Protocol Title: Assessment of a fully-closed loop AID system with a context-aware hyperglycemia pattern detection and dosing algorithm in people with type 1 diabetes

Brief Title: Context Aware AID Study

NCT Number: 06676657

PROTOCOL TITLE: Assessment of a fully-closed loop AID system with a context-aware hyperglycemia pattern detection and dosing algorithm in people with type 1 diabetes

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FUNDING:	NIH
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Background

T1D is characterized by the autoimmune destruction of β cells. These patients rely on the administration of insulin, putting them at significant risk of hypoglycemia and excessive hyperglycemia. Better approaches to helping people avoid hyperglycemia are critical to improve glycemic control and reduce long term complications of diabetes. Continuous glucose monitoring (CGM) has been shown to help T1D patients improve time in range and reduce hyperglycemia [1, 2]. Automated Insulin Delivery (AID) systems have now become an important standard-of-care for people with T1D and have demonstrated a reduction, but not elimination, of hypoglycemia during long-term studies [3-7]. Despite several commercially available AID systems, many people with type 1 diabetes are unable to achieve recommended glycemic goals.[8]

One limitation of current AID systems is that they have no knowledge about behaviors or other contextual patterns that a person is currently experiencing. Contextual patterns can potentially improve the performance of an AID by recognizing patterns of events/situations that are related to changes in glucose. The team at OHSU has developed a context-aware hyperglycemia prediction algorithm incorporated into our iPancreas AID system that will identify contextual pattern data from the participant. This contextual data will be provided

to the automated insulin delivery algorithm to allow for detecting problem patterns that relate to hyperglycemia. When the context-aware detection and dosing algorithm (CADD) is activated, the system will dose a correction insulin bolus when a hyperglycemia pattern is detected.

The goal of this study will be assessing safety and feasibility of this context-aware detection and dosing system to determine if it is merited to run a larger study to evaluate the effectiveness of the algorithm on improving glucose outcomes in people with T1D. Participants will use the system under free-living conditions and will also be asked to complete meals and exercise at specific days and times during the study. The purpose of the prescribed meals and exercise sessions is to generate patterns that may be detected by the context-aware detection and dosing algorithm. Participants will use the CADD system for 3 weeks during a *training period* to identify patterns that lead to excessively high glucose (>250 mg/dL) within the next two hours. Patterns will be given a score based on the likelihood of the pattern leading to an excessively high glucose or a low glucose (<70 mg/dL) in the next two hours. Following this 3-week training period, participants will use the CADD system during an intervention period, whereby the pattern data collected by CADD will be used to dose correction insulin in response to patterns that exceed a certain score indicating that they were associated with excessive high glucose and not low glucose.

We will calculate glucose outcomes during all of the 2-hour periods of time after the pattern-based correction insulin dosing was given. This time period during when we will evaluate glucose outcomes is called the *pattern evaluation window*. We will compare glucose outcomes during these *pattern evaluation windows* comparing the 3-week training period with the 1-week intervention period.

Our hypothesis is that performing the pattern-based correction insulin using CADD during the 1-week intervention period will be safe and effective at nominally improving glucose outcomes compared with the 3-week training period when pattern-based correction insulin was not dosed. We will determine that the system is safe if the percent time in low glucose (<70 mg/dL) is less than 2% and the percent time in very low glucose (<54 mg/dL) is less than 1% during the *pattern evaluation window* during the 1-week intervention compared. We will evaluate feasibility by calculating the percent of time that the CADD could potentially intervene across both the training period and the intervention period. We will further evaluate if the percent time in very high glucose is nominally reduced during the

pattern evaluation windows when using CADD in the 1-week intervention period compared with the 3-week training period. If safety and feasibility are demonstrated, then we will conclude that a larger study on the CADD is needed to determine if it is effective at improving glucose outcomes and reducing very high glucose events.

Primary Objectives

- To assess safety of the CADD system by evaluating the percent time spent in low glucose (<70 mg/dL), very low glucose (<54 mg/d), and very high glucose (>250 mg/dL) during the pattern evaluation windows. We will consider the system sufficiently safe to continue if the percent time in low glucose is less than 2% and if the percent time in very low glucose during the *pattern evaluation windows* is less than 1%.

- To assess feasibility of the CADD system by evaluating the percent time that the CADD is active in detecting hyperglycemic patterns and dosing for them during the *pattern evaluation windows*. Feasibility is met if the pattern evaluation windows represent at least 10% of the study duration.

- To further assess feasibility of the CADD system by evaluating the percent time in very high glucose (>250 mg/dL) during the *pattern evaluation windows* comparing the 1-week intervention period with the 3-week training period. Feasibility is met if the time in very high glucose is nominally lower during the pattern evaluation windows in the 1-week intervention period compared with the training period.

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Secondary Objectives

- Estimate the within- and between-person variability in glucose control metrics to inform the design of a future efficacy trial that will have those metrics as endpoints
- Investigate whether glucose control metrics improve for a majority of participants while using the CADD system

Endpoints

In the table below, percent time *pattern evaluation windows* occurred for the study period is calculated as (minutes in *pattern evaluation window*) / (total minutes) * 100 Percent time in a given CGM range is calculated as (minutes CGM is in range) / (sum of minutes in *pattern evaluation windows*) * 100 OR (minutes CGM is in range) / (total minutes) * 100

Primary endpoints	**Target**

% time CGM <70mg/dL (low glucose) % time CGM <54mg/dL (very low glucose) % time the pattern evaluation windows occurred % time CGM >250mg/dL (very high glucose)	< 2% < 1% ≥ 10% Decrease during 1-week intervention period compared to 3-week training period
Secondary endpoints	**Target**
% time CGM 70 to 180mg/dL (in range) % time CGM 70 to 140mg/dL (in tight range) % time CGM >180mg/dL (high glucose) Coefficient of variation of glucose Insulin delivered (units/kg/day) Hypoglycemia treatments (15g oral carbohydrate) per day	Increase Increase Decrease Decrease Decrease Decrease

Study Type

This is a single-center pilot clinical study evaluating the safety and feasibility and preliminary efficacy and standard deviation assessment to power future larger clinical trials.

Study Population

Study population will be people with type 1 diabetes, ages 18 years of age and older. Older participants are excluded due to higher risk of unrecognized coronary artery disease. Participants under the age of 18 are excluded as it is appropriate to assess safety and efficacy first in and adult population for which we have experience with the OHSU MPC system from prior clinical studies. Up to 16 participants will be screened with the goal to complete studies with 10 total participants. Two replacements will be allowed to achieve 10 complete studies.

Sample Size Considerations

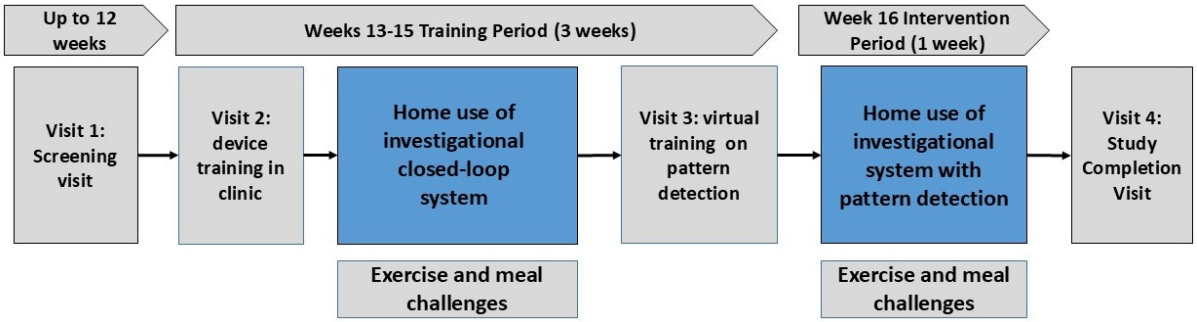
The planned sample size of 10 participants was selected based on availability of resources and the quality of the data that we expect to be able to use for planning purposes based on

our previous trials. Because this is a pilot study, we did not conduct a power analysis and do not plan to conduct formal statistical hypothesis testing. Instead, we will summarize the evidence and provide measures of uncertainty.

Protocol Summary

Participants will be on study for approximately 16 weeks. During the study, participants will wear an Omnipod Dash pod to deliver insulin. Participants will also wear a Dexcom G6 CGM. The CGM system will send sensed glucose data every 5 minutes wirelessly via Bluetooth Low Energy (BTLE) to an Android smartphone running the iPancreas app that includes a model predictive control algorithm along with the CADD algorithm. The MPC algorithm running on the smartphone will calculate the amount of insulin to be delivered to the participant and will transmit this amount wirelessly via BTLE to an Omnipod Dash pod. Participants will complete system training on Day 1 in clinic and then spend the rest of the 4 weeks under free-living conditions. The first 3 weeks of the study will be the training period when the CADD system will collect patterns from the CGM, insulin, and fitness data that lead to high glucose (>250 mg/dL). After the 3-week training period, participants will complete a virtual visit will help the participant to enable the intervention component of the CADD system such that correction insulin will be dosed if a high glucose pattern is detected. When a high glucose pattern is detected during the last 14 days on study, a correction insulin bolus will be given based on the current glucose, participants preset correction factor. Safety will be ensured such that correction insulin from CADD algorithm will only be dosed to bring the participant's glucose levels to 90 mg/dL. Participants will complete aerobic exercise videos twice weekly at home. Participants will also ingest a self-selected meal prior to these prescribed exercise sessions. Subjects will consume a high carbohydrate meal prepared by OHSU Bionutrition once each week at the same approximate time of day (but not on the exercise days). See Figure 1 below for a diagram of the study flow. Protocol amendments will be submitted to the IRB and FDA per the pertinent regulations either for prior approval or as 5-day notice as appropriate

Figure 1: Study Flow Design



Participant Criteria

Inclusion Criteria:

1. Diagnosis of type 1 diabetes mellitus for at least 1 year.
2. Male or female participants 18 and older.
3. A1c or GMI ≥ 7.0% (GMI from last 30 days of CGM data, equation GMI (%) = 3.31 + 0.02392 × [mean glucose in mg/dL] based on prior 30 days of Dexcom CGM data [9]
4. Physically willing and able to perform 30 min of exercise (as determined by the investigator after reviewing the participant's activity level).
5. Current use of an FDA-approved hybrid closed loop system for ≥3 months.
6. Lives with another person age 18 or older who will sleep in the house at night and that can attend the training on using the system.
7. Lives within 40 miles of OHSU
8. Total daily insulin requirement is less than 139 units/day.
9. Able to read, write and understand spoken English
10. Current use of a smartphone so can be contacted by study staff off-campus.
11. Willingness to follow all study procedures, including attending all clinic visits.
12. Willingness to sign informed consent and HIPAA documents.

Exclusion Criteria:

1. GMI or A1c <6.5% or >10.5%
2. Sensor glucose shows < 2% of time above 250 mg/dl in last 30 days.
3. 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.
4. Any cardiovascular disease, defined as a clinically significant EKG abnormality at the time of screening or any history of: stroke, heart failure, myocardial infarction, angina pectoris, or coronary arterial bypass graft or angioplasty. Diagnosis of 2nd or 3rd degree heart block or any non-physiological arrhythmia judged by the investigator to be exclusionary.

5. Renal insufficiency (GFR < 60 ml/min, using the MDRD equation as reported by the OHSU laboratory).
6. Liver failure, cirrhosis, or any other liver disease that compromises liver function as determined by the investigator.
7. History of severe hypoglycemia during the past 6 months prior to screening visit or hypoglycemia unawareness as judged by the investigator. Participants will complete a hypoglycemia awareness questionnaire. Participants will be excluded for four or more R responses.
8. History of diabetes ketoacidosis during the prior 6 months prior to screening visit, as diagnosed on hospital admission or as judged by the investigator.
9. Adrenal insufficiency.
10. Any active infection (example skin infection requiring antibiotics)
11. Known or suspected abuse of alcohol, narcotics, or illicit drugs.
12. Seizure disorder.
13. Active foot ulceration.
14. Peripheral arterial disease.
15. Major surgical operation within 30 days prior to screening.
16. Use of an investigational drug within 30 days prior to screening.
17. Chronic usage of any immunosuppressive medication (such as cyclosporine, azathioprine, sirolimus, or tacrolimus).
18. Bleeding disorder or platelet count below 50,000.
19. Allergy to Fiasp insulin
20. Current administration of oral or parenteral corticosteroids.
21. Any life threatening disease, including malignant neoplasms and medical history of malignant neoplasms within the past 5 years prior to screening (except basal and squamous cell skin cancer).
22. Use of beta blockers or non-dihydropyridine calcium channel blockers.
23. Current use of any medication that can lower glucose other than insulin (ex. Wegovy, Jardiance) with the exception of metformin if dose has been stable for ≥3 months and patient willing to not change dose during study.
24. Gastroparesis
25. Diet consisting of less than 50 grams of carbohydrates per day.
26. A positive response to any of the questions from the Physical Activity Readiness Questionnaire with one exception: participant will not be excluded if he/she takes a single blood pressure medication that doesn't impact heart rate and blood pressure is controlled on the medication (blood pressure is less than 140/90 mmHg).
27. Any chest discomfort with physical activity, including pain or pressure, or other types of discomfort.
28. Any clinically significant disease or disorder which in the opinion of the Investigator may jeopardize the participant's safety or compliance with the protocol.

Participant Recruiting

Participants will be recruited from OHSU clinics, from flyers to be posted in approved places at OHSU or posted on the web to the clinical trials page for the OHSU Schnitzer Diabetes Clinic. Handouts may also be made available to faculty at Providence, Tuality, 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 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. 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 16 participants may be screened in this study. Goal enrollment is 10 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:

1. Protocol deviation having influence on efficacy or safety data as judged by the Investigator.
2. Substantial and repeated non-compliance with trial procedures.
3. Pregnancy.
4. Intention of becoming pregnant.

Visit Procedures

Screening (Visit 1)

Screening will take place within 12 weeks prior to Visit 2. 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 at the clinic 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 participant voices understanding of the informed consent and study requirements. To minimize the possibility of coercion and to ensure that participant is signing the appropriate version of consent, an informed consent checklist will be used by study staff. After the participant has signed the consent, a copy of the consent/authorization form will be given to the participant. The original will be kept for the source document.

Study personnel will review medical history, and medications. Height, weight, pulse, and blood pressure will be obtained. A study investigator will perform a physical examination, excluding breast and pelvic exams. Females of child-bearing potential will take a urine pregnancy test, which must be negative to participate. A venous blood sample will be taken for the following tests: hemoglobin A1C, complete blood count, complete metabolic set (including creatinine, liver set, and electrolytes. If participants have had any of the aforementioned labs performed within the 3 months prior to the screening visit and we can access the results, a venous blood sample will not be taken for that test. An EKG will be obtained for participants either ≥50 years old or with diabetes duration ≥20 years, if not available from prior 3 months. A study investigator will assess inclusion/exclusion criteria and review the participant's medical record for clarification as needed. The participant's insulin pump will be downloaded to review baseline glucose control. A three-digit participant ID number will be assigned to the participant. This visit will take approximately 1.5 hours.

Study Start-up Visit (Visit 2):

This visit should take approximately 2 hours, depending on participant experience. 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). 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 study. We will inquire whether the participant has had changes in their medications and/or medical history to confirm the participant does not meet any study exclusion criteria. A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter. When they arrive, participants will be given 15-20 grams of oral carbohydrate if the CBG reading is less than 70 mg/dl. CBG values > 300 mg/dl will be managed at the discretion of the investigator with a correction bolus and serum ketones will be checked. If serum ketones are ≥ 0.6 mM, the study will not be started and insulin therapy will be guided by a study investigator.

Glucose will be controlled using the OHSU MPC exercise-enabled closed-loop mode with missed mealtime insulin detection algorithm which automatically detects and doses meal insulin if the participant forgets to announce a meal. The wire glucose sensor is sterile and commercially available from Dexcom™ and will be used for single use only as directed by

the manufacturer. The participant will be trained on how to insert a Dexcom G6 CGM sensor into the subcutaneous tissue of the abdomen after appropriate preparation of the abdominal skin per the manufacturer's directions. Participants will be trained how to pair the Dexcom transmitter to the iPancreas app on the smart phone, start and stop a new sensor session and how to enter calibrations. The Dexcom CGM does not require calibrations. As part of the training, study staff will review with the participants that CGM values can be inaccurate. Participants will be instructed to take SMBG readings under the following conditions:

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

An Omnipod (510k#K180045) will be filled with Fiasp insulin. We will use only name brand insulin, not generic insulin. We will provide the participants with Omnipods to replace the Omnipod at home every 72 hours or earlier if needed along with more Fiasp insulin and train participants how to perform this. The Omnipod will be primed and inserted as directed by the manufacturer. Research staff will train participants on the approved Omnipod placement options from the Omnipod User Guide. Participants will wear an exercise watch to inform the controller. Participants will disconnect his/her own pump and remove his/her own insulin infusion set once insulin delivery has started via the Omnipod. The participant will initialize the system and begin the closed-loop study using the iPancreas smart phone application. Two staff will review each of the settings to confirm the settings are inputted correctly. Meal detection will be enabled during waking hours based on participant's usual daily schedule. The participant will be given enough study supplies for the 4 weeks. A study investigator will be available by phone for the entire study period.

Study staff will complete a training with each participant on using the Dexcom CGM, the Omnipod system, and the exercise watch. Participants will be shown how to use the smartphone user interface which includes: entering basal profiles, insulin carb ratios and

sensitivity, activating and deactivating Omnipods, giving meal boluses, carb treatments, entering capillary blood glucose values and ketone levels, addressing alerts, troubleshooting the devices connection to the phone via Bluetooth, and pausing the study. Participants will be advised that they can take insulin prior to meals by announcing carbohydrates to the system. If they forget to announce, there is a feature whereby the system can detect the meal and give some insulin automatically. Participants will be instructed that taking insulin before meals will generally reduce hyperglycemia. Instruction will be given on identifying an Omnipod malfunction. The time required for this training will vary, depending on the experience of each participant, but will be sufficient to help him/her/they become comfortable using the smartphone and changing the Omnipod. If the participant experiences difficulties using the Omnipod during the study period, study staff will be available to educate and support by phone. Training will include that the smart bolus calculator available in open loop mode is a suggestion and that participants should use their judgement on what insulin dose to take as the bolus calculator is not aware of certain circumstances such as illness or alcohol use.

The participant will need to demonstrate competency in operating the system before leaving to continue using the study at home for the next 4 weeks. A competency assessment will be completed on day 1 of the closed-loop visit prior to discharge. Each participant will start the Dexcom sensor and start the Omnipod on their own during onboarding. Participants will need to show competency in entering fingerstick glucose values and announcing meals during the day on campus. Participants will demonstrate competency in the following using a simulated closed-loop study: pausing and resuming a study, using the smart bolus calculator and manual bolus while in pause mode. Participants will be given contact information to call for any problems during the study period. The companion will accompany the participant to receive training (or be previously trained) on treatment in case of severe hypoglycemia episode, including administration of rescue carbohydrates and use of emergency glucagon kit. Companions will also be trained on the closed-loop system. This training may be completed virtually.

The MPC algorithm makes use of an adjustable glucose target that the participant may change based on their preferences. Participants will have the target initially set to 110 mg/dL. The study investigator may adjust the glucose target only for safety as needed for repeated hypoglycemia (CGM < 70 mg/dL). The algorithm will push data up to a cloud server that can be monitored remotely every 5 minutes if needed for safety. The closed-loop system will generate alerts on the smartphone. The participants will all be trained as

to the action required by each alert. Each alert has a specific condition to be met for it to be considered serviced (i.e. enter treatment with oral carbohydrates).

For participant safety, if a sensor value is not available for 20 minutes or communication with the Omnipod lost for more than 30 minutes, the Omnipod will begin insulin delivery according to a pre-set basal profile(s) inputted for the participant at study start. When this occurs for a lost sensor, iPancreas will activate the predictive low glucose suspend feature if the last known sensor value was within the range of 70-140 mg/dl and predicted to fall below 90 mg/dl within thirty minutes or if the sensor glucose is less than 70 mg/dl. Insulin is suspended for 30 minutes, after which basal insulin delivery resumes. When communication with the sensor or Omnipod is restored, the system will automatically resume, updating the IOB accordingly.

Remote Monitoring of Automatic Delivery of Meal Insulin

For all participants, a study investigator will be assigned in the GRM to receive an alert each time a participant receives an auto-meal insulin dose. When the investigator receives this alert, they will log into the GRM and review the insulin bolus amount and glucose trend every 30-60 minutes as clinically indicated, for at least 2-3 hours.

Discharge from inpatient clinic

After the participant is trained and competent using the system, participants will be discharged from the clinic. Capillary blood glucose will be measured prior to discharge. Participants will wait to discharge home if capillary blood glucose is <85 and or >300 mg/dl or at the discretion of the study investigator, and treatment will be at the discretion of the study investigator. Once participant's capillary blood glucose is between 85-300 mg/dl on two capillary blood glucose measurements completed at least 30 minutes apart, they can be discharged home. If the capillary glucose is less than 85mg/dL, participants will be asked to consume 15g of glucose tablets. They can then be discharged if the next capillary glucose measurement 30 minutes later is greater than 85mg/dL. If the capillary blood glucose is <70, participants will be asked to consume 15g of glucose tablets and recheck capillary blood glucose every 15 minutes until >70. If capillary blood glucose is greater than 300mg/dL, participants will be instructed to pause iPancreas closed loop mode, take a correction bolus from the bolus calculator after reviewing this dose with the study investigator who will modify dose if needed considering current insulin on board then

resume iPancreas closed loop mode. The participant can then be discharged home if the next capillary blood glucose measurement 30 minutes later is less than 300 mg/dL or if the CGM glucose trend arrow shows flat arrow (Increasing/decreasing less than 1 mg/dL each minute) or a down arrow (decreasing >30mg/dL in 30 minutes). Participants will be instructed to eat meals and snacks as they normally would at home. Participants will be instructed that his/her companion will be required to stay with them each night while an outpatient.

At Home Study Procedures

Participants will complete an aerobic exercise video twice weekly at home. The exercise videos are approximately 30 minutes long. A list of exercises to be performed is provided in Appendix C. Participants will also ingest a self-selected meal prior to these prescribed exercise sessions. Instructions for the exercise will be provided via video links. Participants will be given an instruction sheet for instructions related to all exercise events as well as carbohydrate treatment before exercise to follow. Participants will also be instructed to wear the smart watch for all exercise to reduce risk of hypoglycemia. They will be advised to wear the watch during waking hours and charge the watch overnight while they are sleeping. Participants will also be instructed to check a CBG before and after exercise**.** Participants will be instructed to enter ALL pre-exercise carbohydrates into the iPancreas app. They will be counseled that failure to enter pre-exercise carbohydrates into the app may increase risk for hypoglycemia with exercise as iPancreas may dose auto-meal insulin due to the rise in glucose from pre-exercise carbohydrate. Participants will be instructed to use the ”Fork and Knife” icon to enter pre-exercise or rescue carbs into the app. They will also be instructed that if their glucose is between 100-145 mg/dL before exercise, they should follow instructions on the exercise card for carb intake. Then, for safety, they should recheck a fingerstick glucose (CBG) 15-25 minutes later during their exercise.

Participants will consume a high carbohydrate dinner prepared by OHSU Bionutrition once each week on the same day at approximately the same time (but not on the exercise study video days). The meals can potentially be picked up all at once and frozen until use.

Participants will be able to contact study staff for any issues with the devices. Study staff will follow-up with participants every 7 days. Staff will review the percent time <70 mg/dL for each participant each week. The study investigator will make a decision to raise the glucose target by 10 mg/dL (i.e. 110 to 120mg/dL) if the percent time <70 mg/dL is greater

than 4%. Participants may receive text messages from study staff with study reminders/instructions.

Severe hypoglycemia is defined as any event that required the assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions. Diabetic ketoacidosis is classified as: symptoms such as polyuria, polydipsia, nausea, or vomiting, serum ketones >1.5 mmol/L or moderate/large urine ketones, either arterial blood pH<7.3 or venous pH<7.24 or serum bicarbonate <15, and treatment provided in a health care facility. If an event of severe hypoglycemia or diabetic ketoacidosis should occur, the study will be halted and a description of the serious adverse event and a new risk mitigation plan will be submitted to the FDA. The study will only resume once FDA approval is received.

We are aware that there is a risk of severe hypoglycemia while the participants are at home. The system will alert if the sensed glucose values fall below 70 mg/dl prompting the participant to obtain a capillary blood glucose sample. Participants will be required to live with at least one other person age 18 or older.

In case of a system error that cannot be corrected immediately with the participant off campus, the participant will be able to go into open-loop mode. This will allow the Omnipod to begin basal insulin delivery for a pre-set basal profile(s) inputted for the participant at the study start. Participants will be able to give meal boluses and corrections through the Omnipod while in open-loop mode. When the error is resolved, the participant can resume closed-loop mode and the system will resume. If the participant goes into open-loop mode, this will be visible on the cloud server and may prompt a telephone call from study staff to determine the issue and the best way to resolve it. The participant may contact study staff at any time during the outpatient portion of the visit.

Virtual Visit to Turn on Pattern Detection on Study Device

At the beginning of week 4, participants will meet with research staff virtually. Staff will instruct the participants how to turn on the intervention component of the CADD algorithm in iPancreas that will deliver correction insulin in response to the high glucose patterns detected. This feature will be password protected and study staff will provide this password at the time of the virtual visit. This feature can be enabled/disabled in the participant's insulin profile settings. Pattern detection will only be enabled during waking hours based

on participant's usual daily schedule. Staff will verify on the cloud server that the correction insulin dosing in response to the high glucose pattern detection is now active. Staff will train the participants about the CADD algorithm including alert messages and dosing displays. Participants will then continue to use iPancreas at home for the next week with the pattern detection and correction insulin dosing feature activated. A study investigator will continue to receive an alert each time a participant receives an auto meal insulin dose to allow for remote monitoring as described earlier. During week 4, the study investigator will also receive a text alert for any auto-correction dose from the CADD algorithm. When the study investigator receives the text alert that a CADD insulin correction was dosed or auto meal insulin was dosed, they will log into the cloud system to evaluate correction bolus given in setting of current insulin-on-board, glucose and glucose trend. They will review GRM about once hourly for 4 hours for CADD dosing events and once every 30-60 minutes for auto-meal dosing events to observe glucose value and trend.

We collect updated contact information for the participant and their emergency contact at each study visit. The study investigator may intervene if they have a safety concern (example, CGM <70mg/dL and rapidly dropping without indication that the participant is interacting with system such as responding to alerts) with a telephone call, text or a personal visit at any time. If in the 4-hour observation window, the participant cannot be reached and sensor glucose is below 54 mg/dl, the companion will be contacted. If the alert is still un-serviced and study staff are unable to reach the participant or the companion, emergency medical services will be contacted (staff attempted to contact both participant and companion 2x each with less than 2 minutes between each call). If the companion is not able to assess of the participant's status within 5 minutes, we will reach out to emergency services. To facilitate this, the phone will track the participant's location and push GPS coordinates to the cloud server approximately every 10 minutes. Cloud coordinates will be pushed with a known, fixed offset to allow for scrambling.

Apart from monitoring of the CADD algorithm and auto-meal insulin, there will not be remote monitoring for this study as we have so far completed 23 participants under IRB#24218/IDE#G220246. During that study the first 5 participants were completed with remote monitoring. A safety analysis showed no safety concerns, which thereby enabled us to study the remaining 18 participants with no safety issues. We will perform remote monitoring when the CADD algorithm or meal detection algorithm automatically doses insulin throughout for all participants

Return to the Outpatient Clinic

After 4 weeks using the study device at home, participants will return to the outpatient clinic. The study will be stopped, 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 exercise watch, Omnipod and Dexcom sensor will be removed from the participant. All infusion and sensor sites will be inspected for signs of irritation or infection. In addition, the sensor will be inspected for the possibility of breakage or fracture. If there is any evidence of sensor breakage, it will be recorded. If an area of inflammation of 1 cm or greater exists around the point of insertion, a de-identified photograph will be taken of the area and the participant will return 1-3 days later for a follow-up visit. A capillary blood glucose value will be taken immediately prior to discharging the participant. Participants will complete a usability survey. Participants will be given oral carbohydrate for values below 85 mg/dl, and if capillary blood glucose is greater than 180mg/dL, participants will be instructed to take a correction bolus from their home insulin pump per their usual home settings after reviewing this dose with the study investigator who will modify dose if needed considering current insulin on board. The participant can then be discharged home if the next capillary blood glucose measurement 30 minutes later is less than 300 mg/dL or if the CGM glucose trend arrow shows flat arrow (increasing/decreasing less than 1 mg/dL each minute) or a down arrow (decreasing >30mg/dL in 30 minutes).

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

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

Safety assessment – First round (first 3 participants) & Second round (next 7 participants)

We will complete an interim analysis after the first 3 participants for the full 4 weeks on study assessing time spent with CGM < 54 mg/dL, <70 mg/dL, and > 250 mg/dL and any adverse events. The first 3 weeks on study will be compared to the final week on study when the CADD dosing is activated. We will also evaluate the auto-meal insulin dosing interim results for CGM < 54 mg/dL, <70 mg/dL, and > 250 mg/dL and any adverse events in

the 4 hours after auto-meal insulin was dosed. We will continue remote monitoring of the auto-meal insulin dosing events for all participants enrolled on study; we will continue to monitor the CADD events for all participants enrolled on study. We will proceed to enroll 7 more participants up to the full total of 10 participants.

Table 1: Schedule of Events

CGM-Continuous Glucose Monitoring system

	Screening	Active Treatment				End of Treatment
Description of visit procedures	Screening visit	Study Start-up visit	Phone check in	Phone check in	Virtual training visit	Study Close-out visit
Visit Number	1	2	3	4	5	6
Visit Window		1-84 days	7 days	7 days	7 days	7 days
Subject-Related Procedures and Assessments						
Consent form	X					
Medical history and medications	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X					
Hypoglycemia awareness survey	X					
Physical Activity Readiness Questionnaire	X					
EKG (if applicable)	X					
Physical examination	X					
Height	X					

Weight	X					
Pulse	X					
Blood pressure	X					
Capillary Blood Glucose (CBG) reading		X				X
Device Training		X			X	
Surveys	X					X
Trial-Related Efficacy and Safety Measures						
AE/SAE assessment including assessment for severe hypoglycemia and DKA		X	X	X	X	X
Download personal data (CGM and pump data)	X					
At Home Exercise Sessions		X	X	X	X	
Examination of sensor site after removal (if applicable)						X
Laboratory						
Hemoglobin A1c	X					
Complete Blood Count (CBC)	X					
Comprehensive Metabolic Panel (CMP)	X					
Pregnancy Test (Urine) for premenopausal women	X	X				
Study Medications or Study Device						
Insulin pump filled with Fiasp insulin (drug & Administration)		X	X	X	X	
iPancreas program (to be downloaded onto participant's study phone)		X	X	X	X	
Exercise watch		X	X	X	X	
Dexcom CGM		X	X	X	X	

Hypoglycemia Treatment Guidelines

CBG < 70 mg/dl or symptoms of hypoglycemia and inability to check CBG due to the acuity of the event

- Give 15 grams of oral carbohydrate.
- Repeat treatment every 15 minutes as needed to raise blood glucose ≥70 mg/dl.

Presence of STUPOR, LOSS OF CONSCIOUSNESS, or SEIZURE

- Administer rescue glucagon per the manufacturer's instructions.
- Verify that insulin is turned off.
- Further management per study investigator.

Hyperglycemia Treatment Guidelines

If the sensed glucose is ≥ 300 mg/dl, the participant will be instructed to check their blood glucose and to check the Omnipod for malfunction. This would include checking for insulin leaks, making sure Omnipod is securely adhered to skin, and check for error messages on the phone running the algorithm.

If capillary blood glucose value is over 300 mg/dl for more than 2 hours or is ≥ 400 mg/dl at any time, the participant will be instructed to check serum ketones using the Abbott Precision Xtra meter and to change out the Omnipod. If serum ketones are over 0.6 mM, the participant will be instructed to contact the study investigator to discuss proper management, including delivering a correction bolus. (see Appendix D 'Safety Instructions for Participants' for instructions provided to participants on when to contact study staff) In addition, the participant will be encouraged to drink sugar-free liquids. If serum ketones are above 1.5 mM at any time, the study will be stopped and insulin will be administered as directed by the on call investigator.

Cleaning and Disinfecting

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

Stopping Rules

Individual study stopping rules

The closed-loop study will be stopped and the participant's own pump will be resumed under the guidance of the on call study investigator if any of the following occur after the start of the study: the participant requests that the treatment be stopped, participant pregnancy, one episode of diabetic ketoacidosis 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, or one episode of severe hypoglycemia defined as a hypoglycemic event resulting in altered consciousness requiring another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Entire study stopping rules

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

The Model Predictive Control (MPC) Algorithm

Our MPC algorithm uses a glucoregulatory model to predict glucose outcomes over a predicted horizon and mathematically solve for the optimal insulin doses across the control horizon to bring the participant to target. The model is updated at each timestep by a Kalman filter, which uses the difference between CGM observations and model predictions to update the physiologic model states. In short, a model-predictive controller

uses a physiologic model to calculate how much insulin is required to bring someone to glucose target, and these predictions are adapted to the specific participant using a Kalman filter.

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

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

The Context Aware Detection and Dosing (CADD) Algorithm

We are integrating an automatic hyperglycemia pattern recognition algorithm called CADD that forecasts when extreme hyperglycemia (>250 mg/dL) may occur in the future and doses correction insulin in advance of these events. The algorithm extends recurrence quantification analysis (RQA)[10] which is an approach for learning system dynamics through pattern detection. It excels particularly in cases of highly variable, mixed-type and multivariate time series data, thereby making it ideally suited for identifying patterns in diabetes data. The CADD algorithm with automated correction dosing may safely prevent excessive hypoglycemia caused by behavioral and dosing patterns. This algorithm identifies patterns in glucose, insulin, carbohydrates, time of day, exercise, and other data

that may be related to extreme hyperglycemia (> 250 mg/dL). When the dosing function is activated, the algorithm will then automatically respond to these patterns and take action by delivering correction insulin based on a user's preset correction factor to a target glucose of 90 mg/dL in response to detected hyperglycemia patterns. Part of the CADD algorithm decision on dosing auto-correction insulin is based on scoring of the likelihood of hyperglycemia given a certain pattern is observed and the risk/benefit ratio of dosing correction insulin. These features have been tuned to maximize safety and efficacy of the algorithm.

Statistical Methods

Because this is a pilot trial, analyses will be descriptive. We will summarize the following:

- Participation
    - numbers of participants assessed for eligibility, exclusion reasons, number enrolled, numbers completing planned and unplanned study contacts
    - numbers and reasons for discontinuation
    - harms and unintended effects observed, including adverse events, serious adverse events, unanticipated problems, and unanticipated adverse device effects
    - dates of recruitment period and follow-up
- Participant baseline demographic and clinical characteristics, such as age, sex, and HbA1c
- Numbers of participants included in analysis & reasons for missing data, if any
- Clinical endpoints
    - Means and standard deviations of % time endpoints listed in the "Endpoints" section above for the training and intervention periods, overall and for the *pattern evaluation windows* as described
    - Changes (within subject) from the training to intervention period and variance estimates
    - Visualizations, such as scatter plots or paired difference plots, of the differences between the training and intervention periods for individual endpoints, as well as summary charts such as heat maps with the endpoints as rows and participants as columns showing the direction and degree of change (e.g. dark green for a larger change in a favorable direction, light red for a smaller change in an unfavorable direction)
    - Bayesian credible intervals using previous studies to inform priors

Confidentiality and Protection of Human Participants

RISKS and BENEFITS

Risks: Given pumps and sensors used within automated glucose control systems are imperfect, there is a risk for hyperglycemia and hypoglycemia, which is mitigated by use of CGM alarms, protocols for managing hypoglycemia and hyperglycemia. A study investigator will be on call at all times for monitoring of CADD algorithm insulin correction doses.

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

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

- Excessive pain or discomfort from either system deployment or during wear period (8 or greater on a 10-point Likert scale)
- Excessive bleeding, defined as requires removal of the device to stop bleeding
- Hematoma, defined as induration at the sensor insertion location (ecchymosis is a known consequence of needle skin puncture or pressure from sensor pod and will not be captured as an AE)
- Edema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Erythema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Local infection, defined as presence of pus at either sensor wire or sensor pod site
- Sensor or introducer needle fracture during insertion/wear/removal. For this reason, the study investigator will inspect each removed sensor for the possibility of breakage or fracture. Any evidence of sensor breakage will be recorded and reported to FDA and the sensor company.

Benefits: The participant will not directly benefit from being in this study.

COSTS

Participants will receive $700 for completion of all study visits with additional stipends for exercise and meal challenges. If participants withdraw early from the study, compensation will be given as follows: $50 for the start-up visit, $150 per 7 study days in the study, $50 for

the study completion visit. There is no compensation for the screening visit. Additional reimbursement will be available for participants who complete the exercise and meal challenges to help compensate for their time. The payment amount will be specified in the informed consent form.

Monitoring Entity

This investigation will be monitored by the principal investigators, Linda Lester, MD and Peter Jacobs, PhD. Drs. Jacobs and Lester have no commercial interest in any of the companies which manufacture any of the devices used in this study.

Data Collection

Participant privacy will be protected by using a three-digit identifying number to code study documents. Study staff will record data required by the protocol onto the Case Report Forms (CRF). Case report forms (CRF) will all be paper for this study. Investigators and research coordinator will verify that the procedures are conducted according to the approved protocol. All paper source documents will be kept in a locked cabinet for a minimum of five years. Original, completed CRF's will be kept with the PI in a designated repository.

Recording of Data

The CRFs will include:

1. Screening form
2. Study Start-up form
3. Investigator Review of Pump Settings form
4. iPancreas Training form
5. Companion Training form
6. Phone call week 1 form
7. Phone call week 2 form
8. Virtual visit for Pattern Detection
9. Study completion visit form
10. Adverse Event form
11. Serious Adverse Event form
12. 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. This data will also be stored in the OregonAPC repository according to IRB protocol 19858. During screening, participants will sign the consent form to store their study data in the data repository. The data to be collected includes: 1) glucose sensor data, 2) blood glucose data, 3) insulin data, 4) physical activity data, and 5) food and exercise data. There are no biological specimens collected during this study.

Monitoring Procedures

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and amendments and clarifications adopted by the 29th (Tokyo, 1975), 35th (Venice, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, South Africa, 1996), 52nd (Edinburgh, 2000), 53rd (Washington, 2002), 55th (Tokyo, 2004), 59th (Seoul, 2008), and 64th (Brazil, 2013) General Assemblies. The investigator will ensure that the study described in this protocol is conducted in full conformance with those principles, the protocol, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IEC requirements relative to clinical studies.

Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual participant. The investigator will also ensure thorough familiarity with the appropriate use and potential risks of use of the study device, as described in this protocol, prior to the initiation of the study.

Adverse Event Reporting

At all study visits, study staff will determine if any adverse events (AEs) have occurred. Disease related events that are chronic in nature and occur as part of the progression of the diabetes disease state (i.e. diagnoses of retinopathy, nephropathy, and neuropathy) will not be captured as adverse events in this study. Hypo- and hyperglycemia will not be considered AEs unless participant has positive ketones or displays symptoms of

hypoglycemia such as: loss of consciousness, slurred speech, hospitalization or EMS services called.

One of the investigators will write up a description of the adverse event/unanticipated problem. All reportable new information (RNI) will be reported to the IRB within five calendar days after the PI learns of the event. RNI is any information that might meet the regulatory definition of an unanticipated problem involving risks to subjects or others or serious or continuing noncompliance that might impact the criteria for IRB approval. The report will be submitted to the IRB by the principal investigator or study coordinator. A summary of all UP's and adverse events, including those that do not meet the requirement for RNI, will be submitted with the continuing review. All AEs will be monitored until adequately resolved or stable. Information regarding AEs that occur during the study will be entered into appropriate CRFs. Such information will include, at a minimum:

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

Definition of Adverse Event

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

Serious Adverse Events

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

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

Exceptions to the SAE definition will include the following:

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

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

Severity of Adverse Events

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

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

Relationship of Adverse Events to Study or Study Device

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

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

Unanticipated Problems

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

Unanticipated Adverse Device Effect (UADE)

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

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

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

Medical Device Reporting (MDR)

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

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

Confidentiality Procedures

Staff will maintain the confidentiality and security of data collected in this study. Paper files will be stored in locked filing cabinets in restricted access offices at site. After the study, source documents will be maintained at the participating clinical center (or offsite record storage facilities) 2 years after a marketing application is approved for our group's decision support device or discontinuance of pursuit of marketing approval. Electronic data will be stored on encrypted: computers, laptops and study smartphones. Electronic data is stored in OneDrive and on a secure HIPAA compliant system run by Prelude Dynamics. Sites will be

invited to upload data using a password protected folder in Microsoft OneDrive. iPancreas data will be housed in a custom cloud database on an OHSU secure server called the GRM (see below). Access to data/specimens is restricted to study personnel. Access to data requires ID/password authentication.

iPancreas Guidance Remote Monitoring (GRM) Cloud Server

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

Protocol Appendix A: Physical Activity Readiness Questionnaire

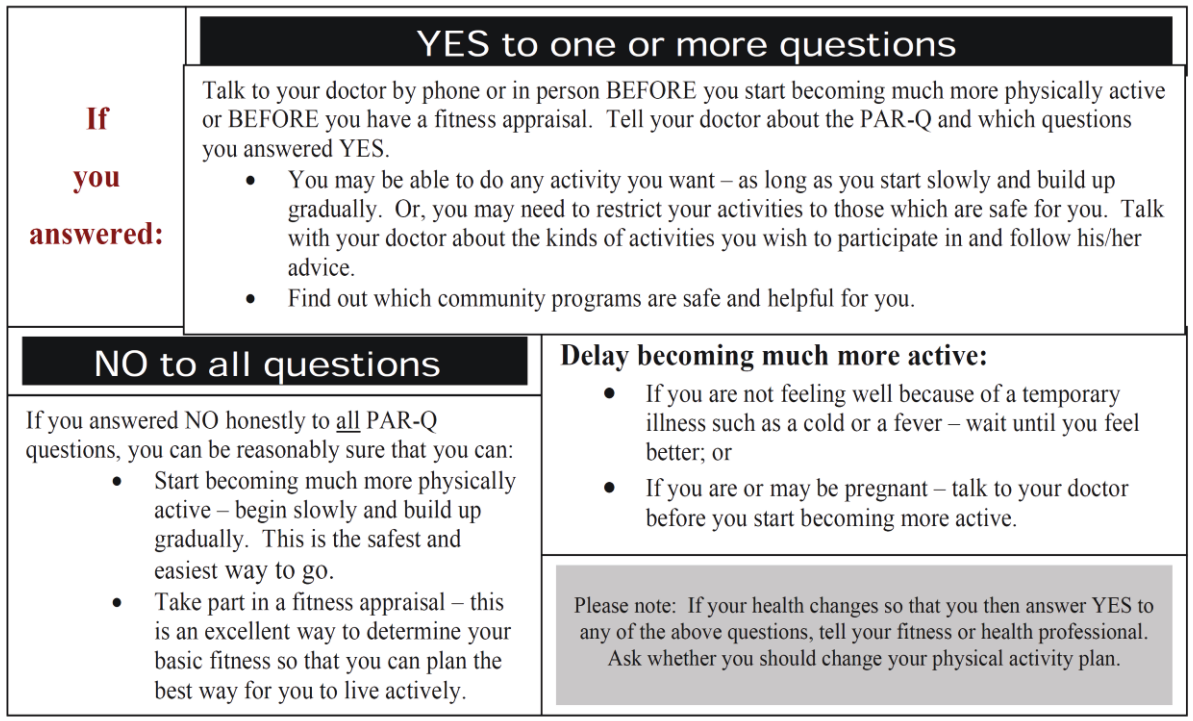
Physical Activity Readiness Questionnaire (PAR-Q) and You

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly:

YES	NO		
☐	☐	1.	Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
☐	☐	2.	Do you feel pain in your chest when you do physical activity?
☐	☐	3.	In the past month, have you had chest pain when you were not doing physical activity?
☐	☐	4.	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5.	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	6.	Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
☐	☐	7.	Do you know of any other reason why you should not do physical activity?



If you answered:	YES to one or more questions
	Talk to your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES. • You may be able to do any activity you want – as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice. • Find out which community programs are safe and helpful for you.

NO to all questions	Delay becoming much more active:
If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can: • Start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go. • Take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.	• If you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or • If you are or may be pregnant – talk to your doctor before you start becoming more active. Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed use of the PAR-Q: Reprinted from ACSM's Health/Fitness Facility Standards and Guidelines, 1997 by American College of Sports Medicine

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 episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself?

Never (A)
Once or twice (R)
Every other month (R)
Once a month (R)
More than once a month (R)

4. In the past year, how often have you had episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose?

Never (A)
1 time (R)
2 times (R)
3 times (R)
4 times (R)
5 times (R)
6 times (R)
7 times (R)
8 times (R)
9 times (R)
10 times (R)
11 times (R)
12 or more times (R)

5. How often in the last month have you had readings < 70 mg/dl with symptoms?

Never
1 to 3 times
1 time/week
2 to 3 times/week
4 to 5 times/week
Almost daily

6. How often in the last month have you had readings < 70 mgdl, without symptoms? R: 5<6, A: 6<5;

Never
1 to 3 times

1 time/week
2 to 3 times/week
4 to 5 times/week
Almost daily

7. How low does your blood sugar need to go before you feel symptoms?

60-69 mg/dl (A)
50-59 mg/dl (A)
40-49 mg/dl (R)
< 40 mg/dl (R)

8. To what extent can you tell by your symptoms that your blood sugar is low?

Never (R)
Rarely (R)
Sometimes (R)
Often (A)
Always (A)

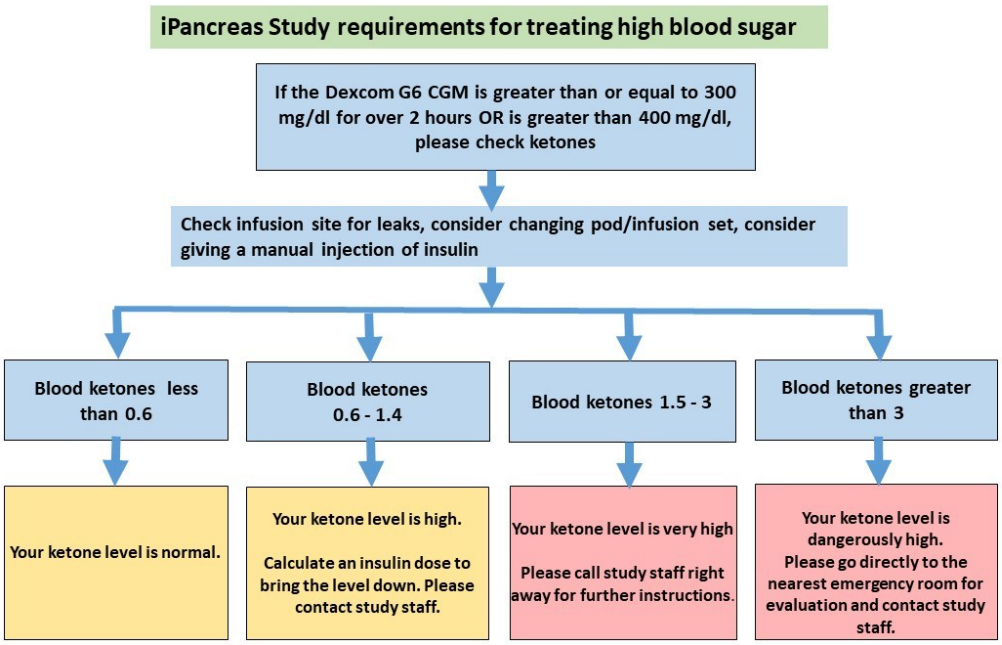
Protocol Appendix C: Aerobic Exercise Video Outline

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

		Jog in Place Hands Raised Side Steps (active recovery) Right Leg Lunge Alternate Forward Back Left Leg Lunge Alternate Forward Back Jog in Place Hands Raised Side Steps (active recovery) Squat to Upper Cut (right foot forward) Right Jab Bounce (right foot forward) Side Steps (active recovery) Squat to Upper Cut (left foot forward) Left Jab Bounce (left foot forward) Side Steps (active recovery) Horse Stance Overhead Reach Side Bend/ Standing Alternating Side Bend Side Jump with Squat Alternating Left Right Right Lateral lunge with Right Knee Drive Pull Up Left Lateral Lunge with Left Knee Drive Pull Up Side steps (active recovery) Horse Stance Overhead Reach Side Bend/ Standing Alternating Side Bend Side Jump with Squat Alternating Left Right Right Lateral lunge with Right Knee Drive Pull Up Left Lateral Lunge with Left Knee Drive Pull Up Side steps (active recovery)

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

Instruction cards:

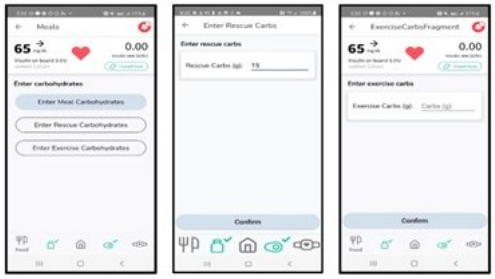


Consume **pre-exercise carbohydrates** per table before ALL exercise completed while on study! (all four weeks & all exercise!)

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

IMPORTANT INFORMATION FOR **ALL** EXERCISE DURING STUDY!!
(study video exercise **AND** all other exercise)

- Check a finger-stick glucose (CBG) before AND after all exercise!
- Remember to **wear the smart watch** for all exercise to reduce risk of hypoglycemia!
- You must **enter ALL pre-exercise carbohydrates** into the iPancreas app
  - If you do not enter pre-exercise carbohydrates into the app, you are at ***increased risk for hypoglycemia with exercise*** as iPancreas may dose auto-meal insulin due the rise in glucose from pre-exercise carbohydrate
  - Remember to use the "Fork and Knife" icon to enter pre-exercise or rescue carbs:



- If your glucose is between **100-145 mg/dL before exercise**, follow instructions on the flipside of this card for carb intake. Then, for safety **RECHECK** a fingerstick glucose (CBG) **15-25 minutes later** during your exercise.

iPancreas Study instructions for when to stop your study for safety

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

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

<insert site study team contact information>

Protocol Appendix E: INSPIRE Questionnaire for Adults with Type 1 Diabetes (Baseline)

We would like ask about your thoughts and feelings about using an automated insulin dosing system (**abbreviated AID**), sometimes called a closed loop system, artificial pancreas or bionic pancreas. We would like you to think about living with diabetes and the things that may be better or worse by using **AID**. **For each of the questions below, please tick (check) the box that best fits your answer. Please answer every question.**

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
1	I will be more hopeful about my future with use of automated insulin dosing (AID).	☐	☐	☐	☐	☐	☐
2	I will worry less about diabetes with AID.	☐	☐	☐	☐	☐	☐
3	AID will reduce my family's concerns about my diabetes.	☐	☐	☐	☐	☐	☐
4	AID will make it easier for me do the things that I want to do without diabetes getting in the way.	☐	☐	☐	☐	☐	☐
5	AID will decrease how often I have low glucose levels.	☐	☐	☐	☐	☐	☐
6	AID will decrease how often I have high glucose levels.	☐	☐	☐	☐	☐	☐

7	AID will help me stay in my target range more often.	☐	☐	☐	☐	☐	☐
8	AID will improve my A1c to target level.	☐	☐	☐	☐	☐	☐
9	AID will make it easy to eat when I want.	☐	☐	☐	☐	☐	☐
10	AID will make it easy to exercise when I want.	☐	☐	☐	☐	☐	☐
		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
11	AID will make managing diabetes easy when I am at work or school.	☐	☐	☐	☐	☐	☐
12	AID will make managing diabetes easy when it comes to my social life/being with friends.	☐	☐	☐	☐	☐	☐
13	AID will help me manage sick days.	☐	☐	☐	☐	☐	☐
14	AID will help me sleep better.	☐	☐	☐	☐	☐	☐
15	I believe that I will have fewer lows during the night with AID.	☐	☐	☐	☐	☐	☐
16	AID will improve my overall quality of life.	☐	☐	☐	☐	☐	☐
17	AID will improve my family's overall quality of life.	☐	☐	☐	☐	☐	☐
		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A

18	AID will make managing diabetes easy when driving (for those who drive) or when traveling.	☐	☐	☐	☐	☐	☐
19	AID will help me manage diabetes when it comes to my sex life.	☐	☐	☐	☐	☐	☐
20	AID will help me manage diabetes when I choose to drink alcohol.	☐	☐	☐	☐	☐	☐
21	AID will help me if I am pregnant.	☐	☐	☐	☐	☐	☐
22	AID will reduce my risk of long term complications.	☐	☐	☐	☐	☐	☐

Thank you for taking part, your answers are very important to us

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