PROTOCOL TITLE: A crossover study to assess the efficacy of a Robust AP closed loop system vs MPC closed loop system

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FUNDING:	NIH
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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% [1] The benefits of optimal glycemic control are well documented, including significant reductions in microvascular disease [2] and to a lesser degree macrovascular disease [3]. There are a multitude of barriers to improved glycemic control, including fear of hypoglycemia, particularly in those with hypoglycemia unawareness, which can lead patients to under-dose insulin despite the known benefits of improved glycemic control [4, 5]. In addition to fear of hypoglycemia, the process of determining the correct insulin dose is challenging and can lead to errors. Ahola et al. found that 64% of patients miscalculated their prandial insulin need, often resulting in repeated hypoglycemia and hyperglycemia [6]. Severe hypoglycemia and hyperglycemia can have significant consequences, including hospitalization. Data from the T1D exchange demonstrated that 11.8% of adults had one or more severe hypoglycemic events and 4.8% developed diabetic ketoacidosis (DKA) in the prior 12 months [7], with an even higher rate of DKA in children [8].

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 [9-14]. In a multi-center study by the AP@home consortium, adults with type 1 diabetes completed two months each of insulin pump therapy and sensor-augmented pump with AP use from dinner to waking up in a

cross-over design [15]. This study was the first to show a reduction in HbA1c, with a reduction of -0.2% between conditions favoring the AP system (p=0.047). In a study by Thabit et al, 24 adults and 16 adolescents each participated for 2 months with use of sensor-augmented pump therapy during the day and for half of the nights used an AP system overnight and the other nights continued sensor-augmented pump therapy [13]. Mean HbA1c for participants was 8.1%. The use of the AP system improved time in target range overnight by 18.4% (61.2% vs 73.2%, p = 0.0004), improved mean glucose by 14.4 mg/dL (p=0.0013), and had no impact on time <70 mg/dL (1.7% vs 1.7%). In a subsequent study, Thabit et al. showed that for 58 adults with T1D who used a single-hormone AP over 12 weeks, better glucose control and lower hypoglycemia were observed as well as a reduced HbA1c (-0.3%) compared with sensor-augmented pump therapy [14].

These studies have proven that AP systems are safe, but they have only demonstrated modest reductions in HbA1c in the patient populations that have been studied thus far. It is very likely that a reduction of HbA1c of 0.2-0.3% is not sufficient to reduce hyperglycemia-related complications. As a comparison, long term complications were significantly reduced in the Diabetes Control and Complications Trial [2] in the case where peoples' HbA1c levels were lowered by 2% in the intensively treated group as compared to the conventional group. Additional data is clearly needed to identify which populations will most benefit from AP systems. The intent of this protocol is to target a high-risk patient population and determine the most effective treatment options.

The study described within this protocol is designed to test the efficacy of a new insulin-only closed-loop algorithm using a model predictive control (MPC) framework that will incorporate a new feature to handle meals that are consumed without a pre-bolus of insulin called the Robust AP (R-AP) system. Model predictive control (MPC) is a control strategy whereby a model is used to predict the response of a system to a receding horizon of inputs. MPC uses the model to predict how the system will respond to current and future inputs and selects an optimal control output based on how well the predicted output of the system matches an optimal control trajectory. The power of MPC is in its predictive ability such that systems, which have very long response times, can be modelled to avoid over or under-delivery of control outputs of the MPC algorithm to the system which thereby lead to instability. An early paper describing an approach to MPC using a glucoregulatory model was Hovorka et al. [16]. This group has gone on to use MPC within their single-hormone control system, which has been evaluated clinically [14]. The group at University of Virginia developed an MPC for use within an AP [17] and they have published results on this algorithm within a multi-center trial [18]. The Padova group has also done work on MPC algorithms within an AP including an algorithm that uses an auto-regressive model that adapts over time called a run-to-run algorithm [19].

The robust R-AP system used in this protocol has been designed to handle a variety of real-world scenarios that are critical to a high-risk patient population. We will test how well the new algorithm handles missed or inaccurate meal announcements. This type of algorithm may significantly improve glucose control over the standard model predictive control (MPC) closed-loop algorithm without these new algorithm features for patients with type 1 diabetes.

Primary Objectives:

- To evaluate performance of the OHSU Robust R-AP closed-loop system as measured by area under the curve (AUC) in the 4 hours following first meal period, versus the OHSU MPC closed-loop system.
- To evaluate performance of the OHSU Robust R-AP closed-loop system as measured by percent of time with sensed glucose between 70 – 180 mg/dl in the 4 hours following the first meal period, versus the OHSU MPC closed-loop system.

Secondary Objective:

- To evaluate performance of the OHSU Robust R-AP closed-loop system versus the OHSU MPC closed-loop system in the 4 hours following the first meal period, as measured by other glycemic outcomes.

Study Hypothesis:

We propose that the use of the OHSU Robust R-AP closed-loop system as compared to the OHSU MPC closed-loop system will decrease AUC and increase the time in range as measured by sensed glucose values.

Endpoints

Primary Endpoint:

- Incremental AUC of postprandial glucose in the 4 hours following the start of first meal. AUC (mg/dL*min) will be calculated using a trapezoidal method [20], which sums all CGM values in the 4 hour period following the meal above the starting glucose.
- Percent of time with sensed glucose between 70 – 180 mg/dl in the 4 hours following the start of first meal.

Secondary Endpoints (all measured in the 4 hours following the start of meals):

- Percent of time with sensed glucose <70 mg/dl across the study duration
- Number of carbohydrate treatments (defined as 15 or 20 grams of carbohydrate)
- Number of provider-administered insulin injections due to hyperglycemia
- 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 per day (in units/kg)

Study Type

This is a single-center, crossover trial designed to compare the glucose control resulting from the use of the OHSU Robust R-AP system as compared to the OHSU MPC AP system.

Study Population

Study population will be adults with type 1 diabetes, ages 18 – 65 years of age. Younger participants are excluded as it is appropriate to assess safety first in the adult population. Fifteen participants will be recruited to participate in studies.

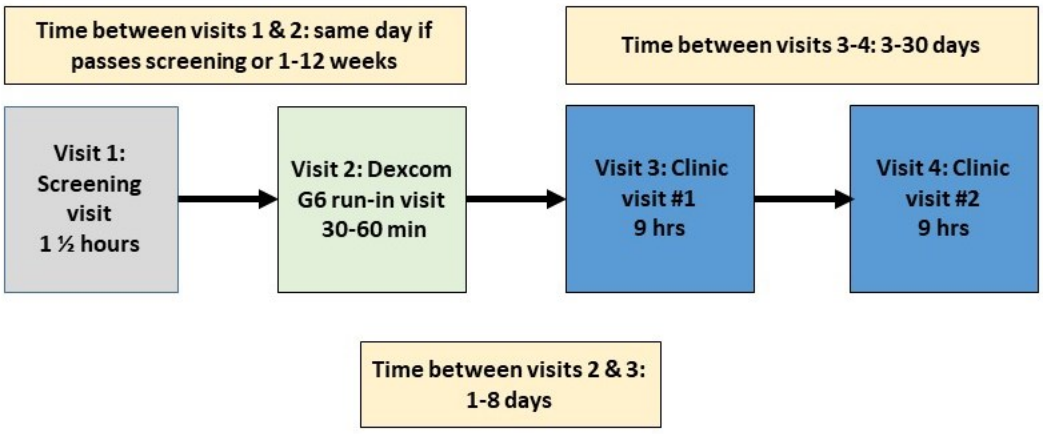
Power Analysis

This study is to obtain feasibility and assessment of variability in the primary outcomes that will inform a future larger, sufficiently powered efficacy study. A sample size of 15 is a feasible number to recruit and complete the study in timely fashion. This sample size will allow adequate estimation of the outcomes and variability of those estimates.

Protocol Summary:

Participants will undergo two visits at OHSU that will evaluate missed meal bolus detection. Participants will arrive at approximately 7am for all visits, be monitored through the afternoon and discharged before dinner. See **Figure 1** for a diagram of the study flow. During each of these intervention visits, participants will wear an Omnipod to deliver insulin and a Dexcom G6 CGM to measure glucose. The closed loop system will receive activity data through a Polar M600 watch worn by the participant. The studies will test the ability of the system to adapt to a missed meal bolus. For one missed meal bolus study, glucose will be controlled using the Robust R-AP closed-loop mode. During the other missed meal bolus study, glucose will be controlled using the MPC closed-loop mode. For the R-AP study, participants will eat self selected meals at 10 am and 2pm. The 10am meal will be the only meal given during the MPC study. The 10am meal will be the same across both arms. A meal bolus will not be given before any meals.

Figure 1: Study Flow Design



Subject Criteria

Inclusion Criteria:

1. Diagnosis of type 1 diabetes mellitus for at least 1 year.
2. Male or female participants 18 to 65 years of age.
3. Current use of an insulin pump for at least 3 months with stable insulin pump settings for >2 weeks.

4. HbA1c ≤ 10.5% at screening.
5. Total daily insulin requirement is less than 139 units/day.
6. Willingness to follow all study procedures, including attending all clinic visits.
7. 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 at the time of screening or any history of: stroke, heart failure, myocardial infarction, angina pectoris, or coronary arterial bypass graft or angioplasty. Diagnosis of 2nd or 3rd degree heart block or any non-physiological arrhythmia judged by the investigator to be exclusionary.
3. Renal insufficiency (GFR < 60 ml/min, using the MDRD equation as reported by the OHSU laboratory).
4. Liver failure, cirrhosis, or any other liver disease that compromises liver function as determined by the investigator.
5. Hematocrit of less than 36% for men, less than 32% for women.
6. 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.
7. History of diabetes ketoacidosis during the prior 6 months prior to screening visit, as diagnosed on hospital admission or as judged by the investigator.
8. Adrenal insufficiency.
9. Any active infection.
10. Known or suspected abuse of alcohol, narcotics, or illicit drugs.
11. Seizure disorder.
12. Active foot ulceration.
13. Severe peripheral arterial disease characterized by ischemic rest pain or severe claudication.
14. Major surgical operation within 30 days prior to screening.
15. Use of an investigational drug within 30 days prior to screening.
16. Chronic usage of any immunosuppressive medication (such as cyclosporine, azathioprine, sirolimus, or tacrolimus).
17. Bleeding disorder, treatment with warfarin, or platelet count below 50,000.
18. Allergy to aspart insulin.
19. 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. Beta blockers or non-dihydropyridine calcium channel blockers.
22. Current use of any medication intended to lower glucose other than insulin (ex. use of liraglutide).
23. Gastroparesis
24. Diets consisting of less than 50 grams of carbohydrates per day.
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 newletter 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.

Up to 18 participants may be screened in this study. Goal enrollment is 15 participants.

Withdrawal Criteria

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

A participant must be withdrawn if the following applies:

- Hypoglycemia during the treatment period posing a safety problem as judged by the investigator.
- Hyperglycemia during the treatment period posing a safety problem as judged by the investigator.
- Protocol deviation having influence on efficacy or safety data as judged by the Investigator.
- Substantial and repeated non-compliance with trial procedures.
- Pregnancy.
- Intention of becoming pregnant.

Visit Procedures

Negative COVID-19 screening is required for face-to-face visits. Study staff will perform COVID-19 screening on all participants and participant households, to ensure that there is no COVID-19 or COVID-19 symptoms. OHSU COVID-19 policy provides the option to complete visits virtually in order to minimize face-to-face contact with participants.

Screening (Visit 1)

Screening will take place within 12 weeks prior to the 1 week run-in period (Visit 2). All screening visits will take place at OHSU's Oregon Clinical Translational Research Institute (OCTRI) outpatient clinic, the Biomedical Engineering Point of Care (BME POC) Laboratory or at the Harold Schnitzer Diabetes Health Center. 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.

A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter and recorded after consenting. Prior to measurement of any blood samples, the meter will undergo quality control testing with two different glucose levels, one high and one low, and both values must fall within the accepted range for a meter to be used.

Study personnel will review medical history, and medications. Height, weight, pulse, and blood pressure will be obtained. A study investigator will perform a physical examination, excluding breast and pelvic exams. 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, than 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. The participant's insulin pump, and if applicable glucose sensor, may 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 insertion visit

The purpose of this visit is to have the participants learn how to insert the Dexcom G6 CGM device. This visit will take 30-60minutes. 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 at

the OHSU OCTRI outpatient clinic, the Biomedical Engineering Point of Care (BME POC) Laboratory or Harold Schnitzer Diabetes Health Center clinic, women of childbearing potential will receive a urine pregnancy test if the last pregnancy test was more than 7 days prior. This test must be negative before further participation is allowed.

Participants will receive training on how to use and calibrate the Dexcom G6 CGM system. 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 or flank after appropriate preparation of the abdominal skin as per the manufacturer's directions. Participants will be trained how to pair the Dexcom G6 transmitter to the Dexcom app on a provided study smart phone to start and stop a new sensor session and how to enter calibrations. 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. The transmitter and sensors can be given to the participant at the CGM insertion visit or delivered via courier.

To reduce the risk of COVID-19 and to comply with OHSU modified operations, sensor insertion visits can be completed using Webex video conferencing software. Study devices, including a urine pregnancy test, will be delivered to participants via a courier. Using the Webex platform, study staff can connect virtually with participants for training on the devices and study procedures while they are at home.

1 day Treatment Visits

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 enter this value into his/her pump calculator and take 80 percent of the correction bolus. 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 3 to 30 days calculated from the day of admission until the start of the next admission. After arrival at the OHSU OCTRI outpatient clinic, the Biomedical Engineering Point of Care (BME POC) Laboratory or Harold Schnitzer Diabetes Health Center clinic at approximately 7am, women of childbearing potential will receive a urine pregnancy test if the last pregnancy test was more than 7 days prior. This test must be negative before further participation is allowed.

An assessment will take place at the beginning of the participant's first closed-loop study. We will inquire whether the participant has had changes in their medications and/or medical history to confirm the participant hasn't developed any study exclusion criteria. A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter. When they arrive, participants will be given 15-20 grams of oral carbohydrate if the CBG reading is less than 70 mg/dl. CBG values > 300 mg/dl will be managed at the discretion of the investigator with a correction bolus and serum ketones will be checked. If serum ketones are ≥ 0. 6 mM, the study will not be started and insulin therapy will be guided by the onsite investigator.

During each visit, glucose will be controlled using either: 1) the OHSU Robust R-AP closed-loop mode or 2) the OHSU MPC closed-loop mode. The order of the visits will be randomized. A code team is available by page at all times in all locations.

An Omnipod will be filled with Novolog or Humalog insulin for all studies. The Omnipod will be primed and inserted into the skin of the participant's abdomen or flank as directed by the manufacturer. Participants will disconnect his/her own pump and remove his/her own insulin infusion set once insulin delivery has started via the Omnipod. Participants will wear a Polar watch to inform the controller. The research staff will initialize the system and begin the closed-loop study. Two staff will review each of the settings to confirm the settings are inputted correctly. A member of the study staff will remain with the participant for the duration of the study with the study investigator on call. Research staff will set up and run the system and respond to all alerts.

The algorithm will push data up to a cloud server that can be monitored remotely every 5 minutes. The iPancreas will generate alerts on the smartphone according to Appendix D. In order to push alerts to study coordinators and study investigators, the cloud server used for remote monitoring will have a drop down menu for study staff to sign in and out for the duration of their monitoring shift. Each study coordinator and investigator listed in the menu will have a cell phone number on file that can receive texts with pushed alerts.

During all studies, sensed glucose data will be wirelessly transmitted via BTLE from the Dexcom G6 transmitter to the insulin-delivery algorithm every five minutes. The insulin-delivery algorithm will calculate insulin doses and will run on a 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 a sensor value is not available for 20 minutes or communication with the Omnipod is lost for more than 30 minutes, the insulin Omnipod will begin insulin delivery according to a pre-set basal profile(s) inputted for the participant at study start. When this occurs for a lost sensor, 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 linear regression of the prior

ten minutes of sensor glucose data. When communication with the sensor or Omnipod is restored, the system will automatically resume, updating the IOB accordingly.

After a run-in period of 2 hours whereby the participants are using the AP algorithms, participants will eat self selected meals around 10 am. During the R-AP study only, another meal will be given four hours later around 2 pm. The self selected meals will have a minimum of 45 g of carbohydrates, and a maximum of 120 g of carbohydrates. These self selected breakfasts will be identical across both study sessions. Participants will not enter a meal bolus for the meals. CBG and blood ketone measurements will be taken every 30 min (for safety purposes only, not for input into the AP systems) until study discharge. If CBG >250mg/dL before the lunch meal, then study will be stopped early and the participant will be given the option to return on a different day for the second meal.

The study will be stopped if:

(1) the CBG reaches > 300 mg/dL with ketones > 0.5 mM,
(2) the CBG reaches > 300 mg/dL for over an hour (even when ketones are <0.5 mM),
(3) the CBG reaches > 450 mg/dL,
(4) participants exhibit nausea or vomiting or both.

The Robust-AP system will use the Missed Meal Detection algorithm to identify a missed meal bolus. If the R-AP system detects a missed meal, the system will send an alert to the user indicating that a meal was detected, and the system will also return the estimated carbohydrate content of the detected meal. The user will be required to acknowledge this alert. The user can modify the carbohydrate content that was estimated by the R-AP system. Then the R-AP will use that carbohydrate content to calculate a meal bolus, which will then be dosed by the R-AP system via insulin pump as described in the equation below. A study investigator will evaluate the meal insulin dose prior to delivery, considering insulin-on-board and time since meal consumption, and the investigator will modify the insulin dose if needed for participant safety. Otherwise, if stopping procedures (1)-(3) are reached, the study investigator will calculate a meal bolus with correction dose as in the equation below. 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 investigator will check the Omnipod site and determine if the insulin should be delivered via the Omnipod, syringe, or via the participant's own insulin pump after it is reconnected. The study team will monitor the participants CGM levels and ketones will be checked every 30 minutes until ketone levels are less than or equal to 0.2 mmol/L. Participants will be provided with plenty of water to drink to avoid dehydration. Additional subcutaneous insulin doses will be given approximately every three hours to treat hyperglycemia at the investigator's discretion. Participants will be evaluated by investigator for possible transfer to the emergency room if ketone level is 3.0 mmol/L or higher or earlier at the discretion of the study investigator.

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

Participants can be discharged after 4pm when: (1) CBG >80 and < 250 mg/dl, (2) ketones ≤ 0.2 mM and (3) the participant is feeling well. For values outside this range, treatment will be at the discretion of the study investigator. 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.

Discharge from 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, Omnipods and Dexcom sensor will be removed from the participant. All infusion sites and the sensor site will be inspected for signs of irritation or infection. In addition, the sensor will be inspected for the possibility of breakage or fracture. If there is any evidence of sensor breakage, it will be recorded. If an area of inflammation of 1 cm or greater exists around the point of insertion, a de-identified photograph will be taken of the area and the participant will return 1-3 days later for a follow-up visit.

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

Hypoglycemia Treatment Guidelines

- **CBG < 70 mg/dl**

  Give 15 grams of oral carbohydrate.

  Repeat treatment every 15 minutes as needed to raise blood glucose ≥70 mg/dl.
- **Presence of STUPOR, LOSS OF CONSCIOUSNESS, or SEIZURE**

  Give 1 mg glucagon IM

  Verify that insulin is turned off.

  Further management per study investigator.

Cleaning and Disinfecting

All devices will be cleaned and disinfected between participants. The smart phone, Dexcom G6 transmitter and Omnipod PDMs are cleaned by study staff. Technicians who are disinfecting units will wash hands thoroughly and wear gloves. All items will undergo intermediate-level disinfection using Oxivir TB disposable wipes. The disinfectant will be applied and allowed to air dry. After disinfection, when the units are completely dry, they will be placed in a sealed bag labeled with participant information.

Stopping Rules

Individual study stopping rules

The closed-loop study will be stopped and open-loop control will be resumed under the guidance of the on call study investigator if any of the following occur after the start of the study: 1)

capillary blood glucose falls to < 40 mg/dl at any time point, 2) serum ketones are above 1.5 mM at any time and 3) seizure or unconsciousness associated with hypoglycemia.

Entire study stopping rules

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

Description of the MPC and R-AP algorithms

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

The R-AP is a modified MPC algorithm. A new feature in the algorithm includes a model for missed meal insulin detection. 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 Missed Meal Insulin Detection. Our Missed Meal Insulin Detection algorithm is unique in that it presumes that the patient will generally announce their meals to the system. However, if the participant does not announce, the algorithm will detect it using machine learning methods, and then adjust dosing based on this detected meal.

Statistical methods

The primary study endpoints are (1) incremental area under the curve (AUC) of glucose in the 4 hours following unannounced meals and (2) percent of time with glucose sensor 70-180 mg/dL. The hypothesis to be tested is the R-AP closed-loop system will increase time in range and decrease AUC as compared to the MPC-AP closed-loop system. We will estimate the difference between systems using a fixed effect in a standard 2x2 crossover model with a random participant effect. While we do not anticipate statistically significant effects for the following, we will also control for sequence (AB or BA) and period (1 or 2).

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 robust-AP and standard MCP visits 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.

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

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

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 $340 for completion of all study visits. If a participant withdraws early from the study, compensation will be given as follows: $40 for the run-in visit and $150 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 $150.

Monitoring Entity:

This investigation will be monitored by the co- investigator Leah Wilson MD. Dr. Wilson has no commercial interest in any of the companies which manufacture any of the devices used in this

study. Drs. Jessica Castle, Peter Jacobs and Joseph El Youssef are inventors on patents regarding the algorithms.

Data Collection:

Participant privacy will be protected by using a three-digit identifying number to code study documents. All paper source documents will be kept in a locked cabinet for a minimum of five years. All data from the study files on the smart phone master controller will subsequently be entered into the authorized electronic OCTRI Cloud database.

Recording of Data:

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

- 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 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/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained regarding these procedures. See IRB protocol 19858 for a complete description of the confidentiality and security of the study data collected during this study to be stored in the OregonAPC repository.

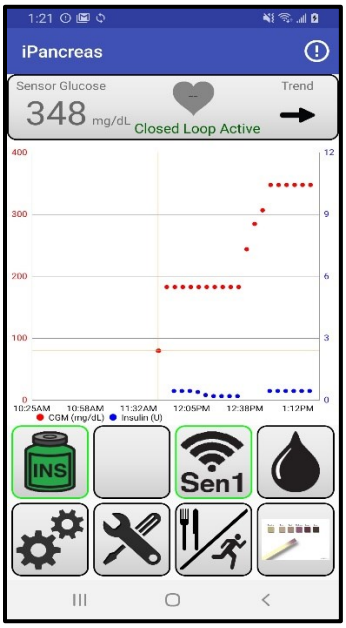
Data for this project will be stored in an AWS server developed by our group that has undergone a security review.

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.

Appendix A: Devices

Insulet Omnipod insulin management system

iPancreas with Dexcom G6 Continuous Glucose Monitoring System which includes Sensor and Sensor Transmitter



Contour Next Blood Glucose Meter

Abbott Precision Xtra Meter

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)

Appendix C: Alert Manager Specifications

#	NAME: Activation criteria	Clearing Criteria	Algorithm specifics	Notification to participant	Re-fire Time (min)	Refractory Period (min)	Coordinator push	Investigator push	Waiting period
4	**cbg_equal_or_under_40**: CBG ≤ 40 mg/dl AND alert 4 not active	User enters CBG > 40 mg/dL after 15 minutes. Once rescue carb are entered, the waiting period starts. If CBG ≥70 at any time, alert clears.	None	"Blood glucose is below 40 mg/dl. Please take 30 gm of rescue carbohydrates and recheck your blood glucose level in 15 minutes. "	5	-	Immediately	Immediately	Waiting period ends when alert 13 is serviced OR clear 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	None	"Blood glucose is below 70 mg/dl. Please take 15 gm of rescue carbohyd	15	-	After 1st re-fire	After 2nd re-fire	Waiting period ends when alert 13 is servi

				rates and recheck your blood glucose level in 15 minutes. "					ced OR clear crite ria is met
6	**sensor_glucose_low:** Sensor glucose < LOW_THRESH AND alert 4 AND alert 5 AND alert 6 not active or refractory & no CBG within last 15 minutes	CBG check OR sensor ≥ LOW_THRESH 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	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	30	120	After 1st re-fire	After 2nd re-fire	-

				levels now."					
8	**sensor_glucose_high:** Sensor glucose ≥ 300 mg/dl for 30 minutes within the last 45 minute period AND alert 8 AND alert 7 AND alert 27 not active or refractory AND no CBG in last 30 minutes	CBG check. OR sensor < 300	None	"Sensor glucose is over 300 mg/dl. Please perform a blood glucose check now."	30	60	After 1st re-fire	After 2nd re-fire	-
10	**Insulin_meal_bolus_failure:** If 50% of meal bolus is still not delivered after 20 minutes.	Auto clears	None	Insulin bolus failed to deliver, please contact the study investigator.	-	-	Immediately	Immediately	-
13	**recheck_cbg:** Alert 4 OR alert 5 in waiting period for 15 minutes	CBG recheck		"Please perform a blood glucose check now."	20	-	After 1st re-fire	After 2nd re-fire	-
14	**no_data_connection:** No connection to the internet or data for 40 minutes	Phone connects to a wifi network or regain cell service		There is no connection of the phone to the internet. Please move	40	-	-	-	-

				back into cell phone or wifi range.					
17	**transmitter_not_reporting:** Sensor is out of date for > 20 minutes AND alert 17 AND alert 18 AND alert 20 not active or refractory	Clears with valid sensor		"A sensor reading has not been received in the last 20 minutes. Please ensure that the phone is within range of the sensor."	20	-	After 1st re-fire	After 2nd re-fire	-
18	**replace_transmitter:** iPancreas sends message to replace the transmitter immediately 60 minutes after activation criteria for alert 17 if clear criteria has not been met	User acknowledgement		"The transmitter is no longer functional. Please replace it immediately."	-	120	-	-	-
19	**sensor_glucose_invalid:** Sensor value is invalid for > 20 Minutes AND alert 19 AND alert 18 AND alert 20 not active or refractory	Clears with valid sensor		"Sensor value is not reporting correctly. Please	20	-	After 1st re-fire	After 2nd re-fire	-

				check your sensor site for problems. Contact the study coordinator if needed."					
20	**replace_sensor:** iPancreas sends message to replace the sensor immediately 60 minutes after activation criteria for 19 if clear criteria has not been met	User acknowledgement		"The sensor may no longer be functioning. Please replace it immediately."	-	120	-	-	-
21	**Insulin_pump_communication_failure:** Basal Insulin Fails to deliver correct amount for 60 minutes OR insulin suspend required and no connection to pump	Successful basal insulin is delivered OR insulin is successfully suspended		"Insulin communication failure. Please move PDM and POD closer to phone"	60 minutes	If alert fires after 10:59 PM, refractory lasts until 6:59AM. No refractory other hours	After 1st re-fire	After 2nd re-fire	-

						of the day.			
25	**phone_battery_low:** Phone battery falls below 20% AND is not charging	If phone is charging or level goes above 20%		"Phone battery low. Please charge"	10	-	After 1st re-fire	After 2nd re-fire	-
26	**maximum_insulin_exceeded**: Insulin Delivery ≥ 35% $TDIR_{adj}$ on last hour	Auto clears		"Max insulin has been exceeded "	-	60	Immediately	Immediately	-
27	**cbg_equal_or_over_400:** CBG ≥ 400 mg/dl AND alert 27 not active or refractory	Ketone check		"Blood glucose is above 400 mg/dl. Please change the insulin pod and check ketone levels now."	15	60	Immediately	Immediately	-
28	**ketone_level_high:** Ketones ≥ 0.6 mmol/L	User acknowledgement		"Ketone levels are high. If not already done, please change the insulin pod. Do	-	-	Immediately	Immediately	-

				not exercise. ”					
29	**Insulin_pump_reservoir_low:** Omnipod has less than 10% of fluid volume remaining.	Pod with greater than 10% volume is connected (i.e. pod is changed)		Your insulin pod is low. Please deactivate your current pod and activate a new insulin pod.	120	-	After 1st re-fire	After 2nd re-fire	-
30	**External_insulin_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 coordinato.	The app determined by the pump’s pulse count that more insulin than was expected was delivered.	Alert for over-insulin delivery: The actual insulin exceeded the expected insulin by XX units.	-	-	Immediately	Immediately	-
31	**Extreme_low_sensor_glucose:** 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.	“Sensor value is extremely low” “Sensor glucose is below 54	10	30	After first re-fire	After second re-fire	-

			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 on the recently cleared extreme_low_sensor_glucose alert	mg/dL. Please perform a blood glucose check now."					
32	**Missed_meal_detection_alert:** This alert triggers if the Missed Meal Detection algorithm detects that carbohydrates were consumed approximately 25 minutes ago.	The user acknowledges the alert and either doses insulin or declines that a missed meal. 20 minutes have passed since the alert trigger.	The missed meal detection alert will trigger if glucose is rising rapidly and the prior carbohydrate intake is indicated by the algorithm. The algorithm presumes the meal was consumed 25 minutes prior to the trigger. The alert will expire after 20 minutes from triggering.	"Your glucose appears to be rising. Did you consume a meal that you want to dose insulin for?"	-	-	-	-	-

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