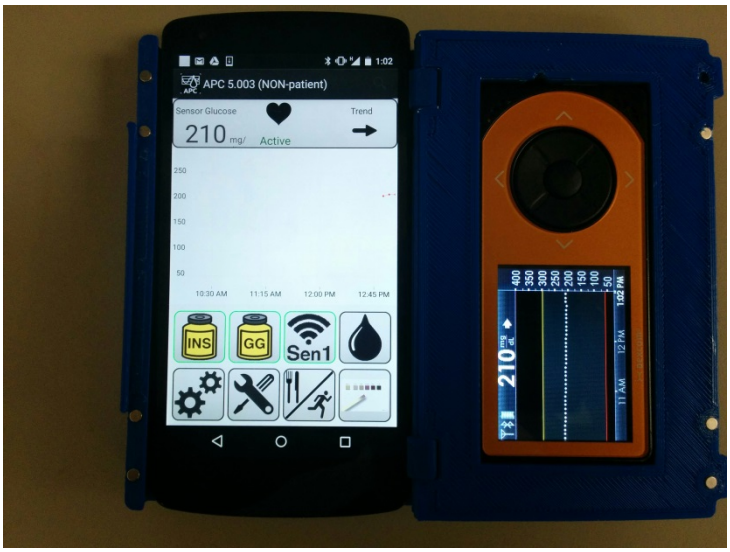
Tandem t:slim pump

Dexcom Share Continuous Glucose Monitoring System which includes Sensor, Sensor Receiver and Sensor Transmitter

Dexcom G5 Continuous Glucose Monitoring System

Google Nexus 5 Smart phone

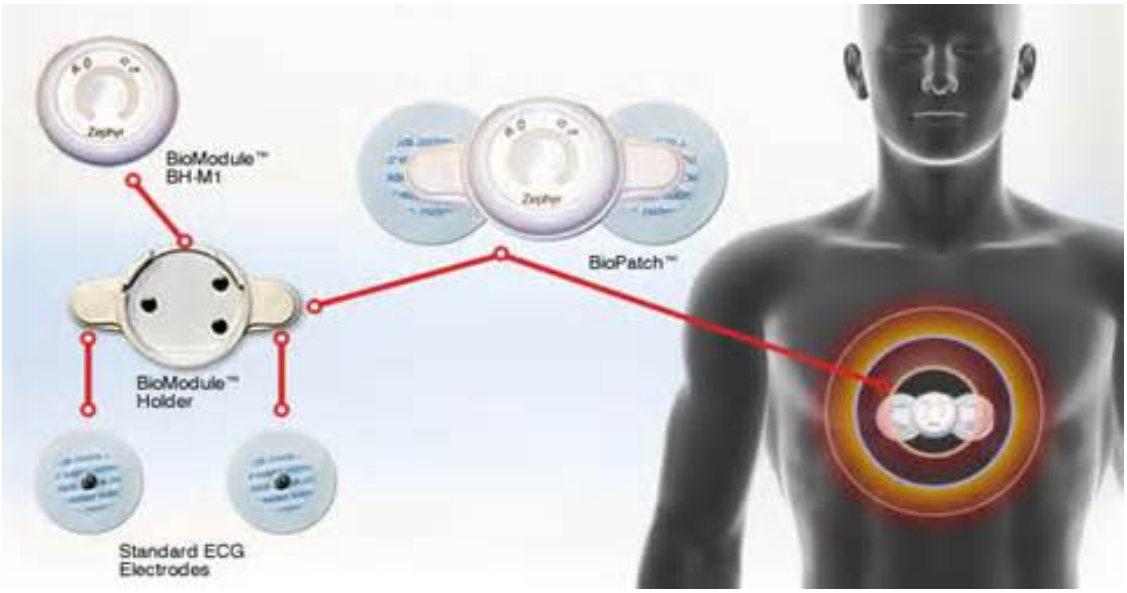
Custom Engineered Phone/Sensor Receiver Case



Contour Next EZ Blood Glucose Meter

Abbott Precision Xtra Meter

Zephyrlife BioPatchBiopatch Heart Rate and Accelerometry Monitoring Device



Appendix C: Hypoglycemia Awareness questionnaire:This survey item will be used to categorize awareness or having reduced awareness of hypoglycemia.

1. Check the category that best describes you: (check one only)

- ☐ I always have symptoms when my blood sugar is low (A)
- ☐ I sometimes have symptoms when my blood sugar is low (R)
- ☐ I no longer have symptoms when my blood sugar is low (R)

2. Have you lost some of the symptoms that used to occur when your blood sugar was low?

- ☐ Yes (R)
- ☐ No (A)

3. In the past 6 months how often have you had moderate hypoglycemia episodes? (Episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself).

- ☐ Never (A)
- ☐ Once or twice (R)
- ☐ Every other month (R)
- ☐ Once a month (R)
- ☐ More than once a month (R)

4. In the past year, how often have you had severe hypoglycemia episodes? (Episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose?)

- ☐ Never (A)
- ☐ 1 time (R)
- ☐ 2 times (R)
- ☐ 3 times (R)
- ☐ 4 times (R)
- ☐ 5 times (R)
- ☐ 6 times (R)
- ☐ 7 times (R)
- ☐ 8 times (R)
- ☐ 9 times (R)
- ☐ 10 times (R)
- ☐ 11 times (R)

- 12 or more times (R)

5. How often in the last month have you had readings < 70 mg/dl with symptoms?

- Never
- 1 to 3 times
- 1 time/week
- 2 to 3 times/week
- 4 to 5 times/week
- Almost daily

6. How often in the last month have you had readings < 70 mgdl, without symptoms? R: 5<6, A: 6<5;

- Never
- 1 to 3 times
- 1 time/week
- 2 to 3 times/week
- 4 to 5 times/week
- Almost daily

7. How low does your blood sugar need to go before you feel symptoms?

- 60-69 mg/dl (A)
- 50-59 mg/dl (A)
- 40-49 mg/dl (R)
- < 40 mg/dl (R)

8. To what extent can you tell by your symptoms that your blood sugar is low?

- Never (R)
- Rarely (R)
- Sometimes (R)
- Often (A)
- Always (A)

Appendix D: Alarm Manager Specifications

If an alarm is pushed to a study investigator, it is repeated every 5 minutes until acknowledged.

Alarm #	Description of Alarm	When Alarm is Considered Serviced	Instructions for Subject	Alarm Refractory Period (minutes)	Alarm pushed to Study Coordinator	Alarm pushed to Study Investigator
2	ARD ≥ 35% for BG ≥ 75	Calibration detected	Sensor inaccuracy has been detected, please calibrate sensors with most recent blood glucose value.	30	If refractory period expires	If refractory period expires two or more times in a row
3	Relative difference ≥ 30 mg/dl if CBG entered is below 75 mg/dl	Calibration detected	Sensor inaccuracy has been detected, please calibrate sensors with most recent blood glucose value.	30	If refractory period expires	If refractory period expires two or more times in a row
4	CBG ≤ 40 mg/dl	NA	CBG is low. Please treat with 30 g of carbs and recheck CBG in 15 minutes.	NA	instantly	instantly
5	CBG < 70 mg/dl and Alert 4 is not active	Rescue carb treatment identified	Blood glucose less than 70 mg/dL, treat with 15 g of carbs and recheck in 15 min.	30	If refractory period expires	If refractory period expires two or more times in a row
6	Sensor < 70 mg/dl without exercise detection and <85 mg/dl with exercise detection and no BG given within 15	Blood glucose value is entered	Sensor is less than 70 mg/dL. Please check blood glucose.	30	If refractory period expires	If refractory period expires two or more times in a row

	minutes and alert 5 inactive					
7	CBG >300 mg/dl	NA	CBG is greater than 300 mg/dl. Please change the insulin infusion and check your ketones.	NA	instantly	instantly
8	Sensor glucose ≥ 300 mg/dl and no BG given within 30 minutes and alert 7 inactive	Blood glucose value is entered	Sensor is greater than 300 mg/dl, please check and enter blood glucose, and check insulin pump for malfunctions	30	If refractory period expires	If refractory period expires two or more times in a row
9	Insulin basal failure	Autoservices if pump communication is restored	Insulin pump communication issue, please check pump and contact study physician	20	If refractory period expires	If refractory period expires two or more times in a row
10	Insulin meal bolus failure	Clears itself either after the meal flag is older than backlog of 15 minutes or there is not a backlog of insulin to deliver	Insulin meal bolus failed to deliver, please contact the study physician.	20	If refractory period expires	Coordinator will call subject and determine issue and consult with investigator to determine if subject should give bolus open loop.
11	Glucagon delivery failure	Autoservices if pump communication is restored	Glucagon pump communication issue, please check pump and contact study physician	10	If refractory period expires	If refractory period expires two or more times in a row

12	Sensor calibration due	Calibration detected	Sensor calibration due now, please check blood glucose and calibrate your receivers.	60	If refractory period expires	If refractory period expires two or more times in a row
13	If Alert 4 or 5 was activated, and no BG given in recent 20 minutes	Blood glucose value is entered	Blood glucose check due now.	20	If refractory period expires	If refractory period expires two or more times in a row
14	Cloud is not updating	Cloud connection restored	There is no connection of the phone to the internet. Please move back into cell phone or Wifi range.	60	If refractory period expires	If refractory period expires two or more times in a row
15	User has sent a bolus command to pump when not in "Pause Mode"	NA	We have detected that you have entered a bolus using the pump. Please only do this when in "Pause Mode". Do not use the pump directly when the AP is running.	NA	Instantly-coordinator will call subject and determine reason for override and consult with investigator to determine if safety is a concern.	
17	Sensor out for > 20 minutes	Autoservices if sensor communication is restored	Sensor has not been acquired in 20 minutes, please check transmitter.	20	If refractory period expires	If refractory period expires two or more times in a row
18	Replace Transmitter	Once fires, disables all sensor alarms for 120 minutes.	Replace transmitter	NA	NA	NA

19	Sensor Value is Invalid	Autoservices if sensor communication is restored	Sensor value is not reporting correctly. Please check sensor.	20	If refractory period expires	If refractory period expires two or more times in a row
20	Replace Sensor	Once fires, disables all sensor alarms for 120 minutes.	Replace sensor	NA	NA	NA
21	Basal insulin delivery failure	Autoservices if a successful bolus is given	Insulin basal delivery Failure, please contact the study physician	20	If refractory period expires	If refractory period expires two or more times in a row
22	Glucagon delivery failure	Autoservices if a successful bolus is given	Glucagon failed to deliver, please contact the study physician	20	If refractory period expires	If refractory period expires two or more times in a row
23	Insulin change due every 72 hours	User must press button to service-every 72 hours	Replace Insulin Fluid	120	If refractory period expires	If refractory period expires two or more times in a row
24	Glucagon change due every 24 hours	User must press button to service-every 24 hours	Replace Glucagon Fluid	120	If refractory period expires	If refractory period expires two or more times in a row

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