PROTOCOL TITLE: A crossover study to evaluate insulin and pramlintide versus insulin alone delivery strategy

Brief Title: Pramlintide AP study

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PROTOCOL TITLE: A crossover study to evaluate insulin and pramlintide versus insulin alone delivery strategy

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Background:

Type 1 diabetes (T1D) is a complex disease and people with T1D are at high-risk of both hyper- and hypoglycemia which can lead to severe acute and chronic complications. Due to the burden and complexity of managing T1D, the vast majority of people with T1D do not reach the target HbA1c of <7% as recommended by the American Diabetes Association. Data from the T1D Exchange, which includes 64 diabetes centers, demonstrated that 69% of patients in the exchange had HbA1c levels of >7.5% [62]. The benefits of optimal glycemic control are well documented, including significant reductions in microvascular disease [63] and to a lesser degree macrovascular disease [64]. Achieving optimal glycemic control requires frequent glucose monitoring by finger-stick and/or continuous glucose monitoring (CGM) in combination with either multiple daily injection (MDI) or insulin pump therapy, or most recently, with an artificial pancreas (AP) system. AP systems automate insulin delivery based on CGM values to minimize hypoglycemia and hyperglycemia, and in some cases also deliver glucagon to prevent and treat hypoglycemia. AP systems have been tested extensively in both the inpatient and outpatient settings [54, 65-69].

Current commercial closed loop systems such as the Medtronic 670g and more recently Tandem's Control-IQ [70, 71] have demonstrated a modest improvement in the percent time in glucose target range (70-180 mg/dL) of 5% for the 670g [72] and 10% for the Control-IQ [71]. However, the benefit is almost entirely due to improved glycemic control overnight when meals are not being consumed as shown by Kovatchev and colleagues [73]. Our group has developed a multi-hormone (glucagon and insulin) closed loop system that improved time in range by 7.6% overall; but as with the commercial systems the majority of benefit was during the overnight hours where it exhibited 100% time in target range (70-180 mg/dL) compared with 62.5% time in range for the control open loop system with predictive low glucose suspend [31] Commercial closed-loop systems and the systems developed by our group are unable to effectively handle meals because the kinetics of subcutaneously delivered insulin are sufficiently slower than the

body's absorption of carbohydrates [36]. This delay in kinetics of insulin relative to meal absorption results in a rapid increase in glucose immediately following a meal that cannot be prevented, even if the appropriate amount of insulin is given at the time of the meal or even prior to meal consumption.

Compounding this problem is the fact that many people struggle to adequately estimate their carbohydrates because they simply do not know the amount of carbohydrates in the food that they are consuming [37]. Our group recently showed that 49% of smaller meals (carbs <30 g) are overestimated by an average of 25.7 +/- 17.2 g while 64% of larger meals (>60 g) are underestimated by an average of 53.6+/-33.8 g by people with T1D under free-living conditions [74]. Furthermore, people with T1D oftentimes forget to announce meals to the closed loop system altogether, leading to insufficient insulin at meal time, followed by possible over-dosing of insulin by the control algorithm immediately after the meal when glucose levels spike, which can then lead to both short-term hyperglycemia and also hypoglycemia hours after the meal [37]. This is why the current commercial closed loop systems require users to announce meals to the system prior to eating. Hybrid closed loop systems use the carbohydrate amount entered by the user to dose the appropriate amount of insulin based on preset insulin to carbohydrate ratios. Requiring a person with T1D to announce meals is both a burden to the person, and as discussed above, missed doses and errors in carbohydrate estimations can lead to serious postprandial hypo- and hyperglycemic outcomes after a meal. The failure of hybrid closed loop systems to appropriately handle meals is the primary reason why these systems do not show a benefit during the daytime compared with manual control.

Integrating pramlintide into a dual hormone hybrid closed loop system is effective at substantially improving time in target range (70-180mg/dL) during the daytime as shown by Haidar and colleagues [75]. When people with T1D dosed a combination of rapid acting insulin and pramlintide, their time in target range was substantially lower following the meal compared with rapid acting insulin alone. Haidar et al. found that time in target range could be increased from 74% (SD 18%) to 84% (SD 13%) when incorporating pramlintide dosed with insulin prior to meals. Pramlintide is a synthetic form of amylin which is released with insulin from the beta cell in normal physiology. People with T1D loose both insulin and amylin secretion due to autoimmune beta cell destruction [38]. Pramlintide is known to substantially blunt rate of appearance of glucose after a meal in T1D as shown by our group in Riddle et al [39] by suppressing glucagon production to prevent hepatic glucose release [40] and delaying gastric emptying [41] via central nervous system effects. The slowing of gastric emptying by pramlintide controls the influx of glucose from the meal to better match the relatively slower kinetics of subcutaneous insulin for disposal of glucose. There is now a co-formulation in development of insulin with pramlintide that will allow for ease of dosing (Adocia Pharmaceuticals). M1Pram contains A21G human insulin analog ("M1"), which most closely matches pharmacokinetics of regular human insulin, along with the amylin analog pramlintide manufactured by AstraZeneca.

We have developed a meal detection and carb-estimation algorithm[2] and we have integrated this algorithm within the context of a dual-hormone insulin and pramlintide closed loop system to enable fully automated closed loop control without requiring people with T1D to enter

carbohydrates to the system. This meal detection and carb-estimation algorithm was shown in a clinical study to detect meals within 25.9 minutes of meal consumption with sensitivity of 83.3% and a false discovery rate of 16.6%. It was shown to reduce time above 180 mg/dL by 10.8%[2].

The clinical study described in this protocol is a safety and efficacy study in order to develop a non-hybrid, fully automated closed loop system that does not require the person to announce meals to the system, and which utilizes the hormone analog pramlintide in combination with insulin to potentially reduce the meal related hyperglycemia and increase the time spent in target range during the daytime.

Primary Objectives:

- To evaluate safety and efficacy of a fixed co-ratio insulin and pramlintide delivery strategy under closed loop control after a meal is detected by the meal detection algorithm
- To evaluate performance of the fully closed-loop system with (1) insulin+pramlintide as compared to (2) insulin-only as measured by incremental area under the curve (iAUC) in the 6 hours following the first meal period

Secondary Objective:

- To evaluate performance of the fully closed-loop system with insulin+pramlintide as compared to insulin-only for other glycemic outcomes

Study Hypothesis:

Our hypothesis is that pramlintide and insulin delivered after a meal by a closed loop system in response to automated meal detection will be well tolerated and will allow for a reduction in the postprandial glucose response as measured by the incremental area under the CGM curve (iAUC) compared with an insulin-only fully closed loop system.

Endpoints

Primary Endpoints:

- Incremental area under the curve (iAUC) of postprandial glucose as measured by CGM in the 6 hours following the start of first meal. iAUC (mg/dL*min) will be calculated using a trapezoidal method [76], which sums all CGM values in the 6 hour period following the meal above the starting glucose.
- Percent of time with sensed glucose between 70 – 180 mg/dl in the 6 hours following the start of first meal.

Secondary Endpoints

- Incremental area under the curve (iAUC) of postprandial glucose as measured by CGM in the 6 hours following the start of second meal. iAUC (mg/dL*min) will be calculated using a trapezoidal method [76], which sums all CGM values in the 6 hour period following the meal above the starting glucose.

- Percent of time with sensed glucose between 70 – 180 mg/dl in the 6 hours following the start of second meal.

(The following secondary outcomes will be measured in the 6 hours following (1) the start of the first meal, (2) the start of the second meal, and (3) full study duration):

- Net area under the curve (netAUC) of postprandial glucose as measured by CGM in the 6 hours following the start of first meal. netAUC (mg/dL*min) will be calculated using a trapezoidal method [76], which sums all CGM values in the 6 hour period following the meal above the starting glucose and subtracts CGM values below the starting glucose.
- Percent of time with sensed glucose <70 mg/dl
- Percent of time with sensed glucose between 70 – 140 mg/dl
- Mean sensed glucose
- Percent of time with sensed glucose <54 mg/dl
- Percent of time with sensed glucose >180 mg/dl
- Percent of time with sensed glucose >250 mg/dl
- Mean amount of insulin delivered (in units and units/kg)
- Mean amount of pramlintide delivered (in mcg and mcg/kg)
- Coefficient of variation
- LBGI
- HBGI
- Safety endpoints (over full study duration):
    - Adverse events
        - Number of adverse events probably or possibly associated with pramlintide administration (see 'Causality Relationship' below)
        - Baxter Retching Faces (BARF)/VAS scale for gastrointestinal issues after first and second meal, see Protocol Appendix D.
        - Mean duration of gastrointestinal issues after first and second meal as reported by participant on BARF/VAS scale, see Protocol Appendix D.
    - Episodes of carbohydrate intake to treat hypoglycemia (defined as 15g carbohydrate intake)
    - Episodes of hypoglycemia defined as CGM <70mg/dL for 10 minutes or more
    - Number of provider-administered insulin injections due to hyperglycemia

Study Type

This is a single-center, crossover trial designed to evaluate glucose outcomes of a fully closed-loop system with insulin+pramlintide dosed in response to meal detection as compared to an insulin alone fully closed loop system.

Study Population

Study population will be adults with type 1 diabetes, ages 18 – 70 years of age. Younger participants are excluded as it is appropriate to assess safety first in the over 18 year old population. We are targeting a total of 35 participants to complete the full study protocol.

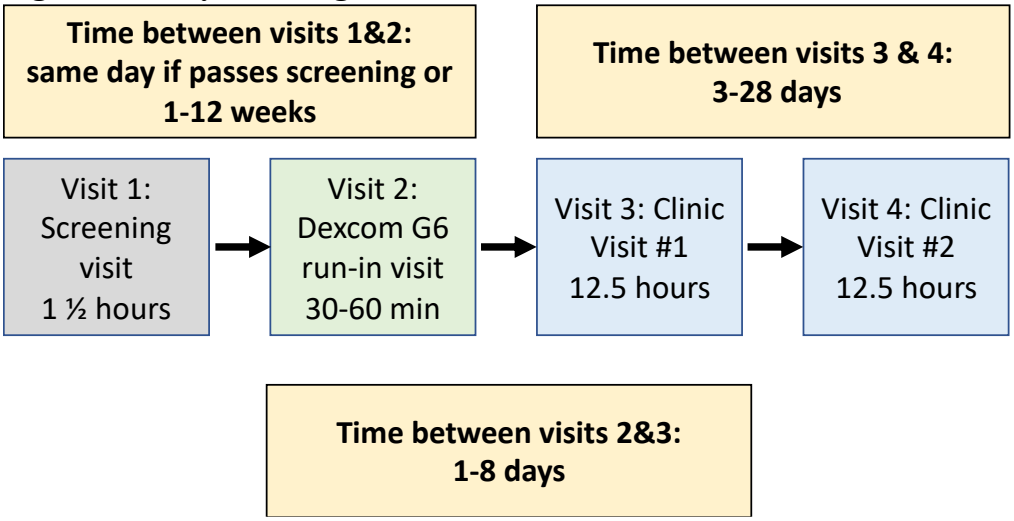
Power Analysis

A sample size of 35 participants provides 90% power to detect a standardized paired mean difference of 0.56 SD, or 80% power to detect a 0.49-SD difference with a two-sided test at the .05 level of significance. This is calculated using a paired t test to approximate a mixed model with treatment, period, and sequence effects. Data from a previous study [24] showed a 0.64-SD reduction with pramlintide in 4-hour postprandial AUC for participants with >40 U bolus insulin per day. We plan to recruit more than half of our study participants from this population and so we expect to observe a slightly smaller reduction in AUC.

Protocol Summary:

Participants will undergo two study visits to evaluate (1) insulin+pramlintide versus (2) insulin-only delivery strategies. The order of the visits will be randomized. Meal scenarios will be identical across all study arms. Participants will arrive at approximately 7:30 am for all visits, be monitored through the afternoon and discharged at approximately 8 pm. During each study visit, participants will wear Omnipod(s) to deliver insulin and/or pramlintide and a Dexcom G6 CGM to measure glucose and a Polar M600 to measure activity levels. See Figure 1 and 2 below.

Figure 1: Study flow diagram



Time	Activity	Hours post meal
7:30 AM	Begin closed loop study	0
8 AM	Breakfast	1
9AM		2
10 AM		3
11 AM		4
12 PM		5
1 PM		6
2 PM	Lunch	1
3 PM		2
4 PM		3
5 PM		4
6 PM		5
7 PM		6
8 PM	Discharge	

Figure 2: Treatment visit timeline

Subject Criteria

Inclusion Criteria:

1. Diagnosis of type 1 diabetes mellitus for at least 1 year.
2. Participants 18 to 70 years of age.
3. Current use of an insulin pump for at least 3 months with stable insulin pump settings for >2 weeks. OR Current use of multiple day injection insulin therapy with stable doses for >2 weeks.
4. Uses a carbohydrate ratio, at least occasionally, to dose meal time insulin
5. HbA1c ≤ 10.5% at screening.
6. Total daily insulin requirement is less than 139 units/day.
7. Willingness to follow all study procedures, including attending all clinic visits.
8. Willingness to sign informed consent and HIPAA documents.

Exclusion Criteria:

1. Individual 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 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. History of severe hypoglycemia during the past 3 months prior to screening visit or hypoglycemia unawareness as judged by the investigator.
6. Participants will complete a hypoglycemia awareness questionnaire. Participants will be excluded for four or more R responses.
7. History of diabetes ketoacidosis during the prior 3 months prior to screening visit, as diagnosed on hospital admission or as judged by the investigator.
8. Adrenal insufficiency.
9. Any active infection requiring treatment (example soft tissue infection requiring antibiotics) .
10. Known or suspected abuse of alcohol, narcotics, or illicit drugs.
11. Seizure disorder.
12. Major surgical operation within 30 days prior to screening.
13. Use of an investigational drug within 30 days prior to screening.
14. Chronic usage of any immunosuppressive medication (such as cyclosporine, azathioprine, sirolimus, or tacrolimus).
15. Bleeding disorder, treatment with warfarin, or platelet count below 50,000.
16. Allergy to aspart insulin.
17. Allergy to NPH insulin.
18. Allergy to pramlintide.
19. Current administration of oral or parenteral corticosteroids.
20. 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).
21. Current use of any medication that may lower glucose other than insulin or pramlintide (ex. use of liraglutide, metformin etc) including the use of GLP1RA medications for weight loss (ex. Wegovy or Zepbound).
22. Gastroparesis
23. Diets consisting of less than 50 grams of carbohydrates per day.
24. Dietary restrictions or allergies to all of the study meal options
25. Any clinically significant disease or disorder which in the opinion of the Investigator may jeopardize the participant's safety or compliance with the protocol.

Subject 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 Subject Recruitment website. 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, from the OHSU diabetes research registry and/or www.clinicaltrials.gov. Participants will be contacted using the approved telephone screening script and email template. 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.

This study will use Epic MyChart® to recruit potential participants. Researchers will work with ITG to identify potential participants based upon the above eligibility criteria. Researchers will create a Reporting Workbench query in epic based on inclusion and exclusion criteria. Potential participants will be sent a MyChart® recruitment message asking them to participate. There is no risk of duplicate invitations as it is based on MyChart® accounts combined with Epic records and no duplication is possible.

Up to 50 participants may be screened in this study. Goal enrollment is 35 participants. 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.

Visit Procedures

Screening (Visit 1)

Screening will take place within 12 weeks prior to the Dexcom G6 training visit (Visit 2). This visit will take approximately 1.5 hours.

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 their 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. Individuals 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 a participant had any of these labs drawn with in the last 6 months and results are available for review within Epic or CareEverywhere for the study investigator to review, then those labs do not need to be drawn at the Screening Visit. A study investigator will assess inclusion/exclusion criteria and may review the participant's medical record for clarification as needed. Participants will complete a hypoglycemia awareness questionnaire, see Protocol Appendix B. The participant's insulin pump, and if applicable glucose sensor, will be

downloaded at the time of the screening visit to assess the participant's insulin settings. A three-digit participant ID number will be assigned to the participant.

Dexcom CGM training visit (Visit 2)

The purpose of this visit is to have the participants learn how to use the Dexcom G6 CGM device using the iPancreas smart phone application on a provided study phone. This visit will take 30-60 minutes depending on user experience. This visit can occur directly after the screening visit if all screening criteria are met OR anytime within 12 weeks of the screening visit. After arrival, 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.

There is the option to make this visit virtual with supplies, including a pregnancy test, shipped to the participant at home. Participants will meet with study staff via WebEx video software.

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™ 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 on 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 calibration. 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 capillary blood glucose (CBG) and use this value to make treatment decisions and 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 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.

Run-in Period

For the three days prior to the pramlintide treatment visit, participants will be instructed to use pramlintide 15 mcg injected subcutaneously via a pen device up to three times daily before each main meal for 1 day then increase to 30mcg before each main meal if tolerating in terms of GI side effects. They will be instructed to initially reduce their usual mealtime insulin doses by 10-20% to accommodate the use of pramlintide, then can increase mealtime insulin dose as needed to target post meal glucose levels <180 or participants preferred post meal glucose levels. The last dose of pramlintide administered at home prior to the treatment visit should be at least 8 hours before the visit.

For participants using basal insulin (such as glargine, Tresiba, or Toujeo insulin) as an evening dose, they will be instructed to take about 1/3 ± 10% of their usual basal insulin dose as a dose of NPH insulin no later than 7 pm the night before each study visit, and to withhold any basal

insulin on the morning of the study. They will be instructed to bring their home basal insulin to the study visit to take a dose prior to discharge.

For participants using basal insulin as a morning dose, they will be instructed to take usual morning basal insulin dose the day prior to each study visit, and to withhold any basal insulin on the morning of the study. The study investigator will calculate a dose to be given a dose of about 1/3 ± 10% of their usual basal insulin dose as a dose of NPH insulin prior to discharge from the study visit. They will be instructed to give their home basal insulin the morning after the study visit as they normally do.

For participants using basal insulin as a twice daily dose, they will be instructed to take usual morning basal insulin dose the day prior to each study visit. On the evening before the study visit, they will be instructed to take 2/3 ± 10% of their usual basal insulin dose as a dose of NPH insulin no later than 7 pm the night before each study visit, and to withhold any basal insulin on the morning of the study. They will be instructed to bring their home basal insulin to the study visit to take a dose prior to discharge.

Insulin Treatment Visit

Participants will be asked to check glucose from CGM at 2am each morning before their treatment visit. If the CGM value is above 150 mg/dl, participants will be asked to take 80% of the correction bolus. If the glucose is less than 100 mg/dL they will be instructed to take 15 grams of carbohydrate. 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 at least 3 days calculated from the day of admission until the start of the next admission. After arrival, 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 each of the participant's closed-loop studies. 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 CBG will be obtained and measured by a Contour Next glucose meter. When they arrive, participants will be given 15 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. The order of the visits will be randomized.

An Omnipod will be filled with aspart insulin. We will use only name brand insulin, not generic insulin. The Omnipod will be primed and inserted into the skin of the participant's abdomen or flank as directed by the manufacturer through the iPancreas smart phone application on a provided study phone. If applicable, participants will disconnect his/her own pump and remove his/her own insulin infusion set once insulin delivery has started via the Omnipod. If, applicable for participants on multiple daily injection therapy at baseline, we will verify time of last long

basal insulin administration. Participants will wear a Polar M600 fitness watch to inform the controller about physical activity. The research staff will initialize the system, input insulin settings and begin the closed-loop study. See Appendix A for a picture of the closed-loop system. Two staff will review each of the settings to confirm the settings are entered correctly. Participant will receive training on using the iPancreas smart phone application. A member of the study staff will remain near to the participant for the duration of the study to address any alerts or issues that arise. The study investigator will be on call for the duration of the study.

The algorithm will push data up to an encrypted, secure Amazon Web Services cloud server that can be monitored remotely every 5 minutes. The iPancreas software will generate alerts on the smartphone. 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 the server 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 Samsung smart phone. The smart phone will wirelessly communicate via BTLE to a PDM communicating to an Omnipod for automated insulin delivery. 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.

If at any time the study staff determines that a sensor can no longer be used, a new sensor will be inserted. 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. Glucose tablets will be provided to the participants.

For participant safety, if communication is lost between the iPancreas app and the Dexcom G6 CGM for ≥20 minutes or the insulin pod ≥30 minutes, the insulin pump shall deliver basal insulin according to pre-set basal rates designated within the iPancreas settings according to given times of day.

When either the CGM or the insulin pump is out for the above time durations, the iPancreas system will activate a predictive low glucose suspend feature if the last known sensor value was within the range of 70-140 mg/dl and predicted to fall below 90 mg/dl within thirty minutes or if the sensor glucose is less than 70 mg/dl. Maximum insulin suspension time is 2 hours. Prediction of sensor glucose is based on data long short term memory neural network (LSTM) algorithm[77]. When communication with the sensor or Omnipod is restored, the system will automatically resume delivering insulin according to the control algorithm, and IOB will be updated accordingly.

Meal Description

After the closed loop study has started, participants will eat the assigned breakfast meal around 8am. The assigned lunch meal will be given six hours later around 2 pm. The meal time may be delayed for safety if participant had a recent low glucose. The selected breakfast and lunch option will be identical across both study arms for each participant. The participant will be requested to complete their meal within 10 minutes. There will not be a premeal insulin bolus.

The participant will select between two or three breakfast and lunch meals options and have these same meals at each study visit. If a food item is unavailable, it will be substituted with the closest available substitute. The caloric size of the meal will be based on DRI Estimated Energy requirement formulas. The meals will be made by the OHSU Bionutrition kitchen. The breakfast meal options will each provide approximately 33% of participants daily energy requirement, with macronutrient composition of 50% carbohydrate, 15% protein and 35% fat. The lunch meal options will provide approximately 40% of the participants daily energy requirement with the same macronutrient composition as the breakfast meal.

Meal detection will be enabled for the study. If iPancreas does not auto-detect the meal after 30 minutes of when they start eating, the study coordinator will assist the participant to enter a meal with a reduction to the amount of carbs entered based on the amount of time since the meal occurred, at the investigator's discretion. Participants will complete a pictorial nausea rating scale for reported nausea at study start and at approximately 6 hours after the first and second meal to report the worse nausea/vomiting they experienced over the prior 6 hours (the Baxter Retching Faces [BARF] scale) (see Protocol Appendix D)[78] and the approximate duration of the nausea.

The MPC closed loop system with the meal detection algorithm can detect if a meal has been eaten, estimate the grams of carbohydrates consumed then dose an insulin bolus based on the estimated grams of carbs, user's carb ratio and estimated time since the meal was consumed. The bolus is delivered automatically. The system reduces the bolus (per calculation below) by 25% as the detection occurs on average 25 minutes after meal is consumed.

$$Bolus(units) = \frac{estimated\ carbohydrates\ (g)}{carb\ ratio\ (\frac{g}{unit})}$$

If CBG >300mg/dL before the lunch meal, then the study will be stopped early and the participant will be given the option to return on a different day for the second meal.

The meal detection algorithm can be enabled or disabled through the insulin profile settings for a given time period. In order to avoid a meal detection before the two scheduled meals, the meal detection algorithm will be disabled through the insulin profile in between the meals.

If stopping criteria for hyperglycemia is reached, the study investigator will calculate a meal bolus with correction dose as in the equation below if no meal bolus was given by the system, otherwise, the investigator will calculate a correction bolus based on current glucose, target

glucose, and correction factor. The final dose that is delivered to the participant will be adjusted if needed by a study investigator considering insulin-on-board, time since meal consumption, and CGM trend. The Omnipod site will be assessed to determine if the insulin should be delivered via the Omnipod, syringe, or via the participant's own insulin pump after it is reconnected.

$$Total\ Insulin\ Bolus = \frac{Carbohydrate\ (g)}{Carbohydrate\ Ratio} + \frac{Current\ glucose - Target\ Glucose}{Correction\ Factor} \text{ - IOB}$$

Discharge from inpatient clinic

The study will be terminated and the participant's own insulin pump or home basal insulin will be restarted. The study investigator will consult with the participant regarding appropriate insulin dosing for the remainder of the day. The Polar watch and Omnipod will be removed from the participant. The participant will wear Dexcom sensor until just prior to discharge to track the glucose and trend arrow. Participants will complete a pictorial nausea rating scale (the Baxter Retching Faces [BARF] scale), if applicable (see Protocol Appendix D)[78]. 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 measured. 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 or via home insulin pen/vial 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).

Participants who will be taking an NPH dose prior to discharge from the clinic and who currently do not use a CGM or are not actively using their personal CGM will continue to use the study CGM for approximately 12 hours after the visit completes. Study staff will complete a phone check-in the next day to remove the CGM. For safety for avoiding hypoglycemia, all participants who take NPH prior to discharge will be asked to check glucose from CGM at 2am the morning after their treatment visit, if the glucose is less than 100 mg/dL they will be instructed to take 15 grams of carbohydrate. If the CGM value is above 150 mg/dl, participants will be asked to take 80% of the correction bolus.

Participants will be given a snack to take with them for the trip home. Participants will also be advised to monitor their glucose for any symptoms of hyperglycemia or hypoglycemia, before their next meal, and at bedtime.

Insulin + Pramlintide Treatment Visit

Participants will be asked to check glucose from CGM at 2am each morning before their treatment visit. If the CGM value is above 150 mg/dl, participants will be asked to take 80% of the correction bolus. If the glucose is less than 100 mg/dL they will be instructed to take 15 grams of carbohydrate. 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 at least 3 days calculated from the day of admission until the start of the next admission. After arrival, 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 each of the participant's closed-loop studies. 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 CBG will be obtained and measured by a Contour Next glucose meter. When they arrive, participants will be given 15 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. The order of the visits will be randomized.

An Omnipod will be filled with aspart insulin. We will use only name brand insulin, not generic insulin. Additionally, a second Omnipod will be filled with Pramlintide (Symlin, AstraZeneca). The iPancreas system will deliver pramlintide in a fixed ratio to insulin at 6 mcg of pramlintide delivered for every 1 unit of insulin. The Omnipod(s) will be primed and inserted into the skin of the participant's abdomen or flank as directed by the manufacturer. The pods will be placed at least 4 inches apart. If applicable, participants will disconnect his/her own pump and remove his/her own insulin infusion set once insulin delivery has started via the Omnipod(s). If, applicable for participants on multiple daily injection therapy at baseline, we will verify time of last long basal insulin administration. Participants will wear a Polar M600 fitness watch to inform the controller about physical activity. The research staff will initialize the system, input insulin settings and begin the closed-loop study. Two staff will review each of the settings to confirm the settings are entered correctly. Participants will receive training on using the iPancreas smart phone application. A member of the study staff will remain near to the participant for the duration of the study to address any alerts or issues that arise. The study investigator will be on call for the duration of the study.

The algorithm will push data up to an encrypted, secure Amazon Web Services cloud server that can be monitored remotely every 5 minutes. The iPancreas software will generate alerts on the smartphone. 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 the server 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 Samsung smart phone. The smart phone will wirelessly communicate via BTLE to a PDM communicating to an Omnipod for automated insulin and pramlintide delivery. 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.

If at any time the study staff determines that a sensor can no longer be used, a new sensor will be inserted. If the participant's blood glucose is < 70 mg/dl or is experiencing symptoms of hypoglycemia, the procedure noted below will be followed. Glucose tablets will be provided to the participants.

- If CBG <70mg/dL occurs during pramlintide treatment visit:
  - Give 15 grams of oral carbohydrate.
  - Repeat treatment every 15 minutes with 15 grams oral carbohydrate as needed to raise blood glucose ≥70 mg/dl.
  - Repeat CBG checks every 15 minutes for 45 minutes to ensure glucose is persistently ≥70 mg/dl.

For participant safety, if communication is lost between the iPancreas app and the Dexcom G6 CGM for ≥20 minutes or the insulin pod ≥30 minutes, the insulin pump shall deliver basal insulin according to pre-set basal rates designated within the iPancreas settings according to given times of day and the pramlintide pump will deliver a fixed ratio of pramlintide to match the pre-set basal rate for insulin.

When either the CGM or the insulin pump is out for the above time durations, the iPancreas system will activate a predictive low glucose suspend feature if the last known sensor value was within the range of 70-140 mg/dl and predicted to fall below 90 mg/dl within thirty minutes or if the sensor glucose is less than 70 mg/dl. Maximum insulin suspension time is 2 hours. Prediction of sensor glucose is based on data long short term memory neural network (LSTM) algorithm[77]. When communication with the sensor or Omnipod is restored, the system will automatically resume delivering insulin according to the control algorithm, and IOB will be updated accordingly.

Meal Description

After the closed loop study has started, participants will eat the assigned breakfast meal around 8am. The assigned lunch meal will be given six hours later around 2 pm. The meal time may be delayed for safety if participant had a recent low glucose. The selected breakfast and lunch option will be identical across both study arms for each participant. The participant will be requested to complete their meal within 10 minutes. There will not be a premeal insulin bolus.

The participant will select between two or three breakfast and lunch meals options and have these same meals at each study visit. If a food item is unavailable, it will be substituted with the closest available substitute. The caloric size of the meal will be based on DRI Estimated Energy

requirement formulas. The meals will be made by the OHSU Bionutrition kitchen. The breakfast meal options will each provide approximately 33% of participants daily energy requirement, with macronutrient composition of 50% carbohydrate, 15% protein and 35% fat. The lunch meal options will provide approximately 40% of the participants daily energy requirement with the same macronutrient composition as the breakfast meal.

Meal detection will be enabled for the study. If iPancreas does not auto-detect the meal after 30 minutes of when they start eating, the study coordinator will assist the participant to enter a meal with the amount of carbs provided by Bionutrition. Participants will complete a pictorial nausea rating scale for reported nausea at study start and at approximately 6 hours after the first and second meal to report the worse nausea/vomiting they experienced over the prior 6 hours (the Baxter Retching Faces [BARF] scale) (see Protocol Appendix D)[78] and the approximate duration of the nausea.

The MPC closed loop system with the meal detection algorithm can detect if a meal has been eaten, estimate the grams of carbohydrates consumed then dose an insulin bolus based on the estimated grams of carbs, user's carb ratio and estimated time since the meal was consumed. The bolus is delivered automatically. The system reduces the bolus (per calculation below) by 25% as the detection occurs on average 25 minutes after meal is consumed. Pramlintide will be delivered at the fixed ratio of 6 mcg for every 1 unit of insulin delivered.

$$Bolus(units) = \frac{estimated\ carbohydrates\ (g)}{carb\ ratio\ (\frac{g}{unit})}$$

If CBG >300mg/dL before the lunch meal, then the study will be stopped early and the participant will be given the option to return on a different day for the second meal.

The meal detection algorithm can be enabled or disabled through the insulin profile settings for a given time period. In order to avoid a meal detection before the two scheduled meals, the meal detection algorithm will be disabled through the insulin profile in between the meals. If the participant experiences significant GI side effects after the first meal, the study investigator will decrease the aggressiveness of the participant's carb ratio 30% such that the participant will receive less pramlintide with their second meal.

If stopping criteria for hyperglycemia is reached, the study investigator will calculate a meal bolus with correction dose as in the equation below if no meal bolus was given by the system, otherwise, the investigator will calculate a correction bolus based on current glucose, target glucose, and correction factor. The final dose that is delivered to the participant will be adjusted if needed by a study investigator considering insulin-on-board, time since meal consumption, and CGM trend. The Omnipod site will be assessed to determine if the insulin should be delivered via the Omnipod, syringe, or via the participant's own insulin pump after it is reconnected.

$$Total\ Insulin\ Bolus = \frac{Carbohydrate\ (g)}{Carbohydrate\ Ratio} + \frac{Current\ glucose - Target\ Glucose}{Correction\ Factor}$$ - IOB

Discharge from inpatient clinic

The study will be terminated and the participant's own insulin pump or home basal insulin will be restarted. The study investigator will consult with the participant regarding appropriate insulin dosing for the remainder of the day, considering pramlintide on board as tracked by the iPancreas system. If this level is elevated,, the participants will be offered an additional meal to eat before they discharge. The study investigator will consult with the participant in regards to a safe mealtime insulin dose given from their home pump or insulin pen.

The Polar watch and Omnipods will be removed from the participant. The participants will wear Dexcom sensor until just prior to discharge to track the glucose and trend arrow. Participants will complete a pictorial nausea rating scale (the Baxter Retching Faces [BARF] scale), if applicable (see Protocol Appendix D)[78]. 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 measured. Participants will be given oral carbohydrate for values below 85 mg/dl with a repeat capillary blood glucose every 15 minutes until glucose is ≥ 85 mg/dL. If capillary blood glucose is greater than 180mg/dL, participants will be instructed to take a correction bolus from their home insulin pump or via home insulin pen/vial per their usual home settings after reviewing this dose with the study investigator who will modify dose if needed considering current insulin on board.

If the initial capillary blood glucose was > 85 mg/dL, 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). If the initial capillary blood glucose was < 85 mg/dL, then the participant will be given oral carbohydrates and we will repeat a fingerstick every 15 minutes until glucose is ≥ 85mg/dL and the CGM trend arrow is flat or trending up, then patient can be discharged.

Participants who will be taking an NPH dose prior to discharge from the clinic and who currently do not use a CGM or are not actively using their personal CGM will continue to use the study CGM for approximately 12 hours after the visit completes. Study staff will complete a phone check-in the next day to remove the CGM. The participants will be asked to check glucose from CGM at 2am the morning after their treatment visit. If the CGM value is above 150 mg/dl, participants will be asked to take 80% of the correction bolus. If the glucose is less than 100 mg/dL they will be instructed to take 15 grams of carbohydrate.

Participants will be given a snack to take with them for the trip home. Participants will also be advised to monitor their glucose for any symptoms of hyperglycemia or hypoglycemia, before

their next meal, and at bedtime. Study staff will call the participant approximately 1 hour after discharge and participant will obtain a fingerstick glucose at that time.

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.

Adverse Events

Causality relationship to Pramlintide administration

The causality of each AE should be assessed by the Investigator according to the following classification:

Probable: Good reason and sufficient documentation to assume a causal relationship.

Possible: A causal relationship is conceivable and cannot be dismissed.

Unlikely: The event is most likely related to etiology other than the pramlintide administration.

Not related: The event occurs before any pramlintide has been started.

Table 1: Schedule of Events

Automated insulin delivery system abbreviated AID

[1] ins/pram visit

	Screening	Active Treatment		End of Treatment
Description of visit procedures	**Screening visit**	**Dexcom CGM insertion visit**	**1st AID visit**	**2nd AID visit**
Visit Number	**1**	**2**	**3**	**4**
Visit Window		**1-84 days**	**1-8 days**	**3-28 days**
Informed Consent	X			
Medical history/	X	X	X	X
Focused physical	X			
Eligibility assessment	X			
Download data from participant's existing insulin pump and glucose sensor (if applicable)	X			
Review medications and doses	X	X	X	X
Hypoglycemia awareness survey	X			
Measure BP, pulse, height and weight	X			
Pregnancy Test (Urine)	X	X	X	X
Hemoglobin A1c	X			
Complete Blood Count (CBC)	X			
Comprehensive Metabolic Panel (CMP)	X			
Adverse Event Reporting		X	X	X
Dexcom G6 CGM and iPancreas usage training		X		
Examination of sensor site after removal (if applicable)			X	X

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.
    - If CBG <70mg/dL occurs during pramlintide treatment visit:
        - Give 15 grams of oral carbohydrate.
        - Repeat treatment every 15 minutes with 15 grams oral carbohydrate as needed to raise blood glucose ≥70 mg/dl.
        - Repeat CBG checks every 15 minutes for 45 minutes to ensure glucose is persistently ≥70 mg/dl.

Presence of STUPOR, LOSS OF CONSCIOUSNESS, or SEIZURE

- Give 3 mg glucagon intranasal
- Verify that insulin and pramlintide are turned off.

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 by study investigator 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, Polar watch 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 or basal insulin 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 including in the absence of hospitalization, severe GI symptoms (i.e. to the point of not being able to tolerate food or liquids 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.

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.

Description of the MPC algorithms

Our exercise-aware model predictive control (exMPC) 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. Exercise is represented by heart rate data collected from a wrist-worn fitness watch. Elevated heart rate is represented by increased glucose disposal in the form of increased insulin sensitivity. In summary, 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. The exMPC algorithm has been described previously and has been clinically evaluated in multiple outpatient studies [79-81].

The Meal Detection feature in the algorithm includes a model for missed meal insulin detection and carbohydrate size estimation[2]. The model includes estimations for carbohydrate consumption based glucose patterns to determine if that person has consumed a meal without announcing it to the system. We refer to this algorithm as the Meal Detection algorithm.

Statistical methods

The primary study endpoints are (1) incremental area under the curve (AUC) of glucose in the 6 hours following unannounced meals and (2) percent of time with glucose sensor 70-180 mg/dL.

The hypothesis to be tested is that pramlintide and insulin delivered after a meal by a closed loop system in response to automated meal detection will improve postprandial glucose control over insulin delivered alone in response to automated meal detection.

Incremental AUC (iAUC) of postprandial glucose (mg/dL*min) will be calculated using a trapezoidal method which sums all CGM values in the 6 hour period following the meal above the starting glucose. (M. M. Tai, "A Mathematical Model for the Determination of Total Area Under Glucose Tolerance and Other Metabolic Curves," Diabetes Care, vol. 17, no. 2, p. 152, 1994, doi: 10.2337/diacare.17.2.152.)

We will estimate the difference between systems using a fixed effect in a standard 2x2 crossover model with a random participant effect. We will also control for sequence (AB or BA) and period (1 or 2), though we do not anticipate statistically significant effects for these parameters.

We anticipate that the primary outcomes will be approximately normally distributed. We will review the appropriateness of this assumption using both goodness-of-fit tests and diagnostic plots, such as quantile-normal plots. If the normality assumption holds, possibly with a transformation of the outcome, we will test the difference between the study arms using a paired t-test. In the case of mild departures from normality or unequal variances at the two time points, we will re-analyze the primary outcome as the difference between the two visits using bootstrapped standard errors, which avoid distributional assumptions. We will use two-sided tests at the 0.05 level of significance.

Missing data: Missing sensed glucose values will be interpolated for up to 30 min segments. Longer periods of missing data will be omitted if they represent <3% of observation time (which will be truncated if a participant leaves the study early). If the missing data are >3% of observation time, we will use available CBG values to interpolate or impute using measurements. In the case that >2 participants fail to complete the study, we will analyze the primary outcome under multiple imputation using baseline values.

Confidentiality and Protection of Human Subjects

RISKS and BENEFITS

Risks: The risks of the protocol procedures are considered minor. Nonetheless, since pumps and sensors used within automated glucose control systems are imperfect, there is a risk for hyperglycemia and hypoglycemia. All studies will have frequent glucose and ketone samplings and a member of the study staff will be present for studies with a study investigator on call at all times.

There is a risk that the meal detection and dosing algorithm will be incorrect (false positive) and dose meal insulin even if a meal has not occurred. While this is a rare event that we have found occurs only about once every 5 days of continuous usage, this does introduce the risk of a hypoglycemia event occurring. We have incorporated an additional safety layer for the meal detection and dosing algorithm that uses the person's correction factor to limit the amount of meal insulin dosed to prevent the person's glucose from dropping below 70 mg/dL, even in the event that the algorithm incorrectly detects a meal.

Pramlintide can cause nausea and more rarely vomiting. These reactions are considered to be somewhat likely. These symptoms may be lessened by the run in period using a low dose of pramlintide. Pramlintide can increase the likelihood of hypoglycemia after a meal. Continuous glucose monitoring will be running at all times to reduce the likelihood of severe hypoglycemia.

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

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

There is risk of IV access site problems such as extravasation, bleeding, irritation, infection. These are generally low risk and will be minimized by employing trained phlebotomy staff, and ensuring that strict sterile and/or antiseptic procedures are followed.

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

COSTS:

Participants will receive $600 for completion of all study visits. If a participant withdraws early from the study, compensation will be given as follows: $50 for the run-in visits and $250 for each of the 2 study visits. 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 $250.

Monitoring Entity:

This investigation will be monitored by the co- investigator Diana Aby-Daniel PA. Diana has no commercial interest in any of the companies which manufacture any of the devices used in this study. Dr. Leah Wilson and Dr. Peter Jacobs 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.

Recording of Data:

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

- Screening form
- G6 Training Visit
- First Closed-loop Study Assessment
- First Closed-loop Study Visit
- Second Closed-loop Study Visit
- Adverse Event form
- Serious Adverse Event form
- 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 and pramlintide data, (4) physical activity data, and (5) food 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.

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

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

Confidentiality Procedures:

To protect confidentiality, standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/ressec.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 an AWS server developed by our group that has undergone a security review.

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.

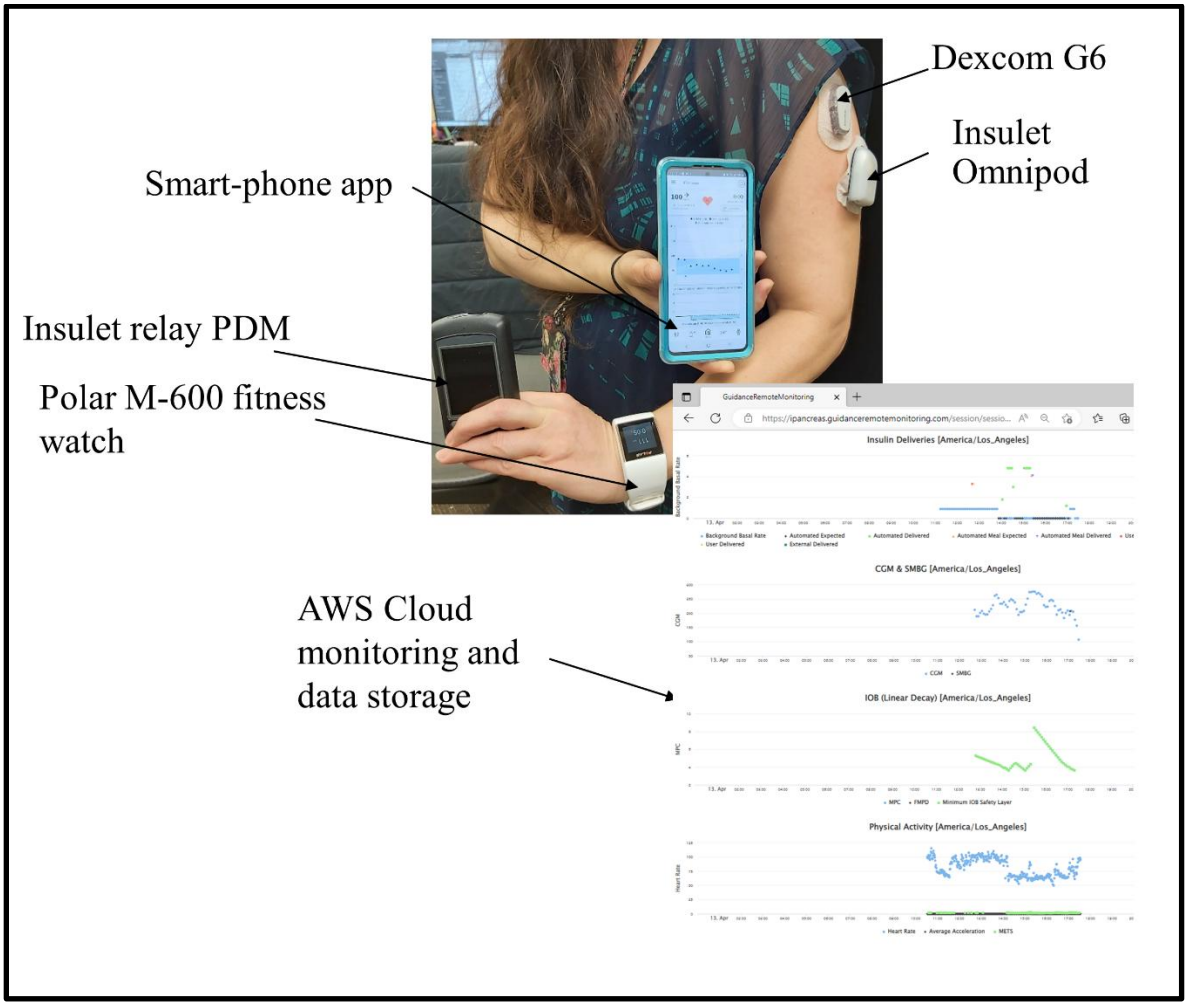
Electronic data will be stored on encrypted: computers, laptops and study smartphones. Electronic data is stored in OneDrive. iPancreas data will be housed in a custom cloud database

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 and pramlintide 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.

Protocol Appendix A: Devices



iPancreas smart phone app with Insulet Omnipod and relay PDM, Dexcom G6 Continuous Glucose Monitoring system, Polar M-600 fitness watch and AWS cloud server

Contour Next Blood Glucose Meter

Abbott Precision Xtra Meter

Protocol Appendix B: 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)

Protocol Appendix C: DRI Estimated Energy Requirement (EER) formulas

BMI category	Age Range	EER equation	Physical Activity Factor
BMI <25 normal weight	Boys 3-8 yrs	88.5-(61.9*age)+PA*(26.7*wt+903*ht)+20	PA=1 if sedentary PA=1.13 if low active PA=1.26 if active PA=1.42 if very active
	Boys 9-18	88.5-(61.9*age)+PA*(26.7*wt+903*ht)+25	
	Girls 3-8 yrs	135.3-(30.8*age)+PA*(10*wt+934*ht)+20	PA=1 if sedentary PA=1.16 if low active PA=1.31 if active PA=1.56 if very active
	Girls 9-18	135.3-(30.8*age)+PA*(10*wt+934*ht)+25	
BMI>25 Overweight/obese	Boys 3-18	114-(50.9*age)+PA*(19.5*wt+1162.4*ht)	PA=1 if sedentary PA=1.12 if low active PA=1.24 if active PA-1.45 if very active
	Girls 3-18	389-(41.2*age)+PA*(15*wt+701.6*ht)	PA=1 if sedentary PA=1.18 if low active PA=1.35 if active PA-1.6 if very active
BMI <25 normal weight	Men ≥19 yr	662-(9.53*age)+PA*(15.91*wt+539.6*ht)	PA=1 if sedentary PA=1.11 if low active PA=1.25 if active PA=1.48 if very active
	Women ≥19 yr	354-(6.91*age)+PA*(9.36*wt+726*ht)	PA=1 if sedentary PA=1.12 if low active PA=1.27 if active PA=1.45 if very active

BMI>25 Overweight/obese	Men ≥19 yr for Weight maintenance	1086-(10.1*age)+PA*(13.7*wt+416*ht)	PA=1 if sedentary PA=1.12 if low active PA=1.29 if active PA=1.59 if very active
	Women ≥19 yr for Weight maintenance	448-(7.95*age)+PA*(11.4*wt+619*ht)	PA=1 if sedentary PA=1.16 if low active PA=1.27 if active PA=1.44 if very active

[82]

Protocol Appendix D: Pictorial Nausea Rating Scale (the Baxter Retching Faces [BARF]/VAS scale)[78]

Investigative Site Instructions: The participant should complete the BARF/VAS for nausea/vomiting discomfort at approximately 6 hours after the first meal (prior to second meal) and six hours after the second meal (prior to discharge) to indicate the worse nausea/vomiting discomfort they have had over the prior 6 hours. Instruct the participant that the facial expressions represent the nausea severity they are experiencing. The face starts as neutral (shown below), but the animation becomes more nauseated as you proceed from 0 to 10.

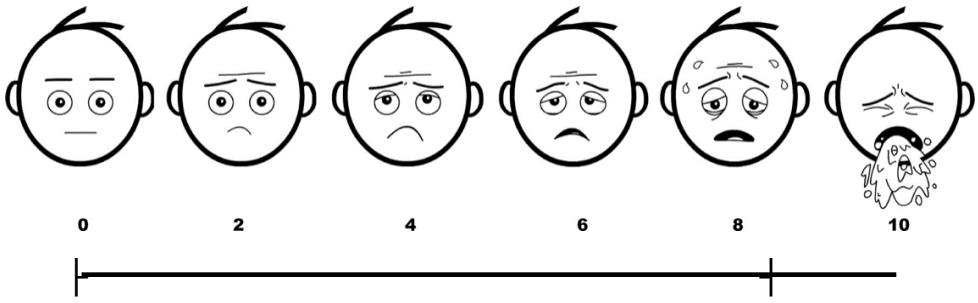
The participant completes the VAS by drawing a single vertical line through the scale corresponding to the perceived intensity (severity) of discomfort matching the facial scale. The goal is for the subject to report the amount of discomfort, if any, remaining at each time point.

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

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

Subject Instructions: Discomfort could include cramping, *abdominal pain, nausea or vomiting*. The further to the right you make indicate, the more intense discomfort you are feeling.

You should normally draw a straight line across the scale to indicate your maximum level of discomfort over the prior 6 hours. However, if you felt no discomfort, you should circle the vertical line on the left end of scale (above the word “no”). If you are currently feeling the worst discomfort possible, you should circle the vertical line on the right end of the scale.



No Discomfort Worst Possible Discomfort

About how long did the nausea last? (please approximate the number of minutes of nausea out of the prior 6 hours)

_____ (minutes)