PROTOCOL TITLE: A randomized, two-way, cross-over study to assess the efficacy of an MPC exercise-enabled closed-loop system vs FMPD exercise-enabled closed-loop system

STUDY SITE:	Oregon Health Science University 3181 SW Sam Jackson Park Rd Portland, OR 97239
FUNDING:	JDRF & Helmsley Charitable Trust
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Background:

Closed-loop systems automate insulin delivery based on continuous glucose monitoring (CGM) values to minimize hypoglycemia and hyperglycemia, and in some cases also deliver glucagon to prevent and treat hypoglycemia. Closed-loop systems have been tested extensively in both the inpatient and outpatient settings. Our group has previously developed both an insulin-only closed-loop system and a dual-hormone (insulin and glucagon) closed-loop system. The novelty of these closed-loop systems are their ability to automatically detect exercise and adjust dosing in response to the exercise. Recently, we completed an outpatient closed-loop study, which tested the OHSU insulin-only closed-loop system with automated exercise detection [1]. Participants participated in four arms in randomized order: current care (their typical diabetes care, which included an insulin pump with or without a sensor), sensor-augmented pump with predictive low glucose suspend (using a t:slim pump and Dexcom G5 sensor with a PLGS algorithm running on the smartphone), insulin-only closed-loop system with exercise detection, and bi-hormonal (insulin + glucagon) closed-loop system with exercise detection. Each arm was 4 days long, with two 12 hour in clinic visits on days 1 and 4, with the remainder of the time spent as an outpatient using a cloud-based remote monitoring system. During the time spent as an outpatient, participants went to work, slept at home, travelled, and even went skiing. Participants performed moderate exercise for 45 minutes at 60% VO2max during both of the in clinic visits as well as performed one at home exercise session. The primary endpoints were percent time in hypoglycemia (CGM <70 mg/dL) and percent time in target (CGM 70-180 mg/dL) expressed as mean (SD). The mean time in hypoglycemia was the lowest with dual-hormone during the exercise period: 3.4±4.5% vs. 8.3±12.6% single-hormone (p=0.009) vs 7.6±8.0% predictive low glucose suspend (p<0.001) vs 4.3±6.8% current care where pre-exercise insulin adjustments were allowed (p=0.49). This type of manual adjustment was not allowed in any other arm and no snacks were given prior to exercise. Time in hypoglycemia was also the lowest with dual-hormone during the entire 4-day study: 1.3±1.0% vs. 2.8±1.7% single-hormone (p<0.001) vs. 2.0±1.5% predictive low glucose suspend (p=0.04) vs. 3.1±3.2% current care (p=0.007). Time in range during the entire study was the highest with insulin-only closed-loop system: 74.3±8.0% vs 72.0±10.8% dual-hormone (p=0.44). The OHSU insulin-only closed-loop system performance

was comparable to those reported in a recent meta-analysis of AP studies [2] which reported a mean time in range of 70.8% using insulin-only closed-loop systems vs 74.3% in our recent study. We have also completed a study on patients with T1D who used the OHSU dual-hormone AP for 22 hours within the hospital during which participants performed mild exercise for 45 minutes on a treadmill [3]. For this study, we used the OHSU bi-hormonal artificial pancreas system that adjusts dosing after an exercise announcement to reduce exercise-related hypoglycemia. Results showed that adjusting hormones during exercise reduced hypoglycemia.

The study described within this protocol is designed to test the efficacy of a new modified insulin-only closed-loop algorithm, a model-predictive control (MPC) algorithm that modulates insulin delivery based on estimated activity level. The potential benefit of this type of algorithm is that it handles exercise not as a discrete event, but it automatically adjusts insulin delivery based on estimated activity level. This type of algorithm may significantly improve glucose control over the FMPD algorithm which is designed only to detect exercise over 4 metabolic equivalent of tasks (METs) for a specific duration of 45 minutes.

Primary Objective:

- To confirm superiority of the OHSU MPC exercise-enabled closed-loop system as measured by percent of time with sensed glucose less than 70 mg/dl as compared to the OHSU FMPD exercise-enabled closed-loop system.

Secondary Objective:

- To confirm superiority of the OHSU MPC exercise-enabled closed-loop as measured by other glucose metrics as compared to the OHSU FMPD exercise-enabled closed loop system.

Study Hypothesis:

We propose that the use of the OHSU MPC exercise-enabled closed-loop system as compared to the OHSU FMPD exercise-enabled closed-loop system will increase the time in range as measured by sensed glucose values.

Endpoints

Primary Endpoint:

- Percent of time with sensed glucose <70 mg/dl across the duration of inpatient day (Day 3 MPC vs. Day 1 FMPD)

Secondary Endpoints:

- Percent of time with sensed glucose between 70-180 mg/dl across the study duration
- Percent of time with sensed glucose between 70-180 mg/dl across the duration of the inpatient day (Day 3 MPC vs. Day 1 FMPD)

- Percent of time with sensed glucose between 70 – 180 mg/dl from the start of the in-clinic exercise session until the start of the next meal
- Percent of time with sensed glucose <70 mg/dl from the start of the in-clinic exercise session until the start of the next meal
- Number of carbohydrate treatments (defined as 15 or 20 grams of carbohydrate)
- Mean sensed glucose
- Coefficient of variation of glucose
- Percent of time with sensed glucose <54 mg/dl
- Percent of time with sensed glucose >180 mg/dl
- Mean amount of insulin delivered per day (in units/kg)

Study Type

This is a single center, randomized, two treatment, crossover trial designed to compare the glucose control resulting from the use of the OHSU MPC exercise-enabled AP system as compared to the OHSU FMPD exercise-enabled AP system.

Study Population

Study population will be adults with type 1 diabetes, ages 21 – 50 years of age. Older participants are excluded due to higher risk of unrecognized coronary artery disease. Younger participants are excluded as it is appropriate to assess safety first in the adult population. Twenty-five participants will be recruited to participate in studies.

Power Analysis

A sample of 24 subjects provides at least 80% power to detect a paired difference for a two-sided Wilcoxon signed-rank test of the difference between use of exercise-enabled MPC algorithm and FMPD algorithm with alpha set at 0.05 for our primary outcome of percent of time <70 mg/dl. We use the sample size for a one-sample t-test, n, with an adjustment factor for the double exponential (or Laplace) distribution of the difference such that the final sample size n' = n/(2/3). We anticipate a mean difference of 1.2 (SD 2.5) based on our prior published AP study data. For normally-distributed secondary outcomes, we have >80% power to detect differences of 0.6 SD or greater using a two-sided one-sample t-test for the mean difference at the 0.05 significance level. These calculations were performed using PASS version. We propose to enroll 25 participants in this study as this will yield more than 80% power as stated above (see Participant Recruiting).

Protocol Summary:

Participants will undergo two approximately 76 hour studies. See **Figure 1 &2** for a diagram of the study flow and structure. During each of these intervention visits, participants will wear an Omnipod to deliver insulin and a Dexcom G6 CGM to measure glucose. The CGM system will provide sensed glucose data every 5 minutes. Sensed glucose data will be wirelessly transmitted via Bluetooth Low Energy (BTLE) from the Dexcom G6 transmitter to the smartphone master controller every five minutes. The smart phone will wirelessly communicate via BTLE to an Omnipod through a PDM (Insulet Corp.). During one of the studies, glucose will be controlled

using the MPC exercise-enabled mode. During another study, glucose will be controlled using the FMPD exercise-enabled mode. The closed loop system will receive activity data through a Polar M600 watch worn by the participant. Participants will arrive at the clinic at approximately 7am for the inpatient visits. Participants will eat breakfast, lunch and dinner at approximately 8am, noon, and 5pm respectively. Participants will perform activities of daily living and exercise. Participants will be discharged at approximately 7pm. Participants will then go home for the remainder of the study visit and perform two exercise sessions at home. Participants will return to OHSU on Day 4 for removal of all devices. The exception to this is for the first 8 participants using the MPC exercise-enable mode. These participants will stay at OHSU during the day and go home to sleep each night (7pm-7am). These participants will use the system in open-loop mode while off campus.

Figure 1: Study Flow Design

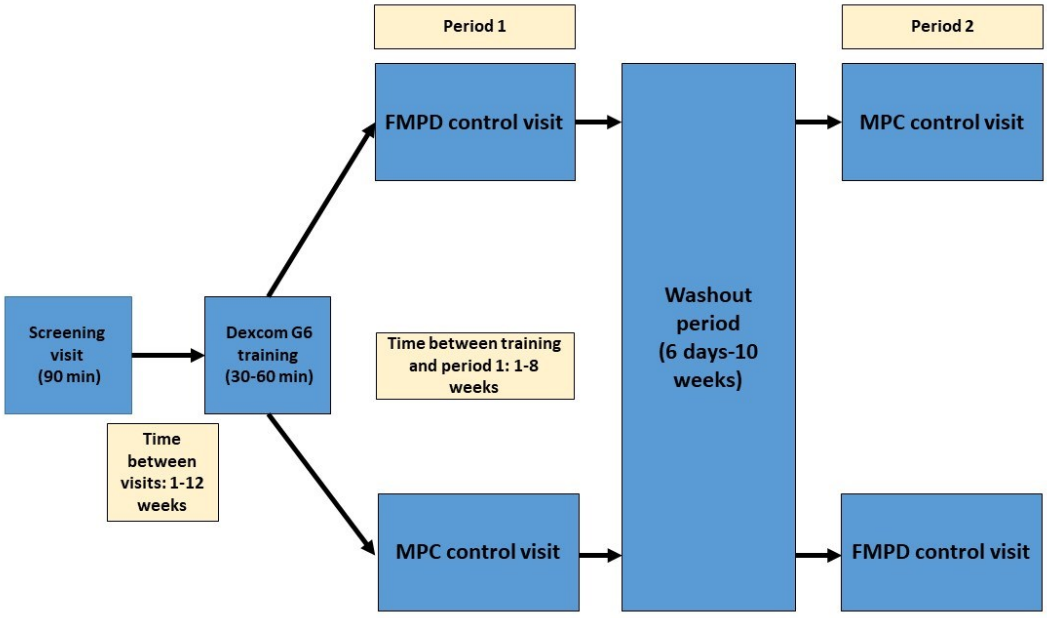
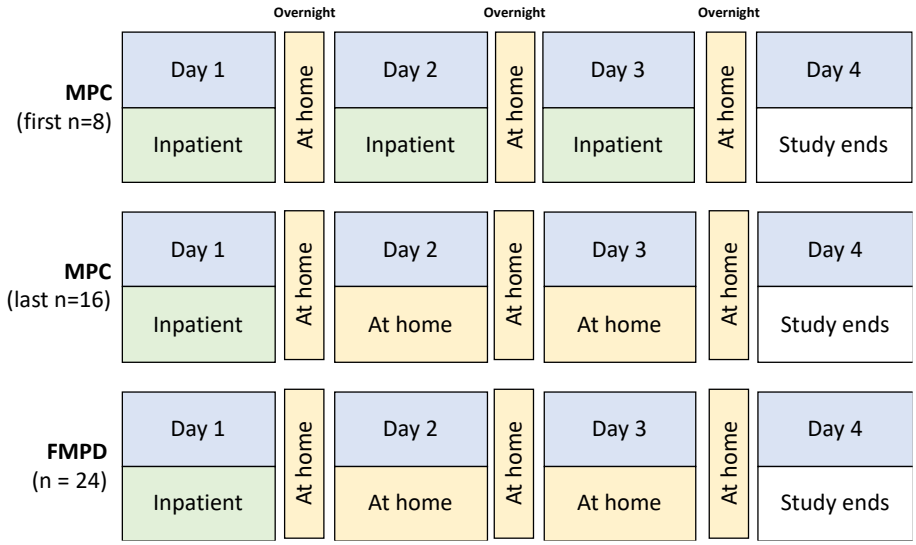


Figure 2: Study structure



Participant Criteria

Inclusion Criteria:

1. Diagnosis of type 1 diabetes mellitus for at least 1 year.
2. Male or female participants 21 to 50 years of age.
3. Physically willing and able to perform aerobic exercise (as determined by the investigator after reviewing the participant's 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 participant 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 participants 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. Participants will complete a hypoglycemia awareness questionnaire. Participants 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 or lispro insulin.
20. Current administration of oral or parenteral corticosteroids.
21. 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).
22. Beta blockers or non-dihydropyridine calcium channel blockers.
23. Current use of any medication intended to lower glucose other than insulin (ex. use of liraglutide).
24. A positive response to any of the questions from the Physical Activity Readiness Questionnaire with one exception: participant 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).

25. Any chest discomfort with physical activity, including pain or pressure, or other types of discomfort.
26. Any clinically significant disease or disorder which in the opinion of the Investigator may jeopardize the participant's safety or compliance with the protocol.

Participant Recruiting:

Participants 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, ads on facebook, electronic newsletter or from the OHSU Participant Recruitment website. The T1D Exchange may send out approved recruitment emails to Glu community users in the Portland/Vancouver area. Handouts may also be made available to faculty at Tuality, Providence, Kaiser, 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 participants. Participants will also be recruited from a list of participants who participated in past OHSU studies who have agreed to be contacted regarding future studies involving Drs. Castle from the OHSU diabetes research registry and/or www.clinicaltrials.gov. Non-english speaking participants 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 participants may be screened in this study. Goal enrollment is 25 participants.

Withdrawal Criteria

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

A participant must be withdrawn if the following applies:

- Hypoglycemia during the treatment period posing a safety problem as judged by the investigator.
- Hyperglycemia during the treatment period posing a safety problem as judged by the investigator.
- Protocol deviation having influence on efficacy or safety data as judged by the Investigator.
- Substantial and repeated non-compliance with trial procedures.
- Pregnancy.
- 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, the AIMS lab in Biomedical Engineering Dept at CHH1 or the Harold Schnitzer Diabetes Health Center. The participant 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 participant ample time to ask questions and consider participation, and ensure that the participant voices understanding of the informed consent and study requirements. To minimize the possibility of coercion and to ensure that participant is signing the appropriate version of the consent, an informed consent checklist will be used by study staff. After the participant has signed the consent, a copy of the consent/authorization form will be given to the participant. 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.

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). If the participant has already had these lab studies done within the past 2 months and the results are available, those results can be used in place of the blood draw. An EKG will be completed. A study investigator will assess inclusion/exclusion criteria and review the participant's medical record for clarification as needed. When feasible, the participant's insulin pump and glucose sensor, if applicable, will be downloaded before enrollment. A three-digit participant ID number will be assigned to the participant. This visit will take approximately 1.5 hours.

One Week Run-in Period

The purpose of this run-in period is to teach participants how to use the Dexcom CGM system using the iPancreas 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 8 weeks prior to the first 76 hour treatment visit. After arrival at the OHSU OCTRI outpatient clinic, the AIMS lab in Biomedical Engineering Dept at CHH1 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 30-60 minutes.

Participants will receive training on how to use and calibrate the Dexcom G6 CGM system including changing out the sensor every 10 days. The wire glucose sensor is sterile and commercially available from Dexcom^{TM} and will be used for single use only as directed by the manufacturer. Participants will be trained to insert the sensor into the subcutaneous tissue of the abdomen after appropriate preparation of the abdominal skin per the manufacturer's directions. Participants will be trained how to pair the Dexcom G6 transmitter to the iPancreas app on the smart phone, start and stop a new sensor session and how to enter calibrations. The Dexcom G6 does not require calibrations. As part of the training, study staff will review with the participants that Dexcom G6 values can be inaccurate. In the event that the participant's symptoms (such as

symptoms of hypoglycemia or hyperglycemia) are discrepant with the G6 CGM reading, then the participants will be instructed to perform a CBG and use this CBG value to make treatment decisions and use the CBG value to calibrate the Dexcom G6 device. Participants will be provided with a copy of the Dexcom G6 user guide.

The CGM alerts will be set at 70 mg/dL and 300 mg/dL. Participants will be trained how to begin a run-in study on the iPancreas app at home after two hours when the sensor warm-up is completed. Participants will be given a Dexcom G6 transmitter and sensor to insert the day before each treatment visit along with a Contour Next meter for measuring their capillary blood glucose.

There is the option to complete this visit via Webex with the study devices delivered to the participant and study staff virtually connecting with participants for training on the devices and study procedures while they are at home. Participants will complete a urine pregnancy test at home provided by study staff if the last pregnancy test was more than 7 days prior.

76 hour Treatment Visits

The participant will be asked to check his/her glucose before driving to the clinic and to bring a snack in the car in case hypoglycemia does occur (in which case, the participant must park and treat the hypoglycemia). After the first treatment visit, the washout period will be 6 days to 10 weeks calculated from the day of admission to the research center until the start of the next admission. The participant 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

An assessment will take place at the beginning of the participant's first closed-loop study. We will inquire whether the participant has had changes in their medications and/or medical history to confirm the participant hasn't developed any study exclusion criteria. A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter. When they arrive, participants 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 and serum ketones will be checked. If serum ketones are ≥ 0. 6 mM, the study will not be started and insulin therapy will be guided by the onsite investigator.

During each treatment visit, glucose will be controlled using either: 1) the OHSU MPC exercise-enabled closed-loop mode or 2) the OHSU FMPD exercise-enabled closed-loop mode. The first 12 hours of the visit will be conducted in the OCTRI inpatient research unit, the Harold Schnitzer Diabetes Health Center or the AIMS lab in the Biomedical Engineering Dept at CHH1. The participants will then go home. For the first 8 participants using the MPC mode, they will stay at OHSU during the day and go home at night, using the system in open-loop mode while off campus. If safety criteria are met, as outlined below, subsequent participants will be at home for the remainder of the intervention period, returning on Day 4 to the clinic to return all devices. A code team is available immediately by page at all times.

Inpatient Visits (~40 hours for first 8 participants, 12 hours for remainder of participants)

An Omnipod (510K#042792) will be filled with Novolog® or Humalog® insulin for all studies. We will use only name brand insulin, not generic insulin. We will provide the participants with kits to replace the pod at home in case of pod malfunction or dislodgement at home. The Omnipod will be primed and inserted as directed by the manufacturer. Research staff will train participants on the approved pod placement options from the Omnipod User Guide. Participants will wear a Polar watch to inform the controller. Participants will disconnect his/her own pump and remove his/her own insulin infusion set once insulin delivery has started via the Omnipod. The research staff will initialize the system and begin the closed-loop study with the correct mode, either FMPD or MPC based on the participant's randomization, using the iPancreas smart phone application. Two staff will review each of the settings to confirm the settings are inputted correctly. The participant will be given enough study supplies for the 76 hour visit. A study investigator will be available in person or by phone for the entire 76 hour visit.

Study staff will complete a training with each participant on using the Dexcom G6, the Omnipod system, and the Polar watch. Participants will be shown how to use the smartphone user interface which includes: entering basal profiles, insulin carb ratios and sensitivity, activating and deactivating Omnipods, giving meal boluses, carb treatments, blood glucose values and ketone levels, addressing alerts, troubleshooting the devices connection to the phone via Bluetooth, and pausing the study. Instruction will be given on identifying an Omnipod malfunction. The time required for this training will vary, depending on the experience of each participant, but will be sufficient to help him/her become comfortable using the smart phone and changing the Omnipod. If the participant experiences difficulties using the Omnipod during the study period, study staff will be available to educate and support by phone. Training will include that the smart bolus calculator available in open loop mode is a suggestion and that participants should use their judgement on what insulin dose to take as the bolus calculator is not aware of certain circumstances such as illness or alcohol use.

The participant will need to demonstrate competency in operating the system before study staff leave the room. A competency assessment will be completed throughout the day of the first closed-loop visit. Each participant will start the G6 sensor and start the Omnipod on their own during onboarding. Participants will need to show competency in accepting exercise detection, entering fingerstick glucose values and announcing meals during the day on campus. Participants will demonstrate competency in the following using a simulated closed loop study: pausing and resuming a study, using the smart bolus calculator and manual bolus while in pause mode, for FMPD: force start exercise, cancel exercise, for MPC: disabling exercise adjustment. Participants will be given a pager number to call for any problems during the 76 hour visit. The companion will accompany the participant to receive training (or be previously trained) on treatment in case of severe hypoglycemia episode, including administration of rescue carbohydrates and use of emergency glucagon kit. Companions will also be trained on the closed-loop system. This training may be completed virtually.

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 iPancreas remotely via a cloud system on the web in the event of any issues. iPancreas

will generate alerts on the smartphone according to Appendix D. The participants 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 participant safety. If the participant does not appropriately respond to the alert in the allotted 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, text or a personal visit at any time. If the participant cannot be reached and sensor glucose is below 50 mg/dl, the emergency contacts provided by the participant will be contacted. If the alert is still un-serviced and study staff are unable to reach the participant or either of the emergency contacts, emergency medical services will be contacted. To facilitate this, the phone will track the participant'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 G6 transmitter to the insulin-delivery algorithm every five minutes. The insulin-delivery algorithm will calculate insulin doses and will run on a smartphone. The smart phone will wirelessly communicate via BTLE to a PDM communicating to an Omnipod for automated insulin delivery.

Both the FMPD and MPC control algorithms include a predictive low glucose suspend algorithm (PLGS). The PLGS algorithm includes (1) an algorithm to predict hypoglycemia and (2) a mechanism to override the controller and shut off insulin if low glucose is predicted by the hypoglycemia prediction algorithm. The predictive low glucose suspend algorithm will be continuously monitoring the trend of blood glucose with every new glucose value. If the sensed glucose is within 70-140 mg/dl and predicted to fall below 90 mg/dl within the next 30 minutes according to the LSTM algorithm, insulin infusion will be turned off. If this occurs, the control algorithm will shut off insulin for a maximum of 120 minutes suspension within any 150 minute window. Suspension will be limited to 180 minutes during the nighttime (11pm-7am). After 5 minutes of insulin suspension, insulin delivery will resume if sensor glucose is above 70 mg/dl and predicted to rise above 120 mg/dl at 30 minutes in the future.

If at any time study staff determines that a sensor can no longer be used, a new sensor will be inserted. In order to ensure safety and to assess sensor accuracy, the participant 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 a capillary blood glucose immediately prior to and immediately following exercise. Participants will be instructed to check a fingerstick glucose at bedtime and again at 2am on exercise days. The participant will be able to check his/her capillary blood glucose more than 2 times a day if they feel they need to. If the participant's

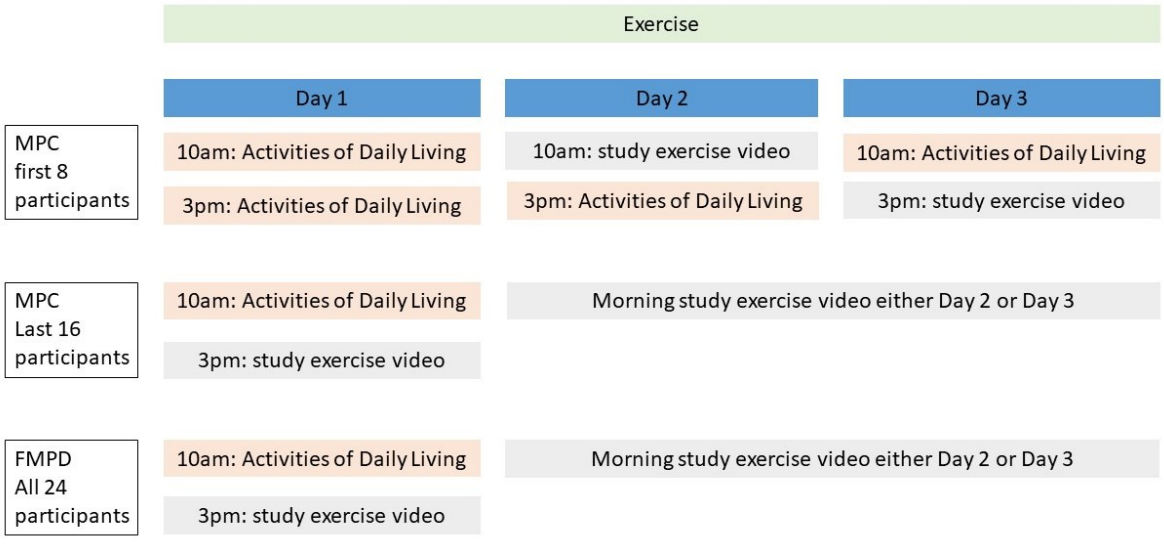
blood glucose is < 70 mg/dl or is experiencing symptoms of hypoglycemia, he/she will be instructed to treat with 15 grams of carbohydrates.

For participant safety, if a sensor value is not available for 20 minutes or communication with the Omnipod is lost for more than 30 minutes, the Omnipod will begin insulin delivery according to a pre-set basal profile(s) inputted for the participant at study start. When this occurs for a lost sensor, iPancreas will 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. Insulin is suspended for 30 minutes, after which basal insulin delivery resumes. When communication with the sensor or Omnipod is restored, the system will automatically resume, updating the IOB accordingly.

Participants will eat breakfast, lunch and dinner at approximately 8am, noon and 5pm respectively. Meals will be announced to the controller. For each meal, food items will be self-selected. The number of grams of carbohydrates will be counted by the participant and entered in the controller. Immediately before eating, each participant will receive 100% (nominal) of his/her typical pre-meal insulin dose based on their insulin to carbohydrate ratio. The same self-selected meals will be offered during FMPD Day 1 and MPC Day 3 inpatient days, and in the event a particular food item is not available, a different item with a similar amount of carbohydrate will be provided.

Participants will perform activities of daily living (ADLs), such as vacuuming, washing dishes, and folding laundry for approximately 30 min at 10am or 3pm depending on the study (see 'Safety assessment – first 8 participants using MPC'). Participants will complete a 30-minute aerobic exercise video at 10am or 3pm. (see 'Safety assessment – first 8 participants using MPC'). See Figure 3 below.

Figure 3: Diagram of Exercise Study Procedures



See Appendix E for Aerobic Video Outline. For participant safety, capillary blood glucose must be 80 mg/dl or higher to begin exercise.

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

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

If the exercise is stopped prematurely, the duration of exercise will be noted by the study staff and if the participant is deemed safe to participate in future studies, the exercise will be stopped after that same time duration for subsequent studies. For participant safety, if capillary blood glucose is < 70 mg/dl at any point during the exercise period, the participant 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. Participants will be given instructions to take additional carbs at the start of exercise as needed based on CGM and trend to avoid post-exercise lows. See Appendix F inpatient instruction card.

Participants will wear a Polar watch for collecting heart rate and accelerometry data. The Polar watch transmits this data to the smartphone controller via Bluetooth. iPancreas will convert the heart rate and accelerometry data into an estimated energy expenditure to determine if the participant is exercising. If the communication is not working between the Polar watch and the smartphone at the time of exercise during the inpatient visit, exercise may be delayed until communication is restored. We are aware that there is a risk of hyperglycemia if the participant stops exercising after a short time with continued adjustments to insulin. When using the FMPD mode: 1) an exercise cancellation option is available on the user interface for up to 30 minutes after the start of exercise that will revert insulin parameters to their nominal values and 2) if exercise is not detected by the algorithm when the participant is actually exercising, an exercise announcement button on the iPancreas user interface will be used. When using the MPD mode, the user can disable the exercise adjustment, thereby removing incoming exercise data for insulin dosing calculations.

Safety assessment – first 8 participants using MPC

Given this is the first human testing of the MPC exercise-enabled mode, the first 8 participants will stay at OHSU during the day for the entire period of using the MPC algorithm and go home to sleep each night (approximately 7pm-7am), using the system in open-loop mode while off campus. These participants will still complete only one in-clinic day for the FMPD arm (Day 1).

The study schedule will be slightly different for the days spent on campus using the MPC algorithm. On Day 1, participants will perform ADLs at 10am and again at 3pm. On Day 2, participants will complete the study aerobic exercise video at 10am and ADLs at 3pm. On Day 3, participants will perform ADLs at 10am and complete the study exercise video at 3pm. For each meal, food items will be self-selected. See Figure 3 above.

For these 8 participants, we are matching Day 1 of the FMPD arm to Day 3 of the MPC arm. Participants will also perform the same activities at the same time on these days, ADLs at 10am and the study exercise video at 3pm.

Capillary blood glucose will be measured with two consecutive blood glucose measurements at least 30 minutes apart prior to discharge. Participants will wait to discharge home at approximately 7pm if capillary blood glucose is <85 and or >300 mg/dl or at the discretion of the study investigator, and treatment will be at the discretion of the study investigator. Investigator will review the physician portal to assess participant's insulin on board before they go home. These participants will use the system in open-loop mode while at home. Participants will be given a snack to take with them in case they develop hypoglycemia or hypoglycemic symptoms on the commute home.

We will complete an interim analysis after the first 8 subjects using the MPC assessing time spent with CGM < 54 mg/dL, <70 mg/dL, and > 300 mg/dL and any adverse events. The MPC data will be compared to the equivalent data from the FMPD studies. If the interim analysis shows that the MPC data is comparable to the FMPD studies and presents no safety concerns, we will proceed to studying the MPC during outpatient visits. If it does not or if there are any instances of severe hypoglycemia or DKA (unrelated to infusion set failure), then the study will be halted, changes will be made as appropriate to algorithm and the protocol and a plan will be submitted to FDA and IRB that will need to be approved before further studies are conducted. After the algorithm adjustments are made, an additional 8 participants will then stay at the research clinic during the day for the entire period of using the MPC algorithm.

The remainder of the participants using the MPC algorithm will be allowed to complete the study as an outpatient after the first approximately 12 hour study visit after 8 participants are deemed safe to sleep at home and successfully completed the MPC arm without any events of severe hypoglycemia or diabetic ketoacidosis. Severe hypoglycemia is defined as event that required the assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Diabetic ketoacidosis is classified as: symptoms such as polyuria, polydipsia, nausea, or vomiting, serum ketones >1.5 mmol/L or moderate/large urine ketones, either arterial blood pH<7.3 or venous pH<7.24 or serum bicarbonate <15, and treatment provided in a health care facility. If an event of severe hypoglycemia or diabetic ketoacidosis should occur, the study will be halted and a description of the serious adverse event and a new risk mitigation plan will be submitted to the FDA. The study will only resume once FDA approval is received.

We are aware that there is a risk of severe hypoglycemia while the participants are at home. The system will alert if the sensed glucose values fall below 70 mg/dl prompting the participant to obtain a capillary blood glucose sample. Participants will be required to live with at least one other person age 18 or older and live within 40 miles of OHSU. All participants 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 participant off campus, the participant will be able to go into open-loop mode. This will allow the Omnipod to begin basal insulin delivery for a pre-set basal profile(s) inputted for the participant at the study start. Participants will be able to give meal boluses and corrections through the Omnipod while in open-loop mode. When the error is resolved, the participant can resume closed-loop mode and the system will resume. If the participant goes into open-loop mode, 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. The participant may contact study staff at any time during the outpatient portion of the visit.

Discharge from inpatient clinic

If the participant'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 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 12 hour inpatient visit, participants will be discharged from the clinic, with the exception of the first 8 participants using MPC exercise-enable mode, as detailed above. Capillary blood glucose will be measured prior to discharge. Participants will wait to discharge home if capillary blood glucose is <85 and or >300 mg/dl or at the discretion of the study investigator, and treatment will be at the discretion of the study investigator. Once participant's capillary blood glucose is between 85-300 mg/dl, they can be discharged home. For all participants using the MPC mode, the investigator will review the physician portal to assess participant's insulin on board before they go home. Participants will be given enough supplies to continue running the study while at home for 2 days. After the participant 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. Participants will be instructed to not eat a meal after he/she leaves the inpatient clinic after the Day 1 visit. Starting the morning of Day 2, participants will be instructed to eat meals and snacks as they normally would. Participants will be instructed that his/her companion will be required to stay with them each night while an outpatient.

For the two days spent as an outpatient, participants will be asked to workout using the study video in the morning at a time of their choice on either Day 2 or Day 3. Participants will be asked to fill out the specifics of the exercise in a journal. Participants will be asked to not exercise on the other day spent at home. During the FMPD visit, participants will be instructed to only accept exercise detection on the app if they are exercising for 20 minutes or longer. Participants will be reminded to check their blood glucose before and after exercise (as soon as possible after exercise but no later than 15 minutes after the completion of exercise). For participant safety, capillary blood glucose must be 100 mg/dl or higher to begin exercise while the participant is at home. Participants will be given instructions to take additional carbs at the

start of exercise as needed based on CGM and trend to avoid post-exercise lows. See Appendix F outpatient instruction card. Participants will be required to have a person age 18 or older who attended a training session on the study present while the participant exercises at home. For at home exercise, the companion will stay after the exercise until the participant's CBG is > 100 mg/dl or for 60 minutes after exercise is completed, whichever is longer. Participants will inform study staff when exercising at home in the MPC arm to allow for more direct remote monitoring. Staff will continue to monitor until exercise is completed and glucose is above 100 mg/dL.

Return to the Outpatient Clinic at OHSU

On the fourth day, participants will return to the AIMS lab in Biomedical Engineering Dept at CHH1, the CTRC clinic, or the Harold Schnitzer Diabetes Health Center in the morning. Participants 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. The study will be terminated and the participant's own insulin pump will be restarted. The study investigator will consult with the participant regarding appropriate insulin dosing for the remainder of the day. The Polar watch, Omnipod and Dexcom sensor will be removed from the participant. All infusion and sensor sites 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 participant will return 1-3 days later for a follow-up visit. A capillary blood glucose value will be taken immediately prior to discharging the participant. Participants 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.

There is the option to complete this visit by Webex. Participants will be given shipping boxes for sending all devices back. Participants will connect with a study coordinator and investigator virtually to complete the visit.

If a study visit is stopped prematurely, such as due to technical problems, the participant 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 IM
- Verify that insulin is turned off.
- Further management per study investigator.

Hyperglycemia Treatment Guidelines

If the sensed glucose is ≥ 300 mg/dl, the participant 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 check for 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 participant will be instructed to check serum ketones using the Abbott Precision Xtra meter and to change out the Omnipod. If serum ketones are over 0.6 mM, the on-call study investigator will be alerted to discuss proper management, including delivering a correction bolus. In addition, the participant 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 participants. The smart phone, Dexcom G6 transmitter, heart rate monitor 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 Oxivir TB 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 participant information.

Stopping Rules

Individual study 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 start 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.

Entire study stopping rules

Triggers for reporting unanticipated problems are seizure, hospitalization, death or any other occurrence considered serious by the PI and Medical Monitor. If any studies are stopped for severe hypoglycemia or diabetic ketoacidosis, then the entire study will be halted. Severe hypoglycemia is defined as event that required the assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Diabetic ketoacidosis is classified as: symptoms such as polyuria, polydipsia, nausea, or vomiting, serum ketones >1.5 mmol/L or moderate/large urine ketones, either arterial blood pH<7.3 or venous pH<7.24 or serum bicarbonate <15, and treatment provided in a health care facility. If an event of severe hypoglycemia or diabetic ketoacidosis should occur, the study will be halted and a description of the serious adverse event and a new risk mitigation plan will be submitted to the FDA. The study will only resume once FDA approval is received. 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.

The Fading Memory Proportional Derivative (FMPD) Algorithm

The FMPD algorithm determines insulin 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. Gain factors determine the degree to which proportional or derivative errors lead to changes in the delivery rate.

For the FMPD exercise-enabled mode, the exercise threshold will be set to 4 METs/min for every participant 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. When exercise is detected while in the FMPD exercise-enabled mode, and the participant 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). 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 participant selects that they are not exercising, iPancreas will present a dropdown menu from which the participant 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 participant 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 participant 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.

The Model Predictive Control (MPC) Algorithm

Our MPC algorithm uses a glucoregulatory model to predict glucose outcomes over a predicted horizon (Np), and mathematically solve for the optimal insulin doses across the control horizon (Nc) to bring the participant to target. The model is updated at each timestep by a Kalman filter, which uses the difference between CGM observations and model predictions to update the physiologic model states. In short, a model-predictive controller uses a physiologic model to calculate how much insulin is required to bring someone to glucose target, and these predictions are adapted to the specific participant using a Kalman filter.

For the MPC exercise-enabled mode, there is a model within the controller that takes as an input the aerobic metabolic expenditure in addition to the CGM and meal inputs. The algorithm uses heart rate and accelerometer data collected on the patient's body to calculate metabolic expenditure. The metabolic expenditure then acts on the model for the insulin dynamics, whereby more energy expenditure and longer duration exercise can lead to a more substantial effect of insulin on the CGM (i.e. the CGM will drop more in response to more intense aerobic exercise and with longer duration exercise). In this way, the model within the MPC control algorithm is always aware of exercise as a continuous input to the system and can respond dynamically to short or long, light, moderate, or intense exercise bouts. We expect that the MPC controller will be able to dynamically adapt to either short or long exercise bouts. We also expect the MPC to dynamically adapt to in-home exercise better, which can be more variable than static exercise that is performed within a clinic under controlled conditions.

Since the MPC mode treats exercise differently than the FMPD mode, some exercise alerts to the user will not populate. The low glucose alert will populate when sensor glucose goes below 70 mg/dl, instead of 85 mg/dl in FMPD mode with exercise detection. The alert not allowing exercise when ketones are above 0.6 mM will not populate while in MPC mode, but the participants will be coached not to exercise when ketones are high.

Statistical methods

The primary study endpoint is percent of time with glucose sensor <70 mg/dL during the inpatient clinic day. The hypothesis to be tested is the MPC exercise-enabled closed-loop system will increase time in range as compared to the FMPD exercise-enabled closed-loop system. As our main approach, we will perform a two-sided Wilcoxon test for the paired differences. This test is widely used and easily interpreted. However, it cannot accommodate missing data or estimate crossover effects, and while we do not anticipate that these will affect our study outcomes, we plan to conduct a supplemental analysis using a linear regression model with bootstrapped standard errors, which do not require distributional assumptions. In resampling for the bootstrap, we will use study subjects as the sampling unit to account for correlation between their repeated observations. The general model is as follows:

$$(1) \qquad Y_{ij} = \beta_0 + \beta_1 Trt_j + \beta_2 Seq_i + \beta_3 Period_j$$

In this model, the outcome Y_{ij} is the percent of time with glucose sensor <70 mg/dL for person i in observation period j. Trt_j represents the treatment arm (MPC=1, FMPD=0). Seq_i is an indicator for sequence (AB vs BA) and $Period_j$ indicates when Trt_j occurred in the sequence. The coefficient β_0 represents the mean response for FMPD, and the coefficient β_1 represents the difference between treatments to be tested. The coefficients β_2 and β_3, mean differences for sequence or period, are both expected to equal zero; a large effect or significance test with p-value <0.05 will be considered evidence of a carryover effect. Hypothesis tests will be two-sided with type I error set to 0.05. Because statistical tests are specified and prioritized *a priori* and our

proposed endpoints are highly related, we will follow recommendations to report p-values and confidence intervals rather than adjust for multiple comparisons.

Model fit and alternatives: Goodness of fit statistics and model fitting diagnostics will be used to assess for influential points and to evaluate alternative model specifications. If needed to compensate for some skew and heteroscedasticity in secondary outcomes, we will use bootstrapped variance estimators and compare these against robust estimates.

Missing data: Our primary approach will include all available data as an intention-to-treat analysis, regardless of whether study subjects completed both arms. An observation will be included if at least 24 hours of data are available. However, we expect very low levels of missingness; in our previous four-arm crossover study, only one subject withdrew before completing at least two arms. Dropped CGM values will be interpolated over short time periods, using capillary values for calibration when available. In the event of ≥10% missingness in either subject data or CGM values, we will analyze outcomes under multiple imputation to compensate for potential bias.

Additional considerations for selected secondary endpoints: The number of carbohydrate treatments will be modeled using model (1) above with Poisson regression for count data. The coefficient of variation of glucose is non-normal without an obvious probability distribution, so that bootstrapping will be our primary approach for this endpoint. Data for percent of time with sensed glucose <54 mg/dl may be sparse; if so, we will present counts of events where glucose went below this level, counting as separate events when the time between them is ≥ 30 minutes.

Confidentiality and Protection of Human Participants

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. 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.

The following events have been identified as possible anticipated device-related adverse events of Dexcom G6 sensor insertion and wear:

- Excessive pain or discomfort from either system deployment or during wear period (8 or greater on a 10-point Likert scale)
- Excessive bleeding, defined as requires removal of the device to stop bleeding
- Hematoma, defined as induration at the sensor insertion location (ecchymosis is a known consequence of needle skin puncture or pressure from sensor pod and will not be captured as an AE)
- Edema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Erythema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal

- Local infection, defined as presence of pus at either sensor wire or sensor pod site
- Sensor or introducer needle fracture during insertion/wear/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 participant may not directly benefit from being in this study; however, their participation may help to advance automated insulin delivery technology.

COSTS:

The participants who stay in clinic each day for the MPC arm will receive $1025. If a participant withdraws early from the study, compensation will be given as follows: $50 for run-in, $225 per in clinic day for the MPC arm, $300 for the FMPD arm.

Otherwise, participants will receive $650 for completion of all study visits. If a participant withdraws early from the study, compensation will be given as follows: $50 for run-in, $300 for the MPC arm and $300 for the FMPD arm. There is no compensation for the screening visit. If a participant is asked to repeat a study due to technical problems, he/she will receive an additional $300.

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:

Participant privacy will be protected by using a three-digit identifying number to code study documents. 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 smart phone master controller will subsequently be entered into the authorized electronic OCTRI 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 G6 Training Visit
3. iPancreas Training
4. Companion Training
5. Day 1 Inpatient MPC Closed-loop Study Visit
6. Day 2 Inpatient MPC Closed-loop Study Visit
7. Day 3 Inpatient MPC Closed-loop Study Visit
8. Day 1 Inpatient FMPD Closed-loop Study Visit
9. Day 4 MPC Closed-loop Study Visit

10. Day 4 FMPD Closed-loop 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. The data to be collected includes: 1) glucose sensor data, 2) blood glucose data, 3) insulin data, 4) physical activity data, and 5) food and exercise data. All data, except for blood glucose, is aggregated by the iPancreas 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 participant. 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.

Adverse Event Reporting

At all study visits, study staff will determine if any adverse events (AEs) have occurred. Disease related events that are chronic in nature and occur as part of the progression of the diabetes disease state (i.e. diagnoses of retinopathy, nephropathy, and neuropathy) will not be captured as adverse events in this study. Hypo- and hyperglycemia will not be considered AEs unless participant 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 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. All AEs will be monitored until adequately resolved or stable. Information regarding AEs that occur during the study will be entered into appropriate CRFs. Such information will include, at a minimum:

- Date of event
- Severity
- Outcome
- Resolution of event

Definition of Adverse Event

An AE is any clinically significant undesirable experience (sign, symptom, illness, or other medical event) meeting the causality definition above that appears or worsens in a participant during a clinical study. A clinically significant event is any event (sign, symptom, lab/imaging abnormality, or diagnosis) that is noteworthy enough to merit documentation in standard medical records (e.g. history and physical, progress notes, clinic visit notes, etc.). Other non-clinically significant events (e.g. colds, minor headaches, etc.) *may* be documented on the comments CRF. Mild hypoglycemia is expected in persons with diabetes using insulin and are typically self-limiting in nature; thus, this will not be captured as an AE. The Medical Monitor will have the final say in determining the causality. Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening; (substantial risk of dying at the time of the adverse event or suspicion that continued use of the device would result in a participant's death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Requires medical or surgical intervention to prevent permanent impairment or damage.

Exceptions to the SAE definition will include the following:

- Elective surgery

- A planned hospitalization for pre-existing condition, without a serious deterioration in health

Any SAE, including death, due to any cause (related or unrelated to the device), that may occur during a clinical study will be reported to the PI and Medical Monitor immediately (within 1 working day of learning of the event).

Severity of Adverse Events

The following definitions may be used to rate severity of AEs:

- **Mild**
  Awareness of signs or symptoms, but easily tolerated; are of minor irritant type that is outside the norm for the disease state or subject; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient. Mild hypoglycemia is expected in diabetes and will not be captured as an AE.
  Example: *ketosis not requiring an ER visit.*
- **Moderate**
  Discomfort severe enough to cause interference with usual activities, requiring treatment due to cognitive impairment, by family member or emergency personnel
  Example: *hypoglycemia with inability to self-treat, requiring third party assistance for treatment and/or an emergency room visit.*
- **Severe**
  Incapacitating, causing inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical evaluation and/or treatment at a health care facility
  Example: *hypoglycemia with loss of consciousness or seizure involvement*

Relationship of Adverse Events to Study or Study Device

The investigator will categorize the relationship of the event to the study or study device as follows:

- **Not Related**
  AE is due to an underlying disease state or concomitant medication or therapy not related to the device, disease or study.
- **Unlikely Related**
  AE has minimum or no temporal relationship to the study device, disease or study participation and/or a more likely alternative etiology exists.
- **Possibly Related**
  AE has a strong temporal relationship to the study device, disease or study procedures and alternative etiology is equally or less likely compared to the potential relationship to the device, disease or study.
- **Probably Related**

AE has a strong temporal relationship to the study device, disease or study and another etiology is unlikely.

- **Definitely Related**
  AE has a strong temporal relationship to the study device, study procedures or disease and another etiology does not exist.

Unanticipated Problems

Unanticipated problems, including study, disease or device-related 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 or if root cause or associations is with study devices.

Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect (UADE) is not expected to occur. An UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including documents such as the protocol, the informed consent document, other study-related documents), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of participants.

During the review of a reported SAE, if the PI and Medical Monitor input determines the severity or extent of the event was not cited in this protocol or associated protocol materials, and the event was classified as, 'possibly related' to the device, the event will be documented as an UADE. If the event is classified as an UADE, the Investigator must notify the IRB and Dexcom will notify the FDA within ten (10) working days of the original SAE notification.

If determined that the UADE presents an unreasonable risk to participants, we will terminate all investigations or parts of investigations presenting that risk as soon as possible, but not later than 5 working days after such determination is made and not later than 15 working days after we first receives notice of the original SAE. We will not resume a terminated study without IRB and FDA approval.

MDR Reportable Events/MDR Reporting

A device issue, whether related to a complaint or not, is an allegation from the participant or study personnel regarding an indication of the failure of a device to meet user expectations for quality or performance specifications. Device issues will be recorded onto appropriate CRFs by site personnel. The CGM and Omnipod devices are currently marketed. Therefore, the PI will follow the required reporting regulations to Dexcom or Insulet if an MDR reportable event occurs.

MDR reportable events are events that manufacturers become aware of that reasonably suggest one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device would likely cause or contribute to a death or serious injury if the malfunction were to recur (21 CFR 803.3).

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.

Data for this project will be stored in OCTRI's installation of REDCap, a highly secure and robust web-based research data collection and management system. Features of REDCap that protect participants' privacy and data security include:

- Physical Security: OCTRI's REDCap software is housed on servers located in ITG's Advanced Computing Center providing locked physical security.
- Electronic Security: The REDCap servers are housed behind both the OHSU firewall and a second ACC firewall. All transmissions of data from the application are encrypted over HTTPS with the industry standard TLS 1.1 protocol (AES 256-bit encryption).
- Controlled User Access: REDCap is employs a robust multi-level security system that enables researchers to easily implement "minimum necessary" data access for their research staff, including specification of data fields that are identifiers. This feature includes “single click” ability to provide completely deidentified (removing all identified data fields and shifting dates) for analysis or other purposes. User activities are logged to enable auditing of all data access. Access is integrated with OHSU's network such that users who are also OHSU employees are authenticated against their OHSU network credentials.
- Data Integrity: REDCap is jointly managed in accordance with OHSU Information Security Directives by ACC staff and members of OCTRI's Biomedical Informatics Program, ensuring fidelity of database configuration and back-ups. User activities are logged to enable auditing of all data changes.

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.

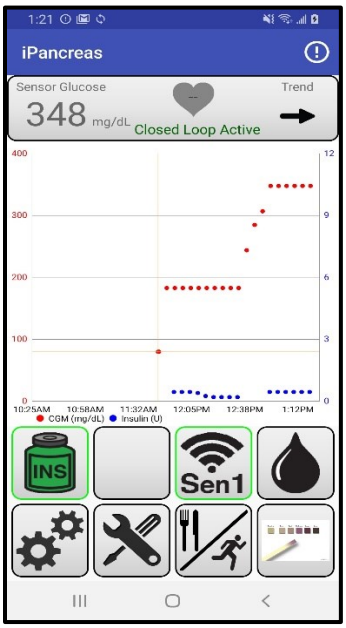
Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

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 G6 Continuous Glucose Monitoring System which includes Sensor and Sensor Transmitter



Contour Next Blood Glucose Meter

Abbott Precision Xtra Meter

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

#	NAME: Activation criteria	Clearing Criteria	Algorithm specifics	Notification to participant	Re-fire Time (min)	Refractory Period (min)	Coordinator push	Investigator push	Waiting period
4	**cbg_equal_or_under_40**: 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.	None	"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 alert 13 is serviced OR clear criteri is met
5	**cbg_under_70:** CBG < 70 mg/dl AND alert 5 not active AND alert 4 not active	CBG entry ≥70 clears alert. Once rescue carbs are entered, the waiting period starts. Alert clears if activation of alert 4 is met	None	"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 alert 13 is serviced OR clear criteri is met
6	**sensor_glucose_low:** Sensor glucose < LOW_THRESH AND alert 4 AND alert 5 AND alert 6 not active or refractory & no CBG within last 15 minutes	CBG check OR sensor ≥ LOW_THRESH	For MPC, LOW_THRESH = 70 mg/dL For FMPD, when not in exercise mode, LOW_THRESH = 70 mg/dL	"Sensor glucose is below LOW_THRESH mg/dl. Please perform a blood glucose check now."	15	60	After 1st re-fire	After 2nd re-fire	-

			For FMPD when in exercise mode, LOW_THRESH = 85 mg/dL						
7	**cbg_equal_or_over_300:** CBG ≥ 300 mg/dl AND alert 27 not active or refractory AND alert 7 not active or refractory	Ketone check	None	"Blood glucose is above 300 mg/dl. Please check the insulin pod for leaking or detachment and check ketone levels now."	30	120	After 1st re-fire	After 2nd re-fire	-
8	**sensor_glucose_high:** Sensor glucose ≥ 300 mg/dl for 30 minutes within the last 45 minute period AND alert 8 AND alert 7 AND alert 27 not active or refractory AND no CBG in last 30 minutes	CBG check. OR sensor < 300	None	"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	**Insulin_meal_bolus_failure:** If 50% of meal bolus is still not delivered after 20 minutes.	Auto clears	None	Insulin bolus failed to deliver, please contact the study investigator.	-	-	Immediately	Immediately	-
13	**recheck_cbg:** 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_data_connection:** 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	**transmitter_not_reporting:** Sensor is out of date for > 20 minutes AND alert 17 AND alert 18 AND alert 20 not active or refractory	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	-
18	**replace_transmitter:** iPancreas 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_glucose_invalid:** 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	**replace_sensor:** iPancreas 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	**Insulin_pump_communication_failure:** Basal Insulin Fails to deliver correct amount for 60 minutes OR insulin suspend required and no connection to pump	Successful basal insulin 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	-

25	**phone_battery_low:** 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	**maximum_insulin_exceeded**: Insulin Delivery ≥ 35% $TDIR_{adj}$ on last hour	Auto clears		"Max insulin has been exceeded"	-	60	Immediately	Immediately	-
27	**cbg_equal_or_over_400:** 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	**ketone_level_high:** 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_pump_reservoir_low:** 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	-

Appendix E: Exercise Video Outline

Aerobic Exercise Video Outline		
Segment	**Segment Time**	**Activities**
Warm-Up Intro (2 min)	**0:00 – 2:00**	**0:00: Welcome! Marching Reach Up** **0:30: Side to Side Kick Back Pull Back** **0:45: Side to Side Kick Back Butt Kick** **1:00: Side to Side Kick Back Butt Kick Reach out** **1:15: Grapevine** **1:30: Grapevine with Arm Circles**
Active Exercise **(30 min)**	**Each activity is performed for 30 seconds**	**1. Modified Jump rope** **2. Jumping jacks** **3. Side to Side Knee Raise (alternate left/right crunch)** **4. Side Steps (active recovery)** **5. Modified Jump rope** **6. Jumping Jacks** **7. Side to Side Knee Raise (alternate left/right crunch)** **8. Side Steps (active recovery)** **9. Arms Alternating A, T and Y with Heal Tap** **10. Left Jab Bounce (left foot forward)** **11. Side Steps (active recovery)** **12. Arms Alternating A, T and Y with Heal Tap** **13. Right Jab Bounce (right foot forward)** **14. Side Steps (active recovery)** **15. Right Leg Lunge Alternate Forward Back**

		16. Left Leg Lunge Alternate Forward Back **17. Jog in Place Hands Raised** **18. Side Steps (active recovery)** **19. Right Leg Lunge Alternate Forward Back** **20. Left Leg Lunge Alternate Forward Back** **21. Jog in Place Hands Raised** **22. Side Steps (active recovery)** **23. Squat to Upper Cut (right foot forward)** **24. Right Jab Bounce (right foot forward)** **25. Side Steps (active recovery)** **26. Squat to Upper Cut (left foot forward)** **27. Left Jab Bounce (left foot forward)** **28. Side Steps (active recovery)** **29. Horse Stance Overhead Reach Side Bend/ Standing Alternating Side Bend** **30. Side Jump with Squat Alternating Left Right** **31. Right Lateral lunge with Right Knee Drive Pull Up** **32. Left Lateral Lunge with Left Knee Drive Pull Up** **33. Side steps (active recovery)** **34. Horse Stance Overhead Reach Side Bend/ Standing Alternating Side Bend** **35. Side Jump with Squat Alternating Left Right** **36. Right Lateral lunge with Right Knee Drive Pull Up** **37. Left Lateral Lunge with Left Knee Drive Pull Up** **38. Side steps (active recovery)**

Appendix F: **Instruction cards for participants to take additional carbs at the start of exercise as needed based on CGM and trend to avoid post-exercise lows**

Inpatient instruction card:

Sensor glucose during exercise in clinic	G6 Trend arrow direction	Action
Ketones above 0.6 mmol/L	all	Stop/do not start exercise. Contact study staff.
Greater than 270 mg/dl with ketones less than 0.6 mmol/L	all	Proceed with exercise.
145-270 mg/dl	all	Proceed with exercise.
Less than 145 mg/dl	↑ or ↗	Proceed with exercise.
	→	Consume 15 grams carbs. Proceed with exercise.
	↘	Consume 25 grams carbs. Proceed with exercise.
	↓	Consume 35 grams carbs. Proceed with exercise.
Less than 80 mg/dl	all	Do not start exercise. Check fingerstick glucose. Consume 15 grams of carbs every 15 minutes until fingerstick glucose is above 80 mg/dl.

Outpatient instruction card:

Sensor glucose during exercise at home	G6 Trend arrow direction	Action
Ketones above 0.6 mmol/L	all	Stop/do not start exercise. Contact study staff.
Greater than 270 mg/dl with ketones less than 0.6 mmol/L	all	Proceed with exercise.
145-270 mg/dl	all	Proceed with exercise.
Less than 145 mg/dl	↑ or ↗	Proceed with exercise.
	→	Consume 15 grams carbs. Proceed with exercise.
	↘	Consume 25 grams carbs. Proceed with exercise.
	↓	Consume 35 grams carbs. Proceed with exercise.
Less than 100 mg/dl	all	Do not start exercise. Check fingerstick glucose. Consume 15 grams of carbs every 15 minutes until fingerstick glucose is above 100 mg/dl.

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[1] J. R. Castle *et al.*, "Randomized Outpatient Trial of Single- and Dual-Hormone Closed-Loop Systems That Adapt to Exercise Using Wearable Sensors," *Diabetes Care,* vol. 41, no. 7, pp. 1471-1477, Jul 2018, doi: 10.2337/dc18-0228.

[2] A. Weisman, J. W. Bai, M. Cardinez, C. K. Kramer, and B. A. Perkins, "Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials," *Lancet Diabetes Endocrinol,* vol. 5, no. 7, pp. 501-512, Jul 2017, doi: 10.1016/S2213-8587(17)30167-5.

[3] P. G. Jacobs *et al.*, "Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy," *Diabetes Obes Metab,* vol. 18, no. 11, pp. 1110-1119, Nov 2016, doi: 10.1111/dom.12707.