PROTOCOL TITLE: A randomized, three-way, cross-over study to assess the efficacy of a dual-hormone closed-loop system with XeriSol™ glucagon vs closed-loop system with insulin only vs a predictive low glucose suspend system

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FUNDING:	National Institute of Health
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Background:

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. Already, the benefit of improved glycemic control compared to current open-loop pump therapy has been demonstrated in several trials. Hovorka et al. recently showed that for people with T1D, glucose control could be improved when using a single-hormonal AP system for 12 weeks under free living conditions compared with sensor-augmented pump (SAP) therapy in a randomized multicenter cross-over trial (1). Participants were in euglycemia for 11% more time using the AP system as compared to SAP therapy. Kropff et al. also recently published results from a long-term single-hormone study showing that when patients with T1D used an AP during evening hours and while sleeping, using SAP during the day, the time spent in euglycemia was increased compared with participants who used SAP 24-hours per day (2). HbA1c dropped more significantly when using the AP (-0·3%) compared with SAP (-0·2%), though the improvement was modest.

Dual-hormone APs that deliver glucagon as well as insulin have also shown promise, especially in helping to prevent hypoglycemia. Glucagon works by breaking down hepatic glycogen, resulting in an increase in circulating glucose. Russell et al. showed how use of a dual-hormonal AP improved time spent in euglycemia and reduced time spent in hypoglycemia and hyperglycemia (3). Our group has shown that the OHSU dual-hormone system effectively manages blood glucose in a clinic setting with great progress using glucagon to reduce hypoglycemic episodes (4, 5).

One of the downfalls of using glucagon is that currently available glucagon formulations can only be used for a short time after reconstitution due to issue of protein aggregration and degradation. For dual-hormone closed-loop systems to become fully automated in the outpatient

setting, it is necessary to develop a stable glucagon solution that can remain in a pump reservoir for several days. Xeris Pharmaceuticals Inc. has developed a stable, soluble liquid glucagon formulation (XeriSol™) that can be injected or administered through an infusion pump (6).

The study described within this protocol is designed to test the efficacy of a dual-hormone closed-loop system utilizing XeriSol™ glucagon over a 3 day period as compared to an insulin-only closed-loop system and to a predictive low glucose suspend system.

Primary Objectives:

- To confirm superiority of the OHSU dual hormone closed-loop system as measured by frequency of hypoglycemia after exercise as compared to the insulin only closed-loop system and the predictive low glucose suspend system.

Secondary Objectives:

- To confirm superiority of the OHSU dual hormone closed-loop system as measured by percent of time with sensed glucose between 70 – 180 mg/dl as compared to the insulin only closed-loop system and the predictive low glucose suspend system.
- To confirm superiority of the OHSU dual hormone closed-loop as measured by other glucose metrics as compared to the insulin only closed-loop system and the predictive low glucose suspend system.

Study Hypothesis:

We propose that the use of the OHSU dual hormone closed-loop system as compared to an insulin only closed-loop system and a predictive low glucose suspend system, will reduce the time spent in the hypoglycemic range after exercise as measured by sensed glucose values.

Endpoints

Primary Endpoint (duration: 4-hours post exercise):

- Percent of time with sensed glucose <70 mg/dl

Secondary Endpoints (duration: entire study):

- Percent of time with sensed glucose between 70 – 180 mg/dl
- Number of carbohydrate treatments (defined as 15 or 20 grams of carbohydrate)
- Mean sensed glucose
- Percent of time with sensed glucose <50 mg/dl
- Percent of time with sensed glucose >180 mg/dl
- Mean amount of insulin delivered in one day (in units/kg)
- Mean amount of glucagon delivered in one day (in mcg/kg)

Study Type

This is a single center, randomized, three treatment, crossover trial designed to compare the glucose control resulting from the use of a dual and single-hormone closed-loop system as compared to a predictive low glucose suspend system.

Study Population
Study population will be adults with type 1 diabetes, ages 21 – 50 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. Nineteen subjects will be recruited to participate in studies.

Power Analysis
A Paired Means Power Analysis was used to carry out a sample size power analysis. A total sample size of 19 achieves 80% power to detect a reduction in percent time in hypoglycemia of 62% when using the dual-hormone (DH) artificial pancreas during the 4 hours after the start of aerobic exercise compared to predictive low glucose suspend (PLGS). Based on prior data in our previous experiments, we found that subjects spent an average of 9.8% time in hypoglycemia (standard deviation of 9.5%) under PLGS and 3.7% time in hypoglycemia using DH (standard deviation of 4.8%).

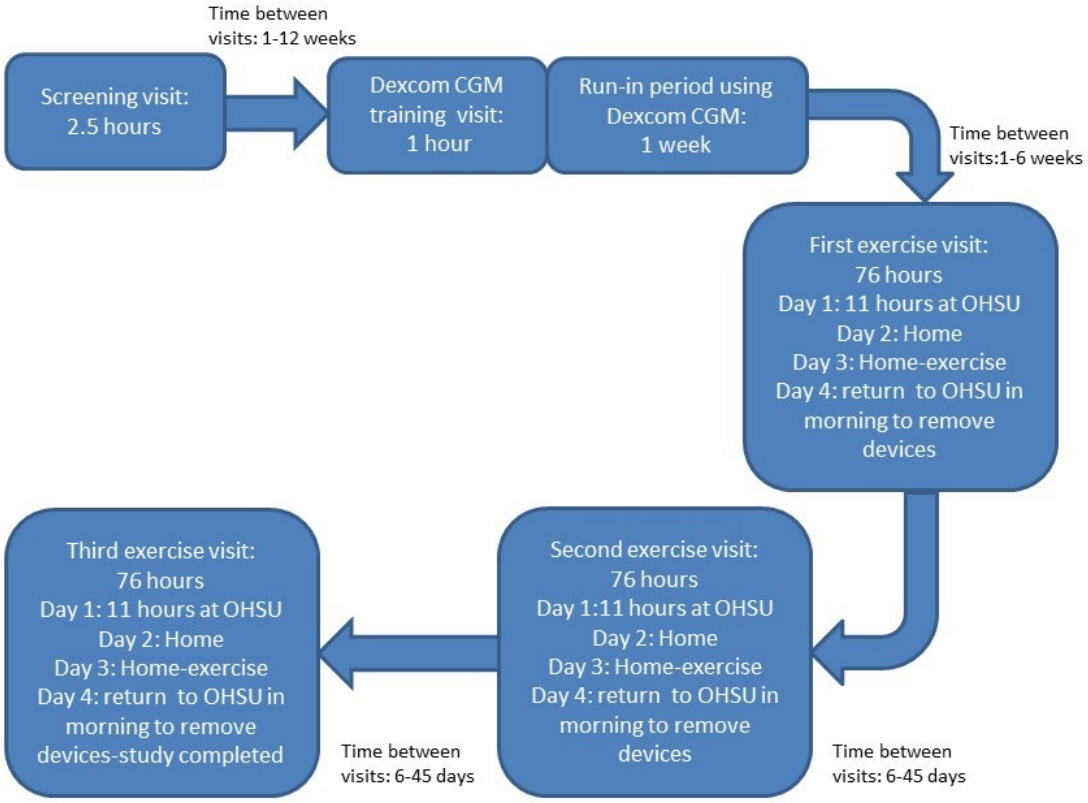
Protocol Summary:
Subjects will undergo three approximately 76 hour studies. See **Figure 1** below for a diagram of the study flow. During each of these intervention visits, subjects will wear an Omnipod to deliver insulin and a Dexcom G5 OR G6 CGM to measure glucose. In the dual-hormone closed-loop study, participants will wear a second Omnipod filled with XeriSol™ glucagon. The first day of the intervention visit will be an 11 hour inpatient visit with the subsequent time spent as an outpatient. The subject will come back to the research center on Day 4 in the morning to remove all devices. During one of the studies, glucose will be controlled using the FMPD dual hormone mode. During another study, glucose will be controlled using the FMPD single hormone mode. The single and dual hormone modes of the controller determine insulin only and insulin with glucagon delivery rates based on proportional and derivative error and contain an exercise detection component. During the other study, glucose will be controlled using a predictive low glucose suspend mode. In this mode, the APC will be programmed with the subject's basal profile(s) which will be transmitted to the Omnipod Personal Diabetes Manager (PDM) and allow for boluses to be inputted by the subjects for meals and corrections using their typical carb ratios and correction factors. However, this system will have a safety feature to suspend insulin delivery when sensor glucose is predicted to go below a threshold. Treatment order will be randomized.

Subjects will arrive at the clinic at approximately 7am for the inpatient visits. Subjects will eat breakfast, lunch and dinner at approximately 8:30am, noon, and 6pm respectively. Subjects will exercise on a treadmill for 45 minutes. Subjects will be discharged approximately 4 hours after exercise begins. The subject will then go home for the remainder of the study visit. Subjects will be given a standardized meal for dinner on Day 1. Subjects will return to OHSU on Day 4 for removal of all devices. During each study, the subject will wear one subcutaneous Dexcom™ G5 OR G6 continuous glucose monitoring (CGM) system. 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 via Bluetooth Low Energy (BTLE) from the Dexcom G5 OR G6 transmitter to the Nexus 5 master controller every five minutes. The controller for all 3 modes is a Google Nexus 5 phone. The smart phone will wirelessly communicate via BTLE to an Omnipod through a

PDM (Insulet Corp.) for automated insulin delivery or in the case of dual-hormone AP, to another Omnipod and PDM to be used for automated glucagon delivery.

A physician or nurse practitioner will be present for study start-up, will be on campus for exercise and will be immediately available on call at all other times. The study investigators 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. During the outpatient portion of the study visits, a study coordinator will be able to access the cloud for monitoring purposes. For safety purposes, all system alerts that are not serviced by the subject will be pushed to the study coordinator/study investigator according to Appendix D.

Figure 1: Study Flow Design



Subject Criteria

Inclusion Criteria:

1. Diagnosis of type 1 diabetes mellitus for at least 1 year.
2. Male or female subjects 21 to 50 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 for at least 3 months with stable insulin pump settings for >2 weeks.
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.
6. Lives within 40 miles of OHSU main campus.
7. HbA1c ≤ 10% at screening.
8. Total daily insulin requirement is less than 139 units/day.
9. Current use of a phone or other device so can be contacted by study staff off-campus
10. Willingness to follow all study procedures, including attending all clinic visits.
11. 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 reported 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 36% for men, less than 32% for women.
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. Subjects will be excluded for four or more R responses.
8. History of Diabetes Ketoacidosis during the prior 6 months prior to screening visit, as diagnosed on hospital admission or as judged by the investigator.
9. Adrenal insufficiency.
10. Any active infection.
11. Known or suspected abuse of alcohol, narcotics, or illicit drugs.
12. Seizure disorder.
13. Active foot ulceration.
14. Severe peripheral arterial disease characterized by ischemic rest pain or severe claudication.
15. Major surgical operation within 30 days prior to screening.

16. Use of an investigational drug within 30 days prior to screening.
17. Chronic usage of any immunosuppressive medication (such as cyclosporine, azathioprine, sirolimus, or tacrolimus).
18. Bleeding disorder, treatment with warfarin, or platelet count below 50,000.
19. Allergy to aspart insulin.
20. Allergy to glucagon.
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).
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 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 19 subjects. Up to four subjects will be replaced if needed, with a total enrollment of up to 23 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 having influence on efficacy or safety data as judged by the Investigator.
4. Substantial and repeated non-compliance with trial procedures.
5. Pregnancy.
6. Intention of becoming pregnant.

Visit Procedures
Screening (Visit 1)
Screening will take place within 12 weeks prior to the 1 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. The subject will be sent the consent form prior to the screening by email so that they can have time to read it fully at their leisure and prepare any questions they might have. Upon arrival and prior to any procedures, study staff will explain the study, give the subject ample time to ask questions and consider participation, and ensure that the subject voices understanding of the informed consent and study requirements. To minimize the possiblity of coercion and to ensure that subject is signing the appropriate version of the consent, an informed consent checklist will be used by study staff. After the subject has signed the consent,a copy of the consent/authorization form will be given to the subject. The original will be kept for the source document.

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. 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 completed. A study investigator will assess inclusion/exclusion criteria and review the subject's medical record for clarification as needed. The subject's insulin pump will be downloaded at this visit. The pump download will allow the investigator to assign an appropriate Total Daily Insulin Requirement (TDIR) to the subject during dosing visits. 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 either be delayed by approximately 1 hour for CBG values of <80 mg/dL, or rescheduled for a different day. 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. This visit will take approximately 2.5 hours.

One Week Run-in Period

The purpose of this run-in period is to teach subjects how to use the Dexcom CGM system using the APC software. For those new to CGM, it is also designed to provide them exposure prior to starting the intervention visits. The one week run-in period will take place within 6 weeks prior to the first 76 hour treatment visit. 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 if the last pregnancy test was more than 7 days prior. This test must be negative before further participation is allowed. This visit will take approximately 1 hour.

Subjects will receive training on how to use and calibrate the Dexcom G5 OR G6 CGM system including changing out the sensor every 7 or 10 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. Subjects will be trained how to pair the Dexcom transmitter to the APC app on the Nexus 5 smart phone, start and stop a new sensor session, how to enter calibrations and how to begin a simulated study.

The Dexcom G5 OR G6 CGM system will be calibrated at home according to the manufacturer's directions. The CGM alerts will be set at 70 mg/dL and 300 mg/dL. Subjects will begin a run-in study at home after two hours when the sensor warm-up is completed. Subjects will be given a Dexcom a transmitter and sensor 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

CGM system. Subjects will be instructed to discontinue the use of acetaminophen for all periods when wearing the Dexcom CGM system.
Each subject will be instructed on how to fill and insert the Omnipod, adjust their basal through the Nexus smart phone, give meal boluses and corrections through the Nexus smart phone and change out the pods. Instruction will be given on identifying infusion malfunction. 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 Nexus smart phone and changing out the infusion pod. If the subject experiences difficulties using the Omnipod during the study period, study staff will be available to educate and support by phone.

The companion accompany the subject to the start of the training visit to receive training on treatment in case of severe hypoglycemia episode, including administration of rescue carbohydrates and use of emergency glucagon kit.

76 hour Treatment Visits
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 6 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. Women of childbearing potential will receive a urine pregnancy test if the last pregnancy test was more than 7 days prior. This test must be negative before further participation is allowed

A capillary blood glucose (CBG) will be obtained and measured by the Contour Next glucose meter given to the subject for prior two visits. 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 halted and insulin therapy will be guided by the onsite investigator.

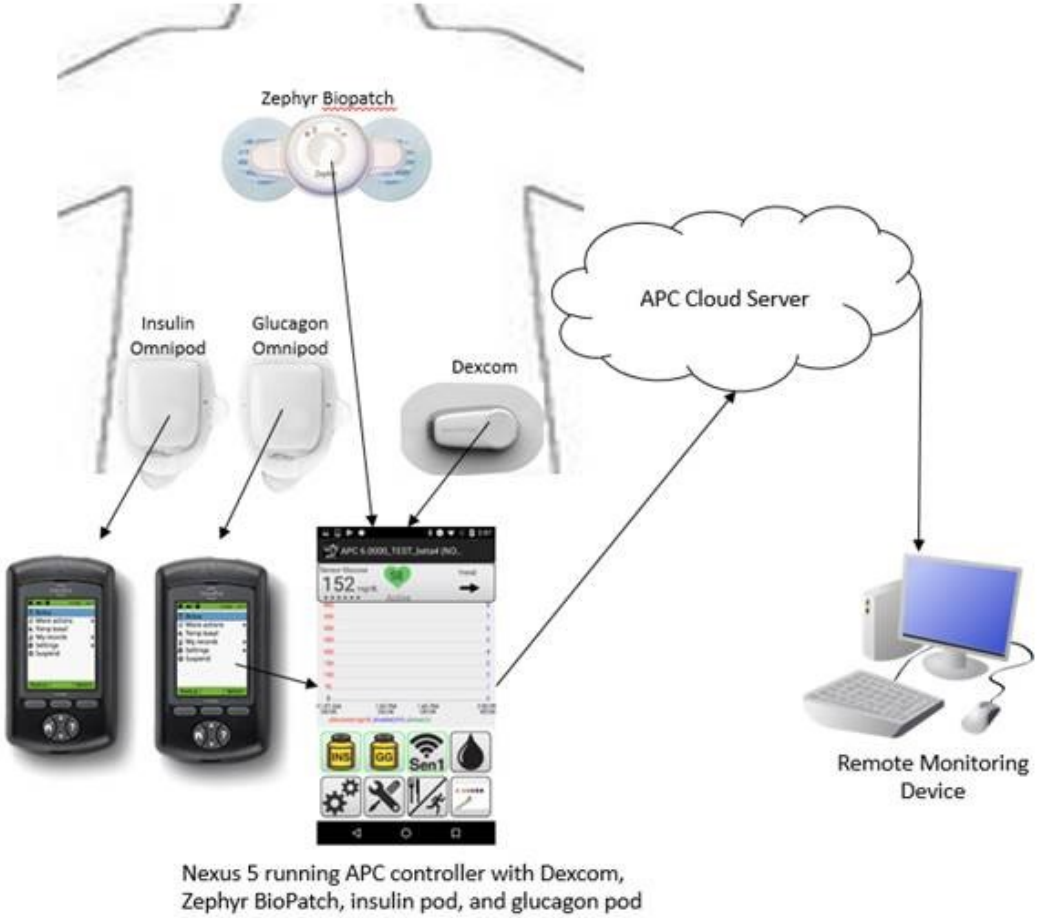
During each treatment visit, glucose will be controlled using either: 1) the single hormone insulin only mode 2) the dual hormone insulin and glucagon mode or 3) the insulin only mode with predictive low glucose suspend. The first 11 hours of the visit will be conducted in the OCTRI inpatient research 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 Day 4 to the clinic to return all devices. A code cart is on site at all locations and a code team is available by page at all times.

Inpatient Visits (11 hours)
An Omnipod will be filled with aspart insulin for all studies, but the dual hormone study will also have an Omnipod filled with XeriSol™ glucagon. Each pod and corresponding PDM will be labeled with a sticker indicating either "insulin" or "glucagon" for clear identification. We will provide the subjects with kits to replace the pods at home in case of pod malfunction or dislodgement at home. We will provide the pods with respective labels ("insulin" or

"glucagon") attached to the outside of the sterile packaging of the pod with instructions to immediately affix to the pod upon opening. The respective insulin or glucagon medication, pods, and all supplies will be provided separate kits that are extensively labeled. During the training, we will instruct patients to fill one pod at a time with only the supplies from that kit out at that time.

The pod will be primed and inserted into the skin of the subject's abdomen or flank as directed by the manufacturer. 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 will be asked to wear an activity watch, such as the Actigraph wGT3X-BT. The activity watch will be used in addition to the Zephyr to collect heart rate and activity data. The activity watch will not be connected to the APC system. See **Figure 2** below for a diagram of the system design. Subjects will disconnect his/her own pump and remove his/her own insulin infusion set once insulin delivery has started via the Omnipod.

Figure 2: Closed-loop System Design



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 enough study supplies for the 76 hour visit. The study investigator will then depart but remain on call.

Study staff will remain to complete a training with each subject on using a Dexcom CGM, the Omnipod system, the Zephyr BioPatch heart rate and accelerometer with the APC app. Subjects will be shown how to use the Nexus 5 controller user interface which includes: entering basal profiles, insulin carb ratios and sensitivity, activating and deactivating pods, meals, carb treatments, blood glucose values and ketone levels, addressing alerts, troubleshooting the devices connection to the phone via Bluetooth, and pausing the study. The subject will need to demonstrate competency in operating the system before study staff leave the room. The subject will keep a journal of all occurrences and symptoms, such as hypoglycemic spells, carbohydrate administrations and device problems while study staff is absent. Subjects will be given a pager number to call for any problems during the 76 hour visit.

The algorithm will push data up to a cloud server that can be monitored remotely every 5 minutes. A study coordinator will be available at all times for the visits with the ability to monitor the APC remotely via a cloud system on the web in the event of any issues. The APC will generate alerts on the smartphone according to Appendix D. The subjects will all be trained as to the action required by each alert. Each alert has a specific condition to be met for it to be considered serviced (i. e. enter treatment with oral carbohydrates). The refractory period is also specific to each alert with shorter refractory periods for alerts that concern subject safety. If the subject does not appropriately respond to the alert in the alotted timeframe, the alert will push to the study coordinator and the on-call investigator according to Appendix D. At that time, the coordinator will pull up the web-based monitoring system. 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. 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 approximately every 10 minutes. Cloud coordinates will be pushed with a known, fixed offset to allow for scrambling.

In order to push alerts to study coordinators and study investigators, the cloud server used for remote monitoring will have a drop down menu for study staff to sign in and out for the duration of their monitoring shift. Each study coordinator and investigator listed in the menu will have a cell phone number on file that can receive texts with pushed alerts.

During all studies, sensed glucose data will be wirelessly transmitted via BTLE from the Dexcom transmitter to the FMPD algorithm every five minutes. The single and dual hormone modes of the algorithm will calculate insulin only or insulin and glucagon doses and will run on a Google Nexus 5 phone. The predictive low glucose suspend mode of the algorithm will deliver insulin according to a pre-set basal profile(s) for the subject, which the subject may change if needed for safety as he or she would normally do. The smart phone will wirelessly communicate

via BTLE to a PDM communicating to an Omnipod for automated insulin delivery, and for the dual hormone closed-loop system, to a second PDM and Omnipod for automated glucagon delivery.

During normal operation, the sensor will be calibrated approximately every 12 or 24 hours. If at any time 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. The sensor will also be recalibrated per the manufacturer's directions 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 ≥ 75 mg/dl or (2) when a sensor is more than 30 mg/dl different than a CBG when the CBG < 75 mg/dl.. Additional calibrations may be ordered at the discretion of the investigator on call.

In order to ensure safety and to assess sensor accuracy, the subject will be asked to check their blood glucose two times during the day (typically before breakfast and at bedtime), for symptoms of hypoglycemia, and in response to system alert (such as for low or high sensor alerts). We will also instruct patients to perform capillary blood glucose immediately prior to and 30-60 minutes following exercise, and at 2-3am on the night following inpatient and outpatient exercise sessions. The subject will be able to check his/her capillary blood glucose more than 2 times a day if they feel they need to. 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 grams of carbohydrates 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.

For subject safety, if a sensor value is not available for 20 minutes or communication with the insulin pod is lost for more than 30 minutes, the insulin Omnipod will begin insulin delivery according to a pre-set basal profile(s) inputted for the subject at study start. When communication with the sensor or pod is restored, the system will automatically resume, updating the IOB accordingly. If sensor glucose values are not being acquired, glucagon delivery will be suspended. 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 insulin suspension time is 2 hours. Prediction of sensor glucose is based on linear regression of the prior ten minutes of sensor glucose data.

Subjects will eat breakfast, lunch and dinner at approximately 8:30am, noon and 6pm respectively. Meals will be announced to the controller. For each meal, 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 80% (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 exercise at approximately 2pm. Subjects will warm-up for 5 minutes then exercise for approximately 45 minutes on a treadmill. 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. If glucose fails to rise above 80 mg/dl after a carbohydrate treatment during exercise, a second treatment of 15 grams will be given. 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.

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 within the range of 70-140 mg/dl if sensor glucose is predicted to fall below 90 mg/dl within thirty minutes. If this occurs on a consecutive turn, the APC system will activate a minimum 30 minute suspension and a maximum of 120 minutes within any 150 minute window. Suspension will be limited to 180 minutes during the nighttime (11pm-7am). After this minimum 30 minutes has lapsed, insulin delivery will resume if sensor glucose is above 70 mg/dl and predicted to rise above 120 mg/dl within the next 30 minutes. 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 predictive low glucose 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 arms.

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. If the communication is not working between the Zephyr and the Nexus 5 at the time of exercise during the inpatient visit, exercise may be delayed until communication is restored. 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 (7). 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.

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 exercising. If the participant acknowledges this and says "Yes", the AP will adjust the dosing. If the subject selects that they are not exercising, the APC will present a dropdown menu from which the subject can select their current activity for logging purposes (e. g. housework). It will also present several choices for the amount of time that exercise detection will be suspended so that the subject will not continuously receive detection alerts during that activity (15, 30 or 60 minute suspension). If the participant says "No", this is considered a false alert because the algorithm has detected exercise, but the participant was not actually exercising. Because these false alerts 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 alert 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.

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.

Discharge from inpatient clinic

If the subject's schedule does not allow them to return to the clinic before the 72 hour mark from the time the first pod was activated, then a new insulin pod (and new glucagon pod if applicable) will be placed as described above approximately 1-2 hours prior to discharge to avoid use of any single pod beyond 72 hours. At the completion of the 11 hour inpatient visit, subjects will be discharged from the clinic. Subjects will complete a VAS injection site discomfort assessment for the glucagon infusion site, if applicable (see Appendix E). Capillary blood glucose will be measured with two consecutive blood glucose measurements at least 15 minutes apart prior to discharge. Subjects will wait to discharge home if capillary blood glucose is <85 and or >300 mg/dl or at the discretion of the study investigator, treatment will be at the discretion of the study investigator. Once subject's capillary blood glucose is between 85-300 mg/dl, they can be discharged home. Subjects will be given enough supplies to continue running the study while at home for 2 days. Subjects will be given a glucose and exercise diary to record the specifics of his/her activities 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 the morning of Day 4 to return all devices and end the study.

We are aware that there is a risk of severe hypoglycemia while the subjects are at home. The system will alert 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 40 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 Omnipod 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 Omnipod while in pause mode. When the error is resolved, the participant can exit pause mode and the closed loop system can be resumed. 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 Omnipods for 2 days of closed-loop treatment at home. 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 study 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.

Return to the Outpatient Clinic at OHSU

On the fourth day, subjects will return to the OCTRI inpatient clinic, the Harold Schnitzer Diabetes Health Center or the Medicine Specialties clinic in the morning. Subjects will be asked to arrive early enough to provide sufficient time to allow the pods to be removed before the 72 hour mark of pod use. Subjects will complete another VAS injection site discomfort assessment for the glucagon infusion site before removal of the Omnipod, if applicable. The study 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, Omnipods and Dexcom sensor will be removed from the subject. All infusion sites and the sensor site will be inspected for signs of irritation or infection. The study investigator will complete the Draize scale assessment for the glucagon infusion site, if applicable (see Appendix F). 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.

Hypoglycemia Treatment Guidelines

- **CBG < 70 mg/dl**
  - Give 15 grams of oral carbohydrate.
  - 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 is turned off.
  - Further management per 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 Omnipod for malfunction. This would include checking for insulin leaks, making sure Omnipod is securely adhered to skin, and for closed-loop studies, making sure there are no error messages on the phone running the algorithm.

If 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, the on call study investigator will be alerted to discuss proper management, including changing Omnipod and delivering a correction bolus. 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 transmitter, heart rate monitors and Omnipod PDMs 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. After disinfection, when the units are completely dry, they will be placed in a sealed bag labeled with subject information.

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 (120 min or more apart within a 4 hour window), 3) capillary blood glucose exceeds 400 mg/dl on two occasions more than 120 minutes apart but outside of the 4 hour window and during that time, the capillary blood glucose has not fallen below 250 mg/dl, 4) serum ketones are above 1.5 mM at any time, 5) seizure or unconsciousness associated with hypoglycemia, or 6) persistent nausea and vomiting thought to be related to glucagon.

Statistical methods

Primary endpoint
The primary study endpoint is percent of time with glucose sensor < 70 mg/dl for the four hours after exercise. The hypothesis to be tested is the dual hormone closed-loop system with exercise detection is superior in reducing hypoglycemia as compared to the insulin only closed-loop system and as compared to the predictive low glucose suspend system. Data will be analyzed using generalized estimating equations, which takes into account correlated data and repeated measures. Data will be analyzed using an intention-to-treat analysis and missing sensed glucose values will be interpolated.

Secondary endpoints
Secondary endpoints will be analyzed using generalized estimating equations and using an intention-to-treat analysis. Missing sensed glucose and missing CBG values will be interpolated. 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 All 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, a capillary blood glucose check will be required. A study investigator will be on call at all times.

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, 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.

XeriSol™ glucagon may cause blood sugars to go too high, which is also unlikely in the low doses that will be given. Rarely, there can be allergic responses to glucagon, such as skin redness, hives, itching of the skin, swelling of the mouth, or breathing difficulties. A few people may experience rapid heartbeat for a short while. There is a potential risk for developing anti-glucagon antibodies from exposure to glucagon. These reactions are considered very unlikely. After glucagon injection, nausea, headache, dizziness and vomiting may occur occasionally. Users may feel a stinging sensation or moderate pain when the medication is injected and redness at the infusion site. Risks and side effects related to the injection of glucagon medicine include:

Likely (10 or more subjects out of 100)	
Not Serious	Serious
Dizziness Headache Nausea Vomiting	None
Less Likely (Between 3-9 subjects out of 100)	
Not Serious	Serious
Weakness Fainting Heart Racing Sweating Thirst Vasodilation (widening of the blood vessels)	None
Rare (2 or less subjects out of 100)	
Not Serious	Serious

Rash	Abdominal pain
Itchiness	Confusion
Back pain	Diarrhea
Nervousness	Indigestion
Sore throat	Pain
Loss of sense of taste	Fainting
Dry mouth	

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 $600 for completion of all study visits. If subjects withdraw early from the study, compensation will be given as follows: $60 for visit 2 and $180 each for visits 3, 4, and 5. There is no compensation for the screening visit. If a subject is asked to repeat a study due to technical problems, he/she will receive an additional $180.

Monitoring Entity:
This investigation will be monitored by the co- investigator Leah Wilson MD. Dr. Wilson has no commercial interest in any of the companies which manufacture any of the devices used in this study. Drs. Jessica Castle, Peter Jacobs and Joseph El Youssef are inventors 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). Only a subject demographics/enrollment log case report form 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). The rest of the CRFs will be collected on paper or entered into Vision9 software through Prelude Dynamics. 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. All data from the study files on the Android Nexus 5 phone will subsequently be entered into the authorized electronic REDCAP Cloud database.

Recording of Data:
Investigators and staff will record data collected during the clinical trial on the CRF's. The CRFs will include:

1. Screening form
2. Dexcom Training Visit
3. APC training

4. Companion training
5. Day 1 Inpatient Dual-hormone Closed-loop Study Visit
6. Day 1 Inpatient Insulin Only Closed-loop Study Visit
7. Day 1 Inpatient Predictive low glucose suspend Study visit
8. Day 4 Dual-hormone Closed-loop Study Visit
9. Day 4 Insulin Only Closed-loop Study Visit
10. Day 4 Predictive low glucose suspend Study visit
11. Phone Update Form
12. Adverse Event form
13. Serious Adverse Event form
14. Concomitant Medications

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

The coded data collected during this study will be used for analysis of the primary and secondary endpoints listed in this protocol. The key to the code for this study will not be stored in the repository and only named study members on this project will have access to the key for this study. Researchers who request data from the repository will not receive any identifiers aside from date and we do not anticipate that the date will allow those researchers to re-identify the data. However, some of the researchers named on this project may use the data from the repository which would mean that the repository data will still be potentially identifiable to those who have access to the key as part of this project. The coded data will also be stored in the OregonAPC repository according to IRB protocol 19858. During screening, all new participants will sign the consent form to store their study data in the data repository. If it is possible, we will attempt to recontact participants who already signed a consent and authorization without the repository information to get their permission to use their data for future research. However, if they cannot be reached for re-consent and it is not possible to re-consent them, we will still use their data for future research as outlined in the HIPAA waiver of authorization form. The data to be collected includes: 1) glucose sensor data, 2) blood glucose data, 3) insulin and glucagon data, 4) physical activity data, and 5) food and exercise data. All data, except for blood glucose, is aggregated by the APC app. The blood glucose data is collected through downloading the Contour Next BG meters and exporting data as an excel file. There are no biological specimens collected during this study.

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. Severe hypoglycemia is defined as an event requiring the assistance of another person to administer carbohydrate, glucagon or resuscitative actions. Severe hyperglycemia is defined as 1) capillary blood glucose exceeds 400 mg/dl on two occasions (120 min or more apart within a 4 hour window), 2) capillary blood glucose exceeds 400 mg/dl on two occasions more than 120 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 3) serum ketones are above 1.5 mM at any time. 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 regarding these procedures. See IRB protocol 19858 for a complete description of the confidentiality and security of the study data collected during this study to be stored in the OregonAPC repository. Paper files will be stored in locked filing cabinets in restricted access offices at OHSU. 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 decision support device or discontinuance of pursuit of marketing approval.

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

Insulet Omnipod insulin management system which includes PDM and Omnipod

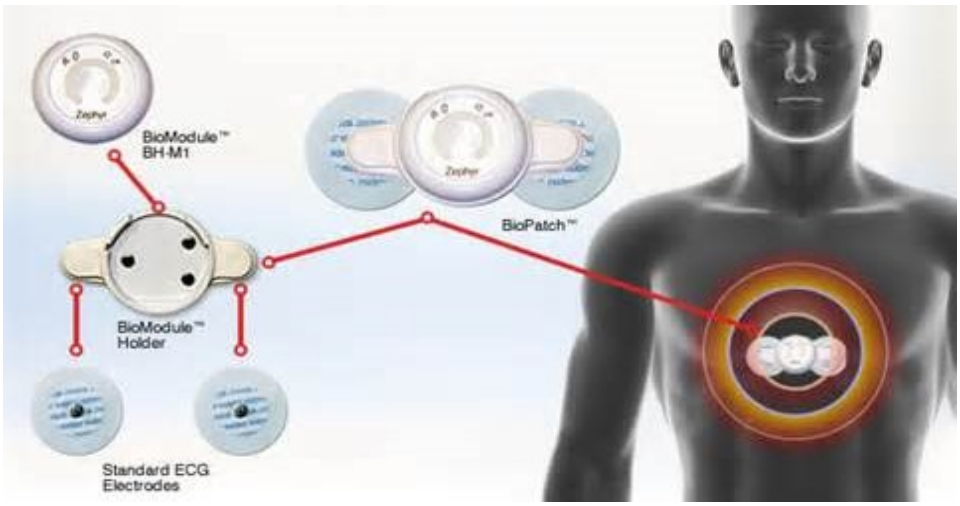
Dexcom G5 OR G6 Continuous Glucose Monitoring System which includes Sensor and Sensor Transmitter

Google Nexus 5 Smart phone

Contour Next 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: Alert Manager Specifications

Alert #	Activation criteria	Clearing Criteria	Notification to subject	Re-fire Time (min)	Refractory Period (min)	Coordinator push	Physician push	Waiting period
2	CBG entered ≥ 75mg/dl with ARD ≥ 35% AND second CBG not entered OR CBG entered < 75mg/dl with AD ≥ 30 mg/dl AND second CBG not entered	CBG entry for calibration. Auto clears at second Re-fire	"Sensor may not be accurate. Please calibrate sensor now."	10	0	After 2st Re-fire	-	-
4	CBG ≤ 40 mg/dl AND alert 4 not active	User enters CBG > 40 mg/dL after 15 minutes. Once rescue Carb are entered the waiting period starts. If CBG>=70 at any time, alert clears.	"Blood glucose is below 40 mg/dl. Please take 30 gm of rescue carbohydrates and recheck your blood glucose level in 15 minutes."	5	-	Immediately	Immediately	Waiting Period ends when alarm 13 is serviced OR Clear Criteria is met
5	CBG < 70 mg/dl AND alert 5 not active AND alert 4 not active	CBG entry ≥70 clears alert. Once rescue Carb are entered the waiting period starts. Alert clears if activation of alert 4 is met	"Blood glucose is below 70 mg/dl. Please take 15 gm of rescue carbohydrates and recheck your blood glucose level in 15 minutes."	15	-	After 1st Re-fire	After 2nd Re-fire	Waiting Period ends when alarm 13 is serviced OR Clear Criteria is met
6	Sensor glucose < 70 (no exercise) OR < 85 mg/dl (exercise) AND alert 4 AND alert 5 AND alert 6 not active or refractory & no CBG within last 15 minutes	CBG check. OR sensor ≥85 with exercise, ≥70 without exercise.	"Sensor glucose is below 70 (85) mg/dl. Please perform a blood glucose check now."	15	60	After 1st Re-fire	After 2nd Re-fire	-

7	CBG ≥ 300 mg/dl AND alert 27 not active or refractory AND alert 7 not active or refractory)	Ketone check	"Blood glucose is above 300 mg/dl. Please check the insulin infusion set for leaking or detachment and check ketone levels now."	30	120	After 1st Re-fire	After 2nd Re-fire	-
8	Sensor glucose ≥ 300 mg/dl for 30 minutes within the last 45 minute period AND alert 8 AND alert 7 AND alert 28 not active or refractory AND no CBG in last 30 minutes	CBG check. OR sensor < 300	"Sensor glucose is over 300 mg/dl. Please perform a blood glucose check now."	30	60	After 1st Re-fire	After 2nd Re-fire	-
10	Active SH/DH mode: More than 50% of meal bolus fails to deliver for 4 cycles. Pause or PLGS mode: if meal bolus fails to deliver for 4 cycles.	Auto clears	Insulin bolus failed to deliver, please contact the study physician.	-	-	Immediately	Immediately	-
12	G6: Last sensor calibration > 24 hours ago G5: Last sensor calibration > 12 hours ago	CBG check and calibration (auto)	"Sensor calibration is due. Please perform a blood glucose check now."	60	720	After 1st Re-fire	After 2nd Re-fire	-
13	Alert 4 OR alert 5 in waiting period for 15 minutes	CBG recheck	"Please perform a blood glucose check now."	20	-	After 1st Re-fire	After 2nd Re-fire	-
14	No connection to the Internet or Data for 40 minutes	Phone connects to a Wifi network or regain cell service	There is no connection of the phone to the internet. Please move back into cell phone or Wifi range.	40	-	-	-	-
17	Sensor is out of date for > 20 minutes AND alert 17 AND alert 18	Clears with Valid Sensor	"A sensor reading has not been received in the last 20 minutes. Please ensure that the phone is within range of the sensor."	20	-	After 1st Re-fire	After 2nd Re-fire	-

	AND alert 20 not active or refractory							
18	APC sends message to replace the transmitter immediately 60 minutes after activation criteria for alert 17 if clear criteria has not been met	User acknowledgement	"The transmitter is no longer functional. Please replace it immediately."	-	120	-	-	-
19	Sensor value is invalid for > 20 Minutes AND alert 19 AND alert 18 AND alert 20 not active or refractory	Clears with Valid sensor	"Sensor value is not reporting correctly. Please check your sensor site for problems. Contact the study coordinator if needed."	20	-	After 1st Re-fire	After 2nd Re-fire	-
20	APC sends message to replace the sensor immediately 60 minutes after activation criteria for 19 if clear criteria has not been met	User acknowledgement	"The sensor may no longer be functioning. Please replace it immediately."	-	120	-	-	-
21	Basal Insulin Fails to Deliver Correct amount for 60 minutes OR insulin suspend required and no connection to pump	Successful Basal INS is Delivered OR insulin is successfully suspended	Insulin communication failure. Please move PDM and POD closer to Phone	60 minutes	If alert fires after 10:59PM, refractory lasts until 6:59AM. No refractory other hours of the day.	After 1st Re-fire	After 2nd Re-fire	-
22	Glucagon fails to deliver for two consecutive cycles	Auto clears , clears if glucagon pump starts delivering	Glucagon failed to deliver. Please move PDM and POD closer to Phone.	-	10	-	-	-
25	Phone Battery Falls Below 20% AND is not charging	If phone is charging or level goes above 20%	"Phone Battery Low. Please Charge"	10	-	After 1st Re-fire	After 2nd Re-fire	-
26	Insulin Delivery ≥ 35% $TDIR_{adj}$ In last hour	Auto clears	"Max Insulin Has been Exceeded"	-	60	Immediately	Immediately	-

27	CBG ≥ 400 mg/dl AND alert 27 not active or refractory	Ketone check	"Blood glucose is above 400 mg/dl. Please change the insulin pod and check ketone levels now."	15	60	Immediately	Immediately	-
28	Ketones ≥ 0.6 mmol/L	User acknowledgement	“Ketone levels are high. If not already done, please change the insulin pod. Do not exercise.”	-	-	Immediately	Immediately	-
29	Insulin Omnipod has less than 10% of fluid volume remaining	Pod with greater than 10% volume is connected (i.e. pod is changed)	Your Insulin Pod is low. Please deactivate your current pod, and activate a new Insulin pod.	120	-	After 1st Re-fire	After 2nd Re-fire	-
30	Glucagon Omnipod has less than 10% of fluid volume remaining	Pod with greater than 10% volume is connected (i.e. pod is changed)	Your Glucagon Pod is low. Please deactivate your current pod, and activate a new Glucagon pod.	120	-	After 1st Re-fire	After 2nd Re-fire	-

Appendix E: Visual Analog Scale (VAS) for Injection Site Discomfort

Investigative Site Instructions: The subject should complete the VAS for Injection Site Discomfort at discharge on Day 1 and after removal of the glucagon Omnipod on Day 4 for each study visit. The subject completes the VAS by drawing a single vertical line through the scale corresponding to the perceived intensity (severity) of discomfort according to the instructions below. The goal is for the subject to report the amount of discomfort, if any, remaining at each time point, as opposed to reporting the transient pain associated with needle insertion.

Note: If a subject is unable to physically complete the questionnaire, the subject will indicate the point on the VAS corresponding to their level of discomfort, and study staff will enter a vertical line at that point. Documentation will be provided on each completed questionnaire as to who completed the form.

Please verify the length of the VAS line to be 100-mm before providing it to the subject.

Subject Instructions: Ignoring any pain from insertion of the Omnipod, please draw a single vertical line through the scale below that corresponds to the intensity (severity) of any discomfort you have felt at the glucagon Omnipod insertion site.

Discomfort could include stinging, burning, tingling, throbbing or pain. The further to the right you make your vertical mark, indicates the more intense discomfort you are feeling.

You should normally draw a straight line across the scale to indicate your current level of discomfort. However, if you are currently feeling no discomfort, you should circle the vertical line on the left end of scale (above the word “no”). If you are currently feeling the worst discomfort possible, you should circle the vertical line on the right end of the scale.

No Discomfort Worst Possible Discomfort

Injection Site Discomfort Description and Duration Questionnaire

Study Personnel Instructions: Question 1a should be should be completed by the subject at discharge on Day 1 and after removal of the glucagon Omnipod on Day 4. Any subject reporting discomfort other than "none," should complete question 1b. Any subject reporting duration of discomfort of "at least 10 minutes" should complete follow-up question 1c at the end of the study visit (i.e., at 180±5 minutes post-injection). The goal is for the subject to report the qualitative nature and duration of discomfort, if any, associated with injection of study drug, ignoring any transient pain associated with needle insertion.

Note: If a subject is unable to physically complete the questionnaire, the subject will provide verbal responses, which will be recorded on the questionnaire by study staff. Documentation will be provided on each completed questionnaire as to who completed the form.

Subject Instructions: Please answer question 1a and, if applicable to you, questions 1b and 1c. In answering these questions, you should ignore any pain from insertion of the needle.

*1a. How would you describe any discomfort you have had at the glucagon Omnipod infusion site since it was inserted? (Check **all** that apply):*

_____None (**Please ignore question 1b.**)

_____Pain (e.g., throbbing, soreness, muscle ache)

_____Itching

_____Tingling, twitching or numbness

_____Irritation (e.g., burning, stinging)

Other or additional comments:_____

1b. About how long did the discomfort last each time? (Check one):

_____Less than 1 minute

_____1-2 minutes

_____3-5 minutes

_____6-9 minutes

_____at least 10 minutes (**Please complete question 1c.**)

1c. In total, how long did the discomfort last each time? (Please enter a number below):

_____ Minutes

Appendix F: Draize Scale

- *Study Personnel Instructions:* The modified Draize Scale as shown in the table below will be used for physical examination/rating of abnormalities at the glucagon injection site.
- The injection site should be examined for formation of both erythema and edema and results recorded in the Case Report Form. Evaluations of the injection site should be performed at the end of Day 4 upon removal of the glucagon Omnipod.

Erythema Formation		**Edema Formation**	
Description	**Score**	**Description**	**Score**
No erythema	0	**No edema**	0
Very slight erythema Barely perceptible	1	**Very slight edema** Barely perceptible	1
Well defined erythema	2	**Well defined edema**	2
Moderate erythema	3	**Moderate edema** Raised approx. 1 mm	3
Severe erythema Beet redness to slight eschar formation	4	**Severe edema** Raised more than 1 mm and beyond exposure area	4

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