PROTOCOL TITLE: A randomized study to compare a fully-closed MPC control algorithm with a commercial hybrid closed-loop algorithm

Brief Title: Two Way Crossover Closed Loop MPC vs Control IQ

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PROTOCOL TITLE: A randomized study to compare a fully-closed MPC control algorithm with a commercial hybrid closed-loop algorithm

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Background:
Closed-loop systems automate insulin delivery based on continuous glucose monitoring (CGM) values to minimize hypoglycemia and hyperglycemia. 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[1-3]. The novelty of these closed-loop systems is their ability to automatically detect exercise and adjust dosing in response to the exercise. In preparation for the study outlined here, we have recently completed two closed-loop studies.

The first study was an outpatient closed-loop study, which tested the OHSU insulin-only closed-loop system using the Fading Memory Proportional Derivative (FMPD) algorithm which modulates insulin delivery using a Proportional-Integral-Derivative (PID) controller with exercise detection when metabolic expenditure goes above a set threshold as compared to a model predictive control (MPC) algorithm that modulates insulin delivery based on estimated activity level every 5 minutes based on accelerometry input. Participants underwent two 76-hour studies in randomized order, one using the FMPD and one using the MPC algorithm. Participants were in clinic for the first 12 hours of each study visit, eating meals and performing activities of daily living and exercise. Then participants went home using the system for the rest of the visit, completing one exercise at home. During the two hours after in-clinic exercise, both algorithms

yielded good results, but the MPC yielded a higher percent time in range (70-180 mg/dl) at 87.5% vs. 76.3% (p=0.0462) and lower time in hypoglycemia (<70 mg/dl) 1.9% vs. 4.6% (p=0.09). The MPC and FMPD arms were not significantly different from each other across the 76 hour visit with time in range for MPC vs FMPD of 74.5% vs. 75.7% and time in hypoglycemia (<70 mg/dL) 1.0% vs. 1.4%.

The second study was performed in clinic and tested the MPC algorithm described above against a modified MPC algorithm with missed meal insulin detection. Participants underwent two 8 hour studies in randomized order, one with and one without missed meal insulin detection. Participants ate two meals four hours apart without administering a meal bolus. During the study using missed meal insulin detection algorithm, the system was designed to identify the meal without an accompanying insulin bolus based on CGM data and give a suggestion for a bolus. The primary endpoint was the positive incremental area under the curve (iAUC) after breakfast. The mean (SD) iAUC was 253.9 (105.9) [mg/dl]*h with the use of the missed meal insulin algorithm vs. 277.5 (159.4) [mg/dl]*h without it. Secondary outcome metrics included % time in hypoglycemia (<70 mg/dL), % time in range (70-180 mg/dL), and time in hyperglycemia (>180 mg/dl). Time in hypoglycemia was less than 2% for both arms. Time in range was higher with the use of the missed mealtime insulin algorithm 33.4 (22.8)% vs. 24.3 (20.2)% without it. Time in hyperglycemia was lowest with the missed mealtime insulin algorithm 64.8 (24.1)% vs. 75.7 (20.2)% without it. The algorithm accurately detected 83.3% of the meals with median detection time of 26 minutes (range = [25,30] minutes).

The study described within this protocol is designed to test the safety and efficacy of the OHSU model predictive control (MPC) algorithm that modulates insulin delivery based on estimated activity level combined with the OHSU missed meal detection algorithm. 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 and notifies users of rises in glucose levels that may have been related to a missed mealtime insulin bolus and automatically delivers an insulin dose to reduce post-prandial hyperglycemia. Participants will be enrolled who currently use the t:slim X2 pump with Control IQ or Omnipod 5 closed loop system.

Primary Objective:

- To confirm non-inferiority of the OHSU MPC exercise-enabled closed-loop system with missed mealtime insulin detection algorithm as measured by percent of time 70-180 mg/dL on Dexcom G6 CGM as compared to use of the participant's personal closed loop delivery system.

Secondary Objective:

- To confirm non-inferiority of the OHSU MPC exercise-enabled closed-loop system with missed mealtime insulin detection algorithm as measured by other glucose metrics as compared to use of the participant's personal closed loop delivery system.

Study Hypothesis:

We propose that the use of the OHSU MPC exercise-enabled closed-loop system with missed mealtime insulin detection algorithm will be non-inferior within a time in range margin of 7% as compared to the participant's closed loop delivery system in patients with elevated baseline A1C values.

Endpoints

Primary Endpoint:

- Percent of time with sensed glucose between 70-180 mg/dl across the study duration

Secondary Endpoints:

- Percent of time with sensed glucose between <70 mg/dl across the study duration
- Percent of time with sensed glucose <54 mg/dl across the study duration
- Percent of time with sensed glucose >180 mg/dl across the study duration
- Mean sensed glucose across the study duration
- Coefficient of variation of glucose across the study duration
- Mean amount of insulin delivered per day (in units/kg) across the study duration

Study Type

This is a multi-center, randomized, two treatment, crossover non-inferiority trial designed to compare the glucose control resulting from the use of the OHSU MPC exercise-enabled AP system with missed mealtime insulin detection algorithm (Intervention Period) as compared to usual care using a closed loop insulin delivery system, either the t:slim X2 pump with Control IQ or Omnipod 5 system (Control Period).

Study Population

Study population will be participants with type 1 diabetes, ages 18 years of age and older. Up to 36 participants will be recruited to participate in studies across two sites.

Power Analysis

A sample of 28 subjects provides at least 80% power for testing our primary endpoint in a non-inferiority framework comparing the exercise-enabled MPC algorithm with missed meal insulin detection to use of participant's personal closed loop system. Assumptions informing this calculation were derived from simulations showing an expected mean percent time in range (70-180 mg/dL) for control IQ that was 3.7% lower (as a difference rather than a ratio) and standard deviations (SDs) for the two conditions of approximately 16 to 19. From this, we assume the SD of the within-subject difference will be approximately 17% and use a one-sided paired t test at the 0.025 level of significance for a mean difference of 3.7% time in range versus 6% as the non-inferiority margin. We plan to recruit up to 36 subjects with goal enrollment of 30 subjects (about 15 at each center).

Protocol Summary:

Participants will undergo one 7-day Intervention Period and one 7-day Control Period in randomized order. During the 7-day intervention study, participants will wear an Omnipod to deliver Fiasp insulin and a Dexcom G6 CGM. 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 smartphone will wirelessly communicate via BTLE to an Omnipod through a Personal Diabetes Manager (Insulet Corp.). The closed-loop system will receive activity data through a Polar M600 watch worn by the participant. Participants will eat one meal in clinic and complete system training on Day 1 and then spend the rest of the 7 days at home. During the 7-day Control Period, the participant will continue their usual diabetes care regimen using a t:slim X2 pump with Control IQ enabled or the Omnipod 5 closed loop system.

Participant Criteria

Inclusion Criteria:

1. Diagnosis of type 1 diabetes mellitus for at least 1 year.
2. Age 18 years and older.
3. Current use of a t:slim X2 insulin pump with the use of Control IQ or the Omnipod 5 system with closed loop enabled with Dexcom G6 or G7 for at least 12 weeks.
4. Willingness to use Fiasp insulin during intervention study
5. Lives with another person age 18 or older who will sleep in the house at night and that can attend the training on using the system.
6. HbA1c or GMI ≥ 7.5% at screening. GMI (%) = 3.31 + 0.02392 × [mean glucose in mg/dL] based on prior 30 days of Dexcom CGM data.[4]
7. Total daily insulin requirement is less than 139 units/day.
8. Current use of a smartphone so can be contacted by study staff off-campus
9. Willingness to follow all study procedures, including attending all clinic visits.
10. 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. HbA1c >10% or ≤6.5% at screening.
3. Percent time < 54 mg/dL of >2% based on prior 30 days of Dexcom CGM data.
4. 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.

5. Renal insufficiency (GFR < 60 ml/min, using the MDRD equation as reported by the site laboratory).
6. Liver failure, cirrhosis, or any other liver disease that compromises liver function as determined by the investigator.
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 Fiasp 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. Current use of beta blockers or non-dihydropyridine calcium channel blockers.
23. Current use of any medication intended to lower glucose other than insulin (ex. use of metformin or liraglutide) or SGLT-2 inhibitors (for diabetes or other indications, ex. use of empagliflozin or ertugliflozin).
24. Gastroparesis
25. Low carbohydrate diet at the time of screening defined as less than 50 grams of carbohydrate per day.
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 2 sites in the United States, one of which will be Oregon Health & Science University (OHSU). 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 60 participants may be screened in this study. Goal enrollment is 30 participants across both sites with up to 6 replacements as needed to collect data from 28 participants. However, re-screening is allowed up to one time per individual, no sooner than 2 weeks and no longer than 3 months and after initial screen. It is anticipated that each site will enroll about 15 participants, but this may be adjusted if needed to complete enrollment in a timely fashion.

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:

- Severe Hypoglycemia during the treatment period (control or intervention period). Severe hypoglycemia is defined as any event that required the assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions.
- Diabetic ketoacidosis during the treatment period (control or intervention period). 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
- Other circumstances that would endanger the health of the participant if they were to continue participation in the study
- 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 first 7-day Visit. 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.

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, and complete metabolic set (including creatinine, liver set, and electrolytes). 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 to obtain the prior 4 weeks of data. A three-digit participant ID number will be assigned to the participant. This visit will take approximately 1.5 hours.

The treatment order will be randomized. The two periods, which are the 7-Day Control Period and 7-Day Intervention Period, will be a minimum of 7 days and a maximum of 8 weeks apart counting from the first day of the first period to the first day of the second period.

A complete list of times when participants will be instructed to take SMBG readings is listed below.

Participants will be instructed to take SMBG readings under the following conditions:

1. If the sensor glucose is <70mg/dL, the system will prompt a SMBG be entered. (intervention period only)
2. If the sensor glucose is ≥ 300 mg/dl for 30 minutes within the last 45 minute period, the system will prompt a SMBG be entered. (intervention period only)
3. If participant's symptoms (such as symptoms of hypoglycemia or hyperglycemia) are discrepant with the Dexcom CGM reading, then the participants will be instructed to perform a SMBG and use this value to make treatment decisions and to calibrate the Dexcom device. (Intervention and control period)
4. If CGM value is unavailable, a SMBG will be required to calculate a correction bolus. (Intervention and control period)
5. Before driving to clinic for study visits. (Intervention and control period)
6. On arrival to clinic for study visits. (Intervention and control period)
7. Before and after exercise if they choose to exercise during the study period. (Intervention and control period)
8. On discharge from clinic for study visits. (Intervention period)

7-Day Control Period

For the 7-Day Control Period, women of childbearing potential will receive a urine pregnancy test if the last pregnancy test was more than 7 days prior. This test must be negative before further participation is allowed. A capillary blood glucose (CBG) will be measured. Participants will complete a virtual visit by WebEx or Microsoft Teams or in person to start this visit. The purpose of this visit is to assist the participant with downloading: 1) the Dexcom Clarity app and sharing their data with the site, 2) the t:connect app and pairing it to their pump on their personal phone 3) Tidepool uploader app or 4) for Omnipod 5 users, logging in to their account at https://insuletid.com/ from a computer/laptop/mobile browser and selecting to connect to

Glooko. If participants already have these apps on their phones, the visit will be used to confirm that data sharing is in place. The participants will continue to use their personal closed loop system, either the t:slim X2 pump with Control IQ or Omnipod 5, and their own insulin during the 7-Day Control Period. They will be instructed to take boluses prior to meals as they usually would. Participants will be asked to check their capillary blood glucose for symptoms of hypoglycemia or hyperglycemia if discrepant with CGM reading and in response to CGM alerts.

Participants will be given an instruction card (see Appendix C) for carbohydrate treatment before exercise to follow, if participants choose to exercise as part of their week. On the seventh day, participants will connect virtually by WebEx or Teams with study staff to share their pump download and confirm Dexcom Clarity data has been shared. A capillary blood glucose (CBG) will be measured. If the participant is not able to send the pump download and/or Clarity data is not being shared, the participant will come into clinic so that staff can download their devices.

7-Day Intervention Period

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). For the 7-Day Intervention Period, 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 7-Day Intervention Period. We will inquire whether the participant has had changes in their medications and/or medical history to confirm the participant does not meet 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 a study investigator.

During the 7-Day Intervention Period, glucose will be controlled using the OHSU MPC exercise-enabled closed-loop mode with missed mealtime insulin detection algorithm. The first approximately 6 hours of the visit will be conducted in clinic. The participants will then go home. The first 5 participants will be conducted at OHSU with remote monitoring. If safety criteria are satisfied, as outlined below, subsequent participants may be enrolled without remote monitoring at any of the sites.

The wire glucose sensor is sterile and commercially available from Dexcom™ and will be used for single use only as directed by the manufacturer. The participant will be trained on how to insert a Dexcom G6 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.

An Omnipod (510K#042792) will be filled with Fiasp insulin. We will use only name brand insulin, not generic insulin. We will provide the participants with Omnipods to replace the Omnipod at home every 72 hours or earlier if needed along with a vial of Fiasp insulin and train participants how to perform this. The Omnipod will be primed and inserted as directed by the manufacturer. Research staff will train participants on the approved Omnipod 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. Since the Dexcom G6 sensor will require a two-hour warm-up, the system will be started in open loop mode with the system delivering their programmed basal rate. Once a sensor value is available, the research staff will initialize the system and begin the closed-loop study 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 7-day study period. A study investigator will be available in person or by phone for the entire 7-day study period.

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, entering capillary blood glucose values and ketone levels, addressing alerts, troubleshooting the devices connection to the phone via Bluetooth, and pausing the study. Participants will be advised that they can take insulin prior to meals or they can allow the system to detect the meal and give insulin automatically. Participants will be instructed that taking insulin before meals will generally reduce hyperglycemia. 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/they become comfortable using the smartphone 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 on day 1 of the closed-loop visit prior to discharge. Each participant will start the G6 sensor and start the Omnipod on their own during onboarding. Participants will need to show competency in 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. Participants will be given contact information to call for any problems during the 7-day study period. 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. Participants will be given an instruction card (see Appendix C) for carbohydrate treatment before exercise to follow, if participants choose to exercise as part of their week. The site investigator will monitor in real-time the first auto-bolus delivered in closed-loop mode for each subject.

The algorithm will push data up to a cloud server that can be monitored remotely every 5 minutes. A study coordinator will be available at all times for the visits with the ability to monitor the closed-loop system remotely via a cloud system on the web in the event of any issues. The closed-loop system will generate alerts on the smartphone according to Appendix B. 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. The first 5 participants will be remotely monitored by study staff as described in more detail below. 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 B for those studies being remotely monitored. 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 staff is remote monitoring and the participant cannot be reached and sensor glucose is below 54 mg/dl, the companion will be contacted. If the alert is still un-serviced and study staff are unable to reach the participant or the companion, emergency medical services will be contacted (staff attempted to contact both participant and companion 2x each with less than 2 minutes between each call). If the companion is not able to assess of the participant's status within 5 minutes, we will reach out to emergency services.. 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.

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 capillary blood glucose before and after exercise (if the participants selects to exercise), for symptoms of hypoglycemia, and in response to system alert (such as for low or high sensor alerts).

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.

The food items will be self-selected by the participant.

Safety assessment – first 5 participants

We are proposing to remove remote monitoring after the successful completion of the first 5 participants if the safety criteria are satisfied. We will complete an interim analysis after the first 5 participants complete both arms of the study assessing time spent with CGM < 54 mg/dL, <70 mg/dL, and > 300 mg/dL and any adverse events. The closed-loop system data will be compared to the equivalent data from the participant's 7-Day Control period with the use of their personal closed loop system, either the t:slim X2 with Control IQ or Omnipod 5 system. If the interim analysis shows that the closed-loop system data is comparable to usual care studies and presents no safety concerns, we will proceed to enrolling participants without remote monitoring. 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 5 participants will then be completed with remote monitoring.

Severe hypoglycemia is defined as any event that required the assistance of another person to 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 the study site that enrolled the participant.

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

At the completion of the 6-hour in-clinic visit, participants will be discharged from the clinic. 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 on two capillary blood glucose measurements completed at least 30 minutes apart, they can be discharged home. If the capillary glucose is less than 85mg/dL, participants will be asked to consume 15g of glucose tablets. They can then be discharged if the next capillary glucose measurement 30 minutes later is greater than 85mg/dL. If the capillary blood glucose is <70, participants will be asked to consume 15g of glucose tablets and recheck capillary blood glucose every 15 minutes until >70. If capillary blood glucose is greater than 300mg/dL, participants will be instructed to pause iPancreas closed loop mode, take a correction bolus from the bolus calculator after reviewing this dose with the study investigator who will modify dose if needed considering current insulin on board then resume iPancreas closed loop mode. The participant can then be discharged home if the next capillary blood glucose measurement 30 minutes later is less than 300 mg/dL or if the CGM glucose trend arrow shows flat arrow (Increasing/decreasing less than 1 mg/dL each minute) or a down arrow (decreasing >30mg/dL in 30 minutes). Participants will be instructed to eat meals and snacks as they normally would at home. Participants will be instructed that his/her companion will be required to stay with them each night while an outpatient.

Return to the Outpatient Clinic

On the seventh day, participants will return to the outpatient clinic. 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 if capillary blood glucose is greater than 180mg/dL, participants will be instructed to take a correction bolus from their home insulin pump per their usual home settings after reviewing this dose with the study investigator who will modify dose if needed considering current insulin on board. The participant can then be discharged home if the next capillary blood glucose measurement 30 minutes later is less than 300 mg/dL or if the CGM glucose trend arrow shows flat arrow (increasing/decreasing less than 1 mg/dL each minute) or a down arrow (decreasing >30mg/dL in 30 minutes).

There is the option to complete this visit by WebEx or Microsoft Teams. 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

- Administer rescue glucagon per the manufacturer's instructions.
- 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 participant will be instructed to contact the study investigator to discuss proper management, including delivering a correction bolus. (see Appendix C 'Safety Instructions for Participants' for instructions provided to participants on when to contact study staff) 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 the participant's own pump will be resumed under the guidance of the on call study investigator if any of the following occur after the start of the study:

the participant requests that the treatment be stopped, participant pregnancy, one episode of diabetic ketoacidosis as defined 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, or one episode of severe hypoglycemia defined as a hypoglycemic event resulting in altered consciousness requiring another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

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 any event that required the assistance of another person to 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 Model Predictive Control (MPC) Algorithm

Our MPC algorithm uses a glucoregulatory model to predict glucose outcomes over a predicted horizon and mathematically solve for the optimal insulin doses across the control horizon 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.

The MPC algorithm shall be capable of automating the detection of meals and delivering a portion of the meal insulin. If a meal is detected that has not been reported by the user (i.e. meal carbohydrates entered with insulin bolus delivered), this shall be called a *missed meal insulin*. When missed meal insulin is detected by the MPC algorithm, the app shall calculate the amount of meal insulin that will be dosed and deliver that insulin without an announcement to the user.

Statistical methods

The primary study endpoint is percent of time in range defined as glucose measured by Dexcom G6 or G7 in the range of 70-180 mg/dL. The hypothesis to be tested is if the MPC exercise-enabled closed-loop system with missed mealtime insulin algorithm will be non-inferior as compared to the participant's personal 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 sensed glucose 70-180 mg/dL for person i in observation period j. Trt_j represents the treatment arm (MPC=1, Control IQ=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 Control IQ, 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 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: Given pumps and sensors used within automated glucose control systems are imperfect, there is a risk for hyperglycemia and hypoglycemia, which is mitigated by use of CGM alarms, protocols for managing hypoglycemia and hyperglycemia, and remote monitoring of the first 5 participants. A study investigator will be on call at all times.

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:

If a participant withdraws early from the study, compensation will be given as follows: $150 for the usual care arm, $100 for a confirmed download for t:slim or Omnipod 5 pump and Dexcom sensor from the usual care arm and $350 for the closed-loop arm. If a participant is asked to repeat a study due to technical problems, he/she will receive an additional $250 for usual care arm with download, $350 for the closed-loop arm. There is no compensation for the screening visit.

Safety Oversight:

Diana Aby-Daniel PA-C will be the study Medical Monitor. Diana Aby-Daniel has no commercial interest in any of the companies which manufacture any of the devices used in this study.

A Data and Safety Monitoring Board (DSMB) will provide safety oversight. The DSMB will meet a minimum of every 3 months. The DSMB will be informed of all cases of severe hypoglycemia and diabetic ketoacidosis irrespective of device relationship, all device-related SAEs, and all UADEs at the time that they occur during the study and will review compiled safety data at periodic intervals. The DSMB also will be informed of any ADEs not meeting criteria for a UADE if the Medical Monitor requests the DSMB review. The DSMB can request modifications to the study protocol or suspension or complete halting of the study if deemed necessary based on the totality of safety data available. Details regarding the DSMB's role are documented in a separate DSMB document.

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.

Recording of Data:

Investigators and staff will record data collected during the clinical trial on the CRF's in a secure HIPAA compliant system run by Prelude Dynamics. The CRFs will include:

1. Screening form
2. iPancreas Training
3. Companion Training
4. Day 1 Intervention Period Study Visit
5. Day 7 Intervention Period Study Visit
6. Day 1 Control Period Study Visit
7. Day 7 Control Period Study Visit
8. Phone Update Form
9. Adverse Event form
10. Serious Adverse Event form
11. 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 OHSU 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 by family member or emergency personnel
Example: *infusion site infection requiring antibiotics prescribed at urgent care.*

- **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: *severe hypoglycemia defined as hypoglycemic event resulting in altered consciousness requiring another person to actively administer carbohydrate, glucagon, or other resuscitative actions.*

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 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.

Medical Device Reporting (MDR)

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:

Staff will maintain the confidentiality and security of data collected in this study. Paper files will be stored in locked filing cabinets in restricted access offices at site. 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. Electronic data will be stored on encrypted: computers, laptops and study smartphones. Electronic data is stored in OneDrive and on a secure HIPAA compliant system run by Prelude Dynamics. Sites will be invited to upload data using a password protected folder in Microsoft OneDrive. iPancreas data will be housed in a custom cloud database on an OHSU secure server called the GRM (see below). Access to data/specimens is restricted to study personnel. Access to data requires ID/password authentication.

iPancreas Guidance Remote Monitoring (GRM) Cloud Server

All of the data collected will be streamed over the Internet (using secure sockets encryption) to an OHSU secure instance of an AWS cloud storage server every 5 minutes. Authentication between the phone and the AWS server is done using OAuth2. Data transmitted between the phone and the AWS server is encrypted using HTTPS/SSL. The code managing authentication and data transfer is Python version 3.7.0. Data acquired from the app is displayed via a physician web portal. The physician web portal user interface is written in Javascript version 1.8.5. There is no personally identifiable data stored with the data sent to the AWS server. The server shall be capable of receiving the following types of data (1) CGM data, (2) blood glucose and ketone data, (3) insulin dosing data, (4) insulin on board, (5) alerts, (6) exercise data, and (7) settings. All types of data shall be indexed by participant ID and by date/time. Data shall be stored on the server in a secure database. Each data packet shall be accompanied by an authentication identifier determined through oauth.

Appendix A: 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 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 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 B: iPancreas Alerts Table

#	NAME: Activation criteria	Clearing Criteria	Algorithm specifics	Notification to participant	Re-fire Time	Refractory Period (min)	Coordinator push (remote monitoring only)	Investigator push (remote monitoring only)	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 min	-	Immediately	Immediately	Waiting period ends when alert 13 is serviced OR clear criteria 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 Future: look back in time to see if taken rescue carbs within 15 min, then don't require rescue carbs.	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 min	-	After 1st re-fire	After 2nd re-fire	Waiting period ends when alert 13 is serviced OR clear criteria 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	sensor ≥ LOW_THRESH OR extreme_low_sensor_glucose is active.	For MPC, LOW_THRESH = 70 mg/dL	"Sensor glucose is below LOW_THRESH mg/dl. Please perform a blood glucose check now."	15 min	60	After 1st re-fire	After 2nd re-fire	-
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 min	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 min	60	After 1st re-fire	After 2nd re-fire	-
10	**Insulin_user_bolus_failure:** If 50% of user bolus is still not delivered after 20 minutes.	User acknowledgement	None	Insulin pump may have failed. At least 50% of your insulin bolus failed to deliver.	-	-	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 min	-	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 min	-	-	-	-
17	**sensor_not_reporting:** Sensor is out of date for > 20 minutes AND alert 17 AND alert 19 AND alert 20 not active or refractory	Clears with valid sensor.	Alert refires every 12 hours	"A sensor reading has not been received in the last 20 minutes. Please ensure that the phone is within range of the sensor. Click here for trouble-shooting guidelines"	12 hours	-	-	-	-
19	**sensor_not_reporting_correctly:** will populate 20 minutes after a temporary sensor issue is received AND alert 17 AND alert 19 AND alert 20 not active or refractory	Clears with valid sensor.	Alert refires every 12 hours	"Sensor value is not reporting correctly. Please check your sensor site for problems. Click here for trouble-shooting guidelines."	12 hours	-	-	-	-
20	**replace_sensor:** iPancreas sends message to replace the sensor immediately after	Clears with valid sensor	Alert refires every 12 hours. Other sensor alerts will not fire during the	"The sensor is no longer functioning. Please replace it immediately."	12 hours	120	-	-	-

	receiving a permanent sensor error.		refractory period of 120 minutes.						
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 min	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 min	-	After 1st re-fire	After 2nd re-fire	-
26	**maximum_insulin_exceeded**: Insulin Delivery ≥ 35% $TDIR_{adj}$ on last hour	User acknowledgement		"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 min	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	Pod with greater than 10% volume is		Your insulin pod is low. Please	120 min	-	After 1st re-fire	After 2nd re-fire	-

	has less than 10% of fluid volume remaining.	connected (i.e. pod is changed)		deactivate your current pod and activate a new insulin pod.					
30	**External_insulin_detected_alert: iPancreas has determined that more insulin has been delivered than expected by observing the insulin pump' pulse count**	None, this alert only goes to the study coordinator and investigator.	The app determined by the pump's pulse count that more insulin than was expected was delivered.	We determined that X.X units of insulin above the expected amount was delivered. Please switch to open loop mode and call study team.	-	-	Immediately	Immediately	-
31	**Sensor_glucose_extremely_low:** This alert fires when CGM is measured to be <= 54 mg/dL.	Measured CGM > 54 mg/dL.	This alert fires if CGM is measured to be < 54 mg/dL. When this alert is active, the sensor_glucose_low is suppressed. If CGM goes from <= 54 to between 70-54 mg/dL, the sensor_glucose_low alert will fire again after the refractory period of 30 minutes expires	"Sensor value is extremely low" "Sensor glucose is below 54 mg/dL. Please perform a blood glucose check now."	10 min	30	After first re-fire	After second re-fire	-

			on the recently cleared sensor_glucose_extremely_low alert						
32	**extreme_hypoglycemia_predicted**: fires when CGM is predicted to be <= 54 mg/dL within the next 30 minutes.	CGM is no longer predicted to be <= 54 mg/dL within the next 30 minutes, or CGM is measured to be <= 54 mg/dL.	This alert fires if the LSTM predicts that the CGM will drop < 54 mg/dL.	Your blood glucose is predicted to drop below 54 mg/dl within 30 minutes. Please consider taking a rescue carbohydrate.	15 min	30	After first re-fire	After second re-fire	-
33	**Watch_not_communicating**		This alert fires if the watch hasn't communicated for last 30 minutes. Alert refires every 12 hours	Your watch hasn't communicated in a while. Please check the connection.	12 hours	-	-	-	
34	**Missed_meal_alert**		This alert is triggered if the missed meal detection algorithm detects a meal and the safety layer for the missed meal detection algorithm calls for a reduction of 50% or more of the meal	Did you consume a meal? Your glucose appears to be rising. Did you consume a meal that you want to dose insulin for?		-	-	-	

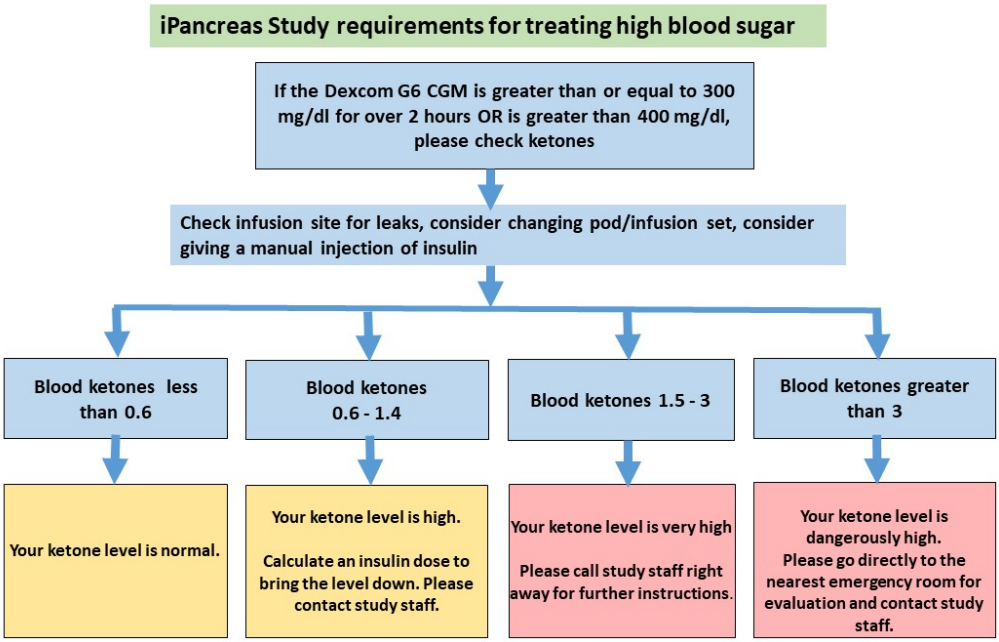
			insulin calculated by the missed meal detection algorithm.						
35	**Pdm_low_battery_alert**	Alert clears when PDM battery goes above 2.5 V.	If the Insulet PDM battery level drops below 2.5V, then this alert triggers. Alert refires every 12 hours	The battery on the PDM is low. Please change the batteries on the PDM.	12 hours	2 hours	-	-	
36	**sensor_session_ended alert**	Alert clears with new sensor session start		Your sensor session has ended. Please replace your sensor immediately.	12 hours	-			
37	**automated_meal_bolus_delivered**	Clears immediately			-	-	Immediately	Immediately	
38	**replace_transmitter:** Dexcom reports that the currently activated transmitter is no longer usable.	User acknowledgement		The transmitter is no longer functional. Please replace it.	12 hrs	-	-	-	

39	**calibrate_sensor:** Dexcom reports that a calibration is required.	User acknowledgement		Sensor calibration is due. Please perform a blood glucose check now.	30 min	-	-	-	
40	**closed_loop_permanently_paused**: The Insulet Omnipod pump controller reports an unexpected error.	User acknowledgement		An unexpected error has occurred and closed loop has been permanently paused. Please contact the study coordinator.	-	-	Immediately	Immediately	
41	**insulet_pod_not_usable**: The Insulet PDM Device reports that the currently activated Omnipod is no longer usable.	User acknowledgement		Your pod is no longer usable. Please replace the pod.	-	-	-	-	
42	**pump_time_out_of_sync:** This alert is triggered if the time on the phone and PDM differ by greater than 5 minutes.	User acknowledgement		A time discrepancy between the phone and t**H**e p**UMP HAS BEEN DETECTED. C**LOSED LOOP CONTROL HAS BEEN	-	-	Immediately	Immediately	

				PERMANENTLY PAUSED.					
43	**re_pair_pdm**: The app detects an issue with the Bluetooth connection to the PDM.	User acknowledgement		Your PDM seems to be having trouble communicating and needs to be un-paired / re-paired. Please disconnect the device from iPancreas. Then go to the Android Bluetooth menu, forget the device, then re-pair it.	-	-	-	-	
44	**insulin_pod_empty:** The app detects the pod is empty.			Your insulin pod is empty. Please replace it immediately.	30 minutes	none	never	never	
45	**insulin_pod_expires_soon:** the app detects that it has been 71 hours since pod was started.			Your insulin pod will expire soon. Please replace it immediately.	60 minutes	none	never	never	

Appendix C: Safety instruction cards for participants for checking ketones, to take additional carbs at the start of exercise as needed based on CGM and trend to avoid post-exercise hypoglycemia, for study stopping rules.

Instruction cards:



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.

iPancreas Study instructions for when to stop your study for safety

Please stop your study in iPancreas, resume your own pump and contact your study team if any of the following occur:

1. Pregnancy
2. You were diagnosed and treated in a health care facility for Diabetic ketoacidosis.
3. One episode of severe low blood sugar where you required another person to give you glucagon, carbohydrates or other treatment actions.

<insert site study team contact information>

Appendix D: Instruction card for participants outlining how to properly replace pods

iPancreas Study - Replacing Omnipods
Pods can be changed out every 3 days or when prompted by iPancreas, whichever occurs first. Follow the steps below to avoid activation errors while changing out pods:
1) Go into the insulin pump screen then click **Replace Omnipod**. 2) Select **Deactive Pod** - this can take up to 2 minutes and will be indicated by 2 beeps from the pod. 3) Once deactivation is successful, confirm pod deactivation by pressing "**Yes, my old pod is deactivated. Continue.**" **It is crucial your current pod is deactivated first before activating other pods** 4) Remove your current pod and discard. 4) Open a new pod package and prepare the new syringe with insulin. 5) Bring your PDM close to the new pod with the window of the top of the PDM touching the pod. 6) Have the app open as you fill your pod as instructed. You should hear the pod beep twice as you fill it. 7) Once the pod is filled, press **Activate Pod** to begin activation. Listen for clicking during this time as the pod primes the cannula. 8) Once pod activation is successful, prepare your new infusion site as prompted by the app. 9) Apply the pod securely, then hold the PDM with the window at the top touching the pod before pressing **Deploy Cannula**. 10) Once the pod is connected and ready to go, the next screen will confirm your Omnipod is active. Pressing **Done** will redirect you to the app homepage where the pump icon at the bottom of the screen will be green with a checkmark.
If you have any trouble with replacing a pod, or would like assistance, please refer to **section 5.2** of the User Guide, or feel free to give us a call at [***enter site contact number here***]**.**

References Cited in this Document

[1] 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.

[2] 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, p. dc180228, 2018/5/9 2018, doi: 10.2337/dc18-0228.

[3] L. M. Wilson et al., "Dual-Hormone Closed-Loop System Using a Liquid Stable Glucagon Formulation Versus Insulin-Only Closed-Loop System Compared With a Predictive Low Glucose Suspend System: An Open-Label, Outpatient, Single-Center, Crossover, Randomized Controlled Trial," Diabetes Care, vol. 43, no. 11, pp. 2721-2729, Nov 2020, doi: 10.2337/dc19-2267.

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