PROTOCOL TITLE: Assessment of a novel sensing catheter during automated insulin delivery in patients with Type 1 Diabetes

STUDY SITE:	Oregon Health Science University 3181 SW Sam Jackson Park Rd Portland, OR 97639
FUNDING:	National Institutes of Health
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Background:

Closed-loop systems are an emerging technology that automate hormone delivery. They are quickly paving the way to revolutionize the treatment of type 1 diabetes. Several categories have emerged: dual-hormone (insulin and glucagon) closed-loop systems and closed-loop systems with insulin only. Already, the benefit of improved glycemic control compared to current open-loop pump therapy has been demonstrated in several trials. Hovorka et al. recently showed that for people with T1D, glucose control could be improved when using a single-hormonal AP system for 12 weeks under free living conditions compared with sensor-augmented pump (SAP) therapy in a randomized multicenter cross-over trial [17]. Participants were in euglycemia for 11% more time using the AP system as compared to SAP therapy. Kropff et al. also recently published results from a long-term single-hormone study showing that when patients with T1D used an AP during evening hours and while sleeping, using SAP during the day, the time spent in euglycemia was increased compared with participants who used SAP 24-hours per day [18]. HbA1c dropped more significantly when using the AP (-0·3%) compared with SAP (-0·2%), though the improvement was modest.

The study described within this protocol is designed to test the efficacy of a single hormone closed-loop algorithm for managing blood glucose in type 1 diabetes using insulin only. In addition, this study will evaluate the feasiblity of measuring glucose continuously in the immediate vicinity of subcutaneous insulin delivery. We hypothesize that with the use of the Pacific Diabetes Technologies continuous glucose monitoring and insulin infusion system, there will be no significant difference, in terms of sensing accuracy, between devices delivering insulin lis-pro and devices delivering saline control.

Primary Objectives:

- To assess the impact of lispro on glucose sensing as compared to a saline control.

Secondary Objectives:

- To assess the glucose control achieved in adults with type 1 diabetes with the use of the OHSU closed-loop system.
- To assess the tolerability of the PDT glucose sensor.

Study Hypothesis:
We propose that the accuracy of the PDT glucose sensor is not impacted by the delivery of lispro insulin as compared to a saline placebo.

Endpoints
Primary Endpoints
- Sensor accuracy as determined by mean absolute difference (MAD) for reference YSI venous blood glucose values ≤75 mg/dL and mean absolute relatives difference for reference YSI venous blood glucose values >75 mg/dL

Secondary Endpoints (duration: entire study):
- Percent of time with sensed glucose between 70 – 180 mg/dl (based on Dexcom G5 CGM)
- Percent of time with sensed glucose <70 mg/dL (based on Dexcom G5 CGM)
- Percent of time with sensed glucose <54 mg/dl (based on Dexcom G5 CGM)
- Percent of time with sensed glucose >250 mg/dL (based on Dexcom G5 CGM)
- Mean sensed glucose (based on Dexcom G5 CGM)
- Number of carbohydrate treatments (defined as 15 or 20 grams of carbohydrate)
- Total amount of insulin delivered (in units/kg)

- Mean score on visual analog scale at 15 and 120 minutes after insertion, and at end of study
- Mean score on Draize scale at end of study

Study Type
This is a single center, one treatment trial designed to compare the sensor accuracy of the PDT sensing catheter when utilized to deliver lispro insulin as compared to a saline control.

Study Population
Study population will be adults with type 1 diabetes, ages 21 – 65 years of age. Younger subjects are excluded as it is appropriate to assess safety first in the adult population. 10 subjects will be recruited to participate in studies.

Power Analysis
Since data have not previously been obtained in humans (variance is unknown), this study is exploratory and not powered.

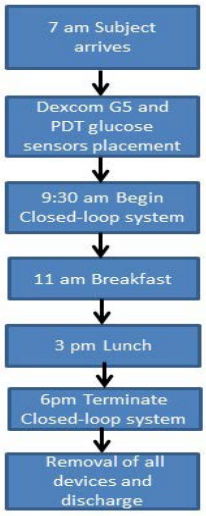
Protocol Summary:
Subjects will undergo one 12 hour inpatient study. During this intervention visit, subjects will wear two t:slim insulin pumps to deliver insulin or saline through two investigational PDT glucose sensing cannulas, and a Dexcom G5 CGM to measure glucose. The subject will come to

the research center at approximately 7am for the inpatient visit. The Dexcom G5 sensor and PDT glucose sensing cannulas will be placed after arrival (see Appendix for a complete description of the PDT device). An 18-22 gauge IV catheter will be placed for blood sampling every 15 minutes after sensor warm-up is complete for measuring blood glucose concentration. After a 2 hour warm-up period for the G5 sensor, glucose will be controlled using the FMPD single hormone mode. The single hormone mode of the controller determines insulin delivery rates based on proportional and derivative errorthrough one t:slim insulin pump. The second t:slim insulin pump will deliver normal saline at the same delivery rates as the insulin. Subjects will eat breakfast and lunch at approximately 11 am and 3 pm respectively. Subjects will have the ability to complete light exercise on a treadmill. The closed loop system will be stopped at approximately 6pm with removal of all devices. See **Figure 1** for a diagram of the study flow.

During the study, the subject will wear one subcutaneous Dexcom™ G5 continuous glucose monitoring (CGM) system. The CGM system will provide sensed glucose data every 5 minutes. The accuracy of the sensed data will be obtained by reference measurements of two YSI venous blood glucose values to calibrate the sensor at the beginning of the closed loop study. Sensed glucose data will be wirelessly transmitted via Bluetooth Low Energy (BTLE) from the Dexcom G5 transmitter to the Nexus 5 master controller every five minutes. The controller is a Google Nexus 5 phone. The smart phone will wirelessly communicate via BTLE to two Tandem t:slim insulin pumps, one for automated insulin delivery and one of automated saline delivery.

A physician or nurse practitioner will be present for study start-up, will be on campus for exercise and will be immediately available on call at all other times. A research nurse will be available at all times. The study investigators retain the authority to modify any aspects of the protocol at his/her discretion if he/she believes the subject's safety is a concern. A study coordinator will be able to access the cloud for monitoring purposes. For safety purposes, all system alerts that are not serviced by the subject will be pushed to the study coordinator/study investigator according to Appendix M.

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 subjects 21 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% at screening.
5. Body Mass Index ≥ 22.
6. Total daily insulin requirement is less than 200 units/day.
7. Willingness to follow all study procedures, including attending all clinic visits.
8. Willingness to sign informed consent and HIPAA documents.

Exclusion Criteria:

1. Female of childbearing potential who is pregnant or intending to become pregnant or breast-feeding, or is not using adequate contraceptive methods. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence.
2. Any cardiovascular disease, defined as a clinically significant EKG abnormality at the time of screening or any history of: stroke, heart failure, myocardial infarction, angina pectoris, or coronary arterial bypass graft or angioplasty. Diagnosis of 2nd or 3rd degree heart block or any non-physiological arrhythmia judged by the investigator to be exclusionary.
3. Renal insufficiency (GFR < 60 ml/min, using the MDRD equation as reported by the OHSU laboratory).
4. Liver failure, cirrhosis, or any other liver disease that compromises liver function as determined by the investigator.
5. Hematocrit of less than 36% for men, less than 32% for women.
6. History of severe hypoglycemia during the past 12 months prior to screening visit or hypoglycemia unawareness as judged by the investigator.
7. History of Diabetic 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 lispro insulin.
19. Allergy to acrylate-based skin adhesives.
20. Need for uninterrupted treatment of acetaminophen.
21. Current administration of oral or parenteral corticosteroids.
22. 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).
23. Beta blockers or non-dihydropyridine calcium channel blockers.
24. Current use of any medication intended to lower glucose other than insulin (ex. use of liraglutide).
25. Any clinically significant disease or disorder which in the opinion of the Investigator may jeopardize the subject's safety or compliance with the protocol.

Subject Recruiting:
Subjects 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, electronic newletter or from the OHSU Subject Recruitment website. Handouts will also be made available to faculty at Providence 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 subjects. Subjects will also be recruited from a list of subjects who participated in past OHSU studies who have agreed to be contacted regarding future studies involving Drs. Castle or El Youssef, from the OHSU diabetes research registry and/or www.clinicaltrials.gov. Non-english speaking subjects 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 25 subjects may be screened in this study. Goal enrollment is 10 subjects.

Visit Procedures
Screening (Visit 1)
Screening will take place within 12 weeks prior to the inpatient visit. All screening visits will take place at OHSU's Oregon Clinical Translational Research Institute (OCTRI) outpatient clinic or at the Harold Schnitzer Diabetes Health Center. The subject will be sent the consent form a week 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 subject ample time to ask questions and consider participation, and ensure that subject voices understanding of the informed consent and study requirements. To minimize the possibility of coercion and to ensure that subject is signing the appropriate version of consent, an informed consent checklist will be used by study staff. After the subject has signed the consent, a copy of the consent/authorization form will be given to the subject. The original will be kept for the source document.

A capilllary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter and recorded after consenting. The Contour Next glucose meter will undergo quality control testing every 30 days with two different glucose levels, one high and low and both values must fall within the accepted range for a meter to be used. Study personnel will review medical

history, and medications. Height, weight, pulse, and blood pressure will be obtained. A study investigator will perform a physical examination, excluding breast and pelvic exams. Females of child-bearing potential will take a urine pregnancy test, which must be negative to participate. A venous blood sample will be taken for the following tests: hemoglobin A1C, complete blood count, complete metabolic set (including creatinine, liver set, and electrolytes). A study investigator will assess inclusion/exclusion criteria and review the subject's medical record for clarification as needed. A three-digit subject ID number will be assigned to the subject. This visit will take approximately 1.5 hours.

12 hour Treatment Visit

The visit will be conducted in the OCTRI inpatient research unit. A code cart is on site at all locations and a code team is available by page at all times. After arrival at the 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.

The subject will be asked to check his/her CBG before driving to the clinic and to bring a snack in the car in case hypoglycemia does occur (in which case, the subject must park and treat the hypoglycemia). The subject will arrive at the research center at approximately 7am.

When they arrive, a capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter. Subjects 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. If carbohydrates or a correction insulin dose is given, blood glucose will be monitored according to the study investigator's orders until the glucose is acceptable to the investigator, and is within the range of 70-300 mg/dl. Serum ketones will also be checked. If the blood ketone value is 0.6 mM or less, the procedure will be started. If serum ketones are ≥ 0. 6 mM, the study will be halted and insulin therapy will be guided by the onsite investigator. Ketones will be measured with the Precision Xtra ketone meter. The Precision Xtra meter will undergo quality control testing every 30 days with two different ketone levels, one high and low and both values must fall within the accepted range for a meter to be used.

Subjects will have a Dexcom G5 sensor inserted. The wire glucose sensor is sterile and commercially available from Dexcom^{TM} and will be used for single use only as directed by the manufacturer. The sensor will be inserted into the subcutaneous tissue of the abdomen or flank after appropriate preparation of the abdominal skin as per the manufacturer's directions. Subjects will be instructed to discontinue the use of acetaminophen for all periods when wearing the Dexcom CGM system.

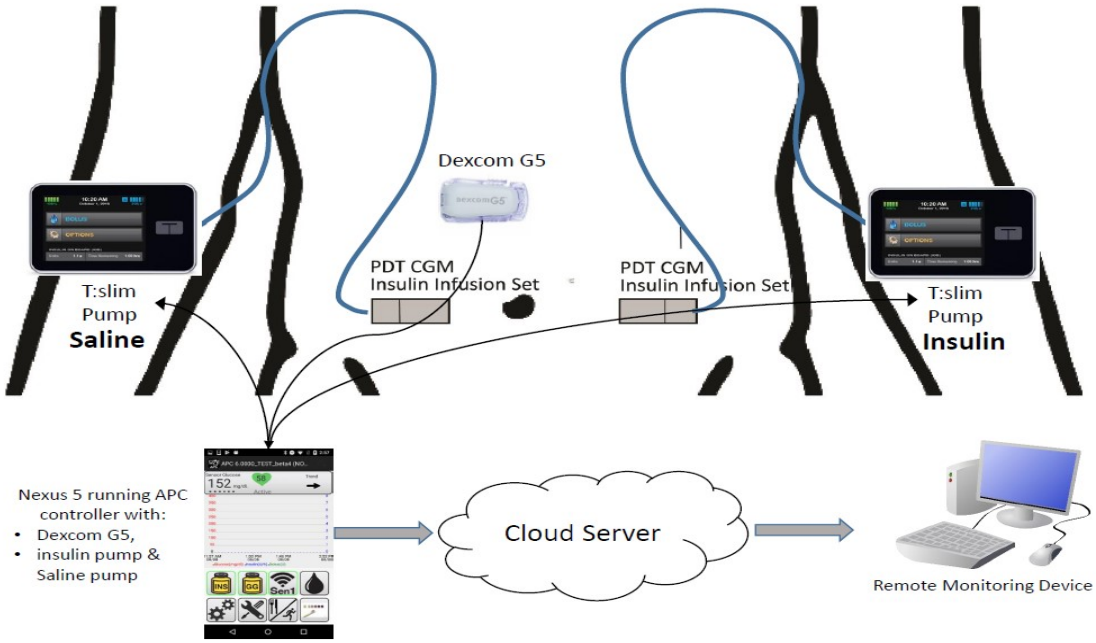
After preparation of the skin with isopropyl alcohol followed by ChloraPrep One-Step (2% chlorhexidine gluconate and 70% isopropyl alcohol), the two investigational PDT glucose sensing cannulas will be inserted subcutaneously in the abdomen, each at least 5 cm from the subject's insulin cannula and at least 5 cm from one another. For subjects allergic to ChloraPrep, isopropyl alcohol will be used. The study investigator (PI or co-investigator, i.e. physician or nurse practitioner who has been trained in internal medicine) will manually insert each cannula into the subcutaneous tissue or will insert the cannula with the aid of a spring-operated insertion device. To ensure proper cannula insertion, a written manual and direct in-person training

(including troubleshooting) will be provided by Pacific Diabetes Technologies The rigid stainless steel cannula will extend 12 mm into the tissue at a 35-45 degree angle (depth beneath skin surface, approximately 7-8 mm). After insertion, a small amount of saline (0.5 ml) will be delivered through each cannula to verify patency. In between usages, the insertion device will be thoroughly cleaned with SaniCloth AF-3 wipes.

The cannula is attached to a sensor housing unit which is affixed to the skin with acrylate-based adhesive tape. An Electronic Module which includes a telemetry unit is connected to the sensor housing. In between use on study subjects, the reusable telemetry unit will be thoroughly cleaned with SaniCloth AF-3 disinfecting wipes. After insertion, the subject will be instructed to avoid vigorous activity until the sensing cannula is removed at the end of the study. The subject will also be asked to keep the device dry. Sensor data (electrical current proportional to glucose level) will be stored within the body-worn electronic module at least once every minute. Sensor data from these investigational sensors will not be used to control the FMPD single hormone algorithm or insulin dosing at any time. The subject will not be able to view the sensor output. A visual analog scale and questionnaire will be given to assess tolerability and pain of the glucose sensing cannulas at 15 and 120 minutes after insertion and just before the glucose sensing cannulas are removed at the end of the study (see Appendix D).

One t:slim infusion pump (Tandem® Diabetes Care) will be filled with lispro insulin and another will be filled with normal saline. Each pump will be attached to one of the PDT sensing cannulas. See **Figure 2** below for a diagram of the system design. Subjects will disconnect his/her own pump and remove his/her own insulin infusion set once insulin delivery has started via the t:slim pump. Note: The Zephyr Biopatch will not be used in this study to push heart rate data into the APC system to enable exercise detection.

Figure 2: Closed-loop System Design



An 18-22 gauge IV catheter will be placed for measuring blood glucose concentration. When closed loop study is started, a small amount of blood will be collected every 15 minutes until discharge from the unit at 6pm. A heating pad will be placed on the subject's arm to facilitate blood draws and to arterialize venous blood, which allows for frequent measurement of blood glucose and to prevent spurious decline of venous blood glucose from glucose uptake by muscle and fat during slow capillary flow. These arterialized venous samples will be analyzed using a Yellow Springs Instrument (YSI) 2300D Stat Plus Analyzer to obtain a glucose level. In the event the YSI is not available, the sample will be analyzed using a Contour Next blood glucose meter. Normal saline will be infused at a rate of ~25 ml/hr to keep the IV catheter patent. It is possible that the IV catheter will not remain patent, in which case another will be placed. In a blood-sparing technique, venous blood will be withdrawn from the IV catheter using a double stop-cock method. One side of the stop-cock is used to pull ~ 5 mL of saline-blood admixture. The other side of the stop-cock is used to pull approximately 0.5 ml for collection with the saline-blood admixture re-infused after collection. The double stop-cock method is a fully closed system apart from the very brief interval at the time of a blood sample where a new sterile syringe is connected to collect the next sample. This procedure is performed by a research nurse. There will be ~18-20 ml of blood collected per study with a maximum blood draw volume of 30 mL.

After the Dexcom G5 warm-up period is completed, the research staff will initialize the system and begin the closed-loop study. The second t:slim pump will deliver normal saline at the same rate as the insulin pump. The study investigator will then depart but remain on call.

The algorithm will push data up to a cloud server that can be monitored remotely every 5 minutes. A study coordinator will be present once the closed loop study begins to run the YSI analyzer with the ability to monitor the APC remotely via a cloud system on the web in the event of any issues. This will allow study staff to give immediate assistance with any difficulties using the APC controller. The APC will generate alerts on the smartphone according to Appendix M. The subjects will all be trained as to the action required by each alert. Each alert has a specific condition to be met for it to be considered serviced (i. e. enter treatment with oral carbohydrates). The refractory period is also specific to each alert with shorter refractory periods for alerts that concern subject safety. If the subject does not appropriately respond to the alert in the alotted timeframe, the alert will push to the study coordinator and the on-call investigator according to Appendix M. At that time, the coordinator will pull up the web-based monitoring system. For safety, the Nexus 5 phone will track the subject's location and push GPS coordinates to the cloud server approximately every 10 minutes. Cloud coordinates will be pushed with a known, fixed offset to allow for scrambling.

In order to push alerts to study coordinators and study investigators, the cloud server used for remote monitoring will have a drop down menu for study staff to sign in and out for the duration of their monitoring shift. Each study coordinator and investigator listed in the menu will have a cell phone number on file that can receive texts with pushed alerts.

During all studies, sensed glucose data will be wirelessly transmitted via BTLE from the Dexcom G5 transmitter to the FMPD algorithm every five minutes. The FMPD will calculate insulin doses and will run on a Google Nexus 5 phone. The smart phone will wirelessly

communicate via BTLE to a t:slim insulin pump for automated insulin delivery. For subject safety, if BTLE communication between the phone and insulin pump is disrupted for more than 20 minutes, the system will revert to basal insulin delivery for a pre-set basal profile(s) inputted for the subject at the study start until Bluetooth connectivity is restored. When communication with the pump is restored, the system will automatically resume, updating the IOB accordingly.

If at any time the study staff determines that a sensor can no longer be used, a new sensor will be inserted, which will be calibrated after two hours and then used to run the closed-loop system. The sensor will also be recalibrated per the manufacturer's directions if the sensor becomes inaccurate. An inaccurate sensor is defined as a sensor with a value difference of 35% or more compared to a CBG. Additional calibrations may be ordered at the discretion of the investigator on call. Trained study staff will be present to assist the subject with entering blood glucose measurements for calibration into the APC controller.

In order to ensure safety and to assess the PDT sensor accuracy, the subject will have his/her blood glucose measured every 15 minutes during the closed loop study. If the subject'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 and glucose tablets will be available for rescue treatment. The study investigator retains the authority to check blood glucose at more frequent time points at his/her discretion.

For subject safety, if a sensor value is not available or communication with the insulin pump is lost for more than 20 minutes, the insulin pump will begin insulin delivery according to a pre-set basal profile(s) inputted for the subject at study start. When this occurs for a lost sensor, the APC system will also activate a predictive low glucose suspend feature. The predictive suspend feature will activate within the range of 70-140 mg/dl if sensor glucose is predicted to fall below 90 mg/dl within thirty minutes. If this occurs on a consecutive turn, the APC system will activate a minimum 30 minute suspension and a maximum of 120 minutes within any 150 minute window. After this minimum 30 minutes has lapsed, insulin delivery will resume if sensor glucose is above 70 mg/dl and predicted to rise above 120 mg/dl within the next 30 minutes. As long as sensor glucose is above 140 mg/dl, the predictive suspend feature will not activate. Prediction of sensor glucose is based on linear regression of the prior ten minutes of sensor glucose data. When communication with the sensor is restored, the system will automatically resume, updating the IOB accordingly.

Subjects will eat breakfast and lunch at 11am and 3pm respectively. Meals will be announced to the controller. For each meal, food items will be self-selected from the hospital menu with subjects asked to pick meals of 80-150 grams of carbohydrates. The number of grams of carbohydrates will be entered in the controller. Trained study staff will be present to assist subjects with entering of all meal carbohydrate amounts into the APC controller. The APC will automatically calculate and deliver 80% (nominal) of his/her typical pre-meal insulin dose based on their insulin to carbohydrate ratio through the tslim insulin pump.

The Fading Memory Proportional Derivative (FMPD) algorithm will determine the insulin delivery rates for the closed-loop studies. The FMPD algorithm determines insulin delivery rates based on proportional error, defined as the difference between the current glucose level and the target level, and the derivative error, defined as the rate of change of the glucose. Each of these

errors is calculated over a time interval. The "fading memory" designation refers to weighting recent errors more heavily than remote errors. This weighting provides an adaptive component to the algorithm. In simple terms, the insulin rate is increased for high or rising glucose levels. Gain factors determine the degree to which proportional or derivative errors lead to changes in insulin delivery rates. Positive proportional errors (glucose level above target) and positive derivative errors (rising glucose level) call for an increase in the insulin delivery rate. With regards to the glucose target, % of premeal insulin bolus: these are current nominal values that may be adjusted within the FDA approved minimum and maximum range for each adjustable parameter.

In case of a system error that cannot be corrected immediately, the subject will be able to to pause the APC system. Pausing will allow the t:slim pump filled with insulin to begin basal insulin delivery for a pre-set basal profile(s) inputted for the subject at the study start. If there is a pending meal bolus in the insulin back log, the pause mode will be delayed to allow the bolus to finish delivering. Subjects will be able to give meal boluses and corrections through the t:slim pump delivering insulin while in pause mode. When the error is resolved, the participant can exit pause mode and the closed loop system can be resumed. If the subject pauses the system, 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.

Subjects will have the ability to perform light exercise, but exercise will not be required. Following the 2 hour warm-up period and start of the APC system at 9:30 AM, subjects may exercise for 20 minutes per each 3 hour period. The study coordinator or a nurse will be present with the subject throughout the study (after starting the APC system) and will provide assistance (e.g. operating the treadmill) if necessary. The subject's blood glucose will be checked prior to exercise, and exercise will only be permitted if pre-exercise blood glucose > 100 mg/dL.

At approximately 6pm, the closed-loop study will be terminated and the subject's own insulin pump will be restarted. The IV catheter will be removed. The study investigator will consult with the subject regarding appropriate insulin dosing for the remainder of the day. The HR monitor and Dexcom G5 sensor will be removed. The glucose sensing cannula units will be slowly removed and the sensor data uploaded. Only trained personnel will be allowed to remove the devices. The personnel who will be allowed to remove the devices will include the investigators (PI, Co-I) and the clinical coordinator. The infusion sites and sensor site will be inspected for signs of erythema/edema and assessed using the Draize Scale (see Appendix F). In addition, the Dexcom G5 sensor and glucose sensing cannulas will be inspected for the possibility of breakage or fracture. If there is any evidence of sensor breakage, it will be recorded. A de-identified photograph will be taken of the sensor insertion areas and the devices. If an area of inflammation of 1 cm or greater exists around the point of insertion, the subject will return 1-3 days later for a follow-up visit.

Due to the fact that the subject's usual diabetes routine has been interrupted, it is recognized that this final period of time represents an important period for subject safety. As the subject departs from the study center, it will be important for the subject to monitor blood glucose frequently and to be able to call the study physician if questions arise. More specifically, in order to be discharged, subject's blood glucose must be greater than 90 and less than 300 and the subject

must be feeling well without nausea or other symptoms. If glucose is less than 90, he will be given 15 grams of rapidly acting oral carbohydrate. CBG will be repeated every 15 minutes (with repeat oral carbohydrate treatment if CBG < 90) until CBG exceeds 90, at which time the subject will be discharged.

If blood glucose exceeds 300, the study physician will determine a correction dose of insulin after evaluating the current insulin-on-board value. In addition, blood ketones will be measured. If the ketone value is over 3 mM, the subject will be sent to the OHSU Emergency Department. If the ketone value is between 0.6 and 3.0, the study physician will administer a correction dose, provide oral hydration, and keep measuring blood ketones hourly. The subject will be discharged only when the ketone value is less than 0.6 mM.

A research staff member will telephone the subject the next day to check on health status.

If a study visit is stopped prematurely, such as due to technical problems, the subject 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

- **BG < 70 mg/dl**
  - Give 15 grams of oral carbohydrate.
  - Repeat treatment every 15 minutes as needed to raise blood glucose ≥70 mg/dl.
- **BG < 50 mg/dl**
  - Verify that insulin pump is turned off
  - Give 100 mL of 10% dextrose through the IV cannula
  - Repeat BG measurement after dextrose infusion complete and repeat process until BG > 70 mg/dl.
  - If no IV access available, give 30 grams of oral carbohydrate, further treatment as per study investigator.
- **Presence of STUPOR, LOSS OF CONSCIOUSNESS, or SEIZURE**
  - Give 1 mg glucagon SC or if IV cannula is patent, 100-300 mL of 10% dextrose STAT. Glucagon will be administered by needle and syringe that are provided with GlucaGen emergency kits.
  - Verify that insulin is turned off.
  - Further management per study investigator.

Hyperglycemia Treatment Guidelines

If the sensed glucose is ≥ 300 mg/dl for longer than 30 minutes or reaches >400 mg/dL, the subject will be instructed to check their blood glucose and study staff will examine the insulin infusion site and will check the subject's serum ketones every hour while sensed glucose is ≥ 300 mg/dl. If serum ketones are over 0.6 mM, the on call study investigator will be alerted to discuss proper management, including changing insulin infusion set and delivering a correction bolus. In addition, the subject 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 subjects. The smart phone, Dexcom G5 transmitter, the glucose sensing cannula insertion devices and telemetry units 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 SANI-CLOTH AF3 Germicidal 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 subject information.

Stopping Rules
The subject may withdraw at will at any time or at the discretion of the Investigator.

A subject must be withdrawn if any of the following applies:

1. Hypoglycemia: After initial stabilization, one episode of severe hypoglycemia (requiring the assistance of another person) or one episode of venous blood glucose < 50 mg/dl.
2. Hyperglycemia: After initial stabilization, venous blood glucose > 400 mg/dl for over 30 minutes.
3. Ketoacidosis: Venous blood glucose > 250 mg/dl accompanied by serum ketone level > 1.5 mM.
4. Protocol deviation having influence on efficacy or safety data as judged by the Investigator.
5. Substantial and repeated non-compliance with trial procedures
6. Pregnancy
7. Intention of becoming pregnant

The study may be stopped if the glucose sensing cannulas have repeated inability to acquire sensor data, such as telemetry issues.

Data Analysis
Note that it was not possible to carry out a formal sample size power analysis for this feasibility study since data have not previously been obtained in humans (variance is unknown). However, we expect the sample size proposed here (10) is adequate to detect a difference between the insulin formulation and saline, based on our earlier studies in swine. The data obtained in this study will be used to calculate variance so that formal power analyses can be used for subsequent, more formal, studies.

This study design will allow a comparison of sensing accuracy after insulin vs after saline administration through the sensing cannula. For example, this study design will allow assessment of the magnitude of artifact, if any, from the insulin preservatives, as was noted in pig studies with the non-redox mediator sensor. It will also assess the potential for underestimation of glucose due to uptake into fat as a result of local insulin delivery [19], [20].

For each subject, we plan to acquire data from the PDT sensor which is represented by an

electrical current in nanoamperes (nA). We will match these sensor values with YSI values which are in units of mg/dL. We will then do a linear least squares regression between the YSI glucose and the sensor current to create an equation that estimates the actual glucose from the sensor current. This equation will have the form of y=mx + b, whereby y is the estimated glucose (mg/dL), m is the slope (mg/dL/nA), x is the current measured by the sensor (nA), and b is the intercept or background current (nA). The slope and intercept will be estimated for each patient and for both the saline sensing catheters and the insulin sensing catheters. We will then do a t-test between the slopes and the intercepts comparing these values between the saline sensing catheters and the insulin sensing catheters. The hypothesis is that the null hypothesis (the mean value of both the slope and intercept values are identical between the saline and insulin sensing catheters) is true which will be estimated by a p-value being greater than 0.05.

Another key end point will be glucose sensor accuracy (absolute difference, relative difference, and absolute relative difference) during insulin vs during saline delivery. These metrics will be calculated by using two types of calibration schemes: a one-point calibration with fixed offset, performed prospectively before meal administration, as described earlier [21]; and a retrospective all point calibration as proposed for early device evaluation, as proposed by Heinemann and Lodwig [22]. In addition to mean and median absolute difference, mean and median relative difference, and mean and median absolute relative difference, other accuracy metrics will include signed difference (bias). Error grid analyses will include Clarke, Parkes and continuous analyses. Bland-Altman analysis will be used to stratify accuracy as a function of glucose level.

In addition to the glucose sensing data described above, the subjects enrolled in the proposed clinical study will be asked to provide tolerability scores, which will include visual analog scales, to assess their level of comfort. During the study, skin irritation (Draize scores) will also be recorded. The tolerability and Draize scores will provide key data that will be used to support subsequent device modifications that reduce discomfort and skin irritation.

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 Venous blood glucose will be sampled every 15 minutes during the study. The closed-loop system will issue alerts and will be remote monitored during each visit with unserviced alerts being pushed to the study coordinator and investigator. If sensed glucose goes below 70 mg/dl or above 300 mg/dl for these studies, a venous blood glucose check will be required. A research nurse will be present at all times. A study investigator will be on call at all times.

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

There is a small risk of Dexcom G5 sensor fracture, and in such a case, a piece of the sensor could be left in the tissue after sensor removal. For this reason, the study investigator will inspect each removed sensor for the possibility of breakage or fracture. Any evidence of sensor breakage will be recorded and reported to FDA and the sensor company.

There is a small risk of infection at the insertion sites. This will be minimized by proper sterilization of the device and the subject's skin.

Investigational PDT glucose sensing cannula:
There is a small risk of material from the PDT glucose sensing being left in the body. This risk will be minimized by manufacturing controls to ensure that materials are properly adhered and sensors are slowly withdrawn from the subject. Mild to moderate, short-lived pain from sensor insertion is likely. This will be minimized by using a cannula with minimal diameter and injection depth.

There is a small chance that the needle from the blood draw at the screening visit will cause bleeding, a bruise, an infection or fainting.

There is a small chance that the IV catheter will get an infection and cause swelling, redness and pain. Rarely, an IV catheter can cause a serious infection in the blood or heart valves.

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

COSTS:
Subjects will receive $250 for completion of the inpatient visit. There is no compensation for the screening visit. If a subject is asked to repeat a study due to technical problems, he/she will receive an additional $250.

Monitoring Entity:
This investigation will be monitored by Dr. Joseph El Youssef. Dr. El Youssef has no commercial interest in any of the companies which manufacture any of the devices used in this study.

Data Collection:
Subject 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 paper Case Report Forms (CRF). Only a subject demographics/enrollment log case report form will be entered into REDCAP, a clinical research electronic data application designed to support traditional case report form data capture for research studies housed at Oregon Health Science University and administered by the Oregon Clinical and Translation Research Institute (OCTRI). 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. All data from the study files on the Android Nexus 5 phone will subsequently be entered into the authorized electronic REDCAP Cloud database.

Data Repository

The de-identified 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. The purpose of this data repository is to store the following de-identified data collected during the study described in this protocol: 1) blood glucose data, 2) sensor and blood glucose data, 3) insulin infusion data 4) blood ketone data, 5) rescue carbohydrate data, 6) meal data and 7) responses to questionnaires. There are no biological specimens collected from this study that will be stored in the repository.

Recording of Data:

Investigators and staff will record data collected during the clinical trial on the CRF's. Case report forms (CRF) for this study will be paper forms only. The CRFs will include:

1. Screening form
2. Day 1 Inpatient Closed-loop Study Visit
3. Phone Update Form
4. Adverse Event form
5. Serious Adverse Event form
6. Concomitant Medications

The Principal Investigators may authorize other personnel to make entries in the CRF.

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 subject. 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 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.

Triggers for reporting unanticipated problems are seizure, hospitalization, death or any other occurrence considered serious by the PI. If ongoing monitoring of the closed-loop studies reveals studies repeatedly being terminated because of unresponsive hyperglycemia or repeated serious hypoglycemia (resulting in altered mental status, loss of consciousness, or seizure) believed not amenable to revisions in control system parameter tuning, then the study will be discontinued immediately. If studies in two subjects are stopped for severe hypoglycemia or severe hyperglycemia, then the entire study will be halted. Severe hypoglycemia is defined as an event requiring the assistance of another person to administer carbohydrate, glucagon or resuscitative actions. Severe hyperglycemia is defined as 1) venous blood glucose exceeds 400 mg/dl on two occasions (120 min or more apart within a 4 hour window), 2) venous blood glucose exceeds 400 mg/dl on two occasions more than 120 minutes apart but outside of the 4 hour window and during that time, the venous blood glucose has not fallen below 250 mg/dl, or 3) serum ketones are above 1.5 mM at any time. 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.
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 subject 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 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. 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:

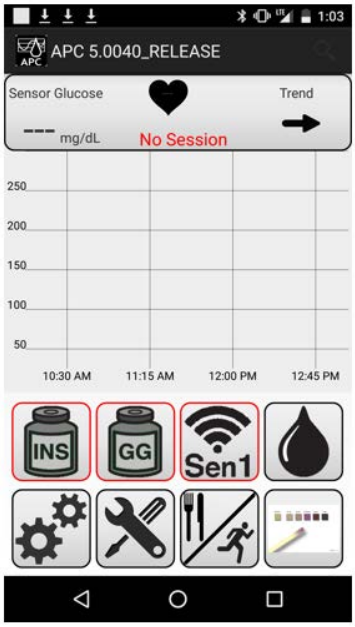
To protect confidentiality, standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to 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. 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

Tandem t:slim pump

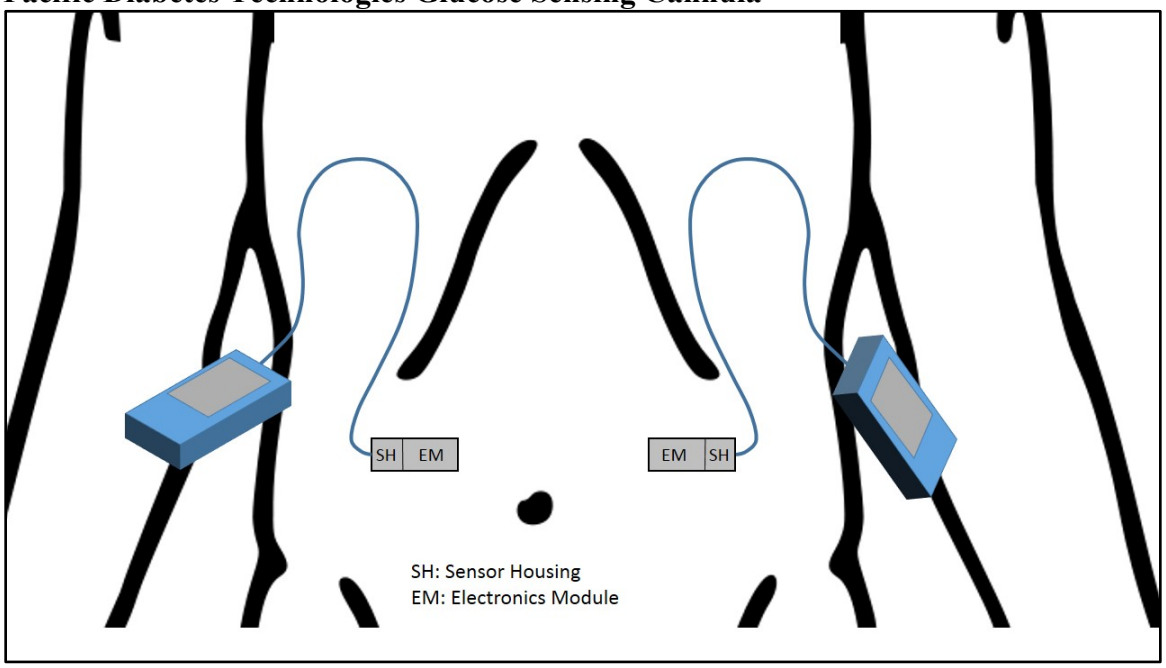
Dexcom G5 Continuous Glucose Monitoring System which includes Sensor and Sensor Transmitter along with the controller, Google Nexus 5 smart phone



Contour Next Blood Glucose Meter

Abbott Precision Xtra Meter

Pacific Diabetes Technologies Glucose Sensing Cannula



Appendix B: Alert Manager Specifications

Alarm #	Description of Alarm	When Alarm is Considered Serviced	Instructions for Subject	Alarm Refractory Period (minutes)	Alarm pushed to Study Coordinator	Alarm pushed to Study Investigator
2	ARD ≥ 35% for BG ≥ 75	Calibration detected	Sensor inaccuracy has been detected, please calibrate sensors with most recent blood glucose value.	30	If refractory period expires	If refractory period expires two or more times in a row
4	CBG ≤ 40 mg/dl	NA	CBG is low. Please treat with 30 g of carbs and recheck CBG in 15 minutes.	NA	instantly	instantly
5	CBG < 70 mg/dl and Alert 4 is not active	Rescue carb treatment identified	Blood glucose less than 70 mg/dL, treat with 15-20 g of carbohydrate and recheck in 15 minutes.	30	If refractory period expires	If refractory period expires two or more times in a row
6	Sensor < 70 mg/dl without exercise detection and < 85 mg/dl with exercise detection and no BG given within 15 minutes and alert 5 inactive	Blood glucose value is entered	Sensor is less than 70 mg/dL. Please check blood glucose.	30	If refractory period expires	If refractory period expires two or more times in a row
7	CBG >300 mg/dl	NA	CBG is greater than 300 mg/dl. Please	NA	instantly	instantly

			change the insulin infusion and check your ketones.			
8	Sensor glucose ≥ 300 mg/dl and no BG given within 30 minutes and alert 7 inactive	Blood glucose value is entered	Sensor glucose is greater than 300 mg/dl, please check and enter blood glucose, and check insulin pump for malfunctions	30	If refractory period expires	If refractory period expires two or more times in a row
9	Insulin pump communication issue	Autoservices if pump communication is restored	Insulin pump communication issue, please check pump and contact study physician	60 minute initial fire, 20 minute refractory	If refractory period expires during daytime hour of 07:00-22:59 (no nighttime escalation 23:00-06:59)	If refractory period expires two or more times in a row during daytime hour of 07:00-22:59 (no nighttime escalation 23:00-06:59)
10	Insulin meal bolus failure	Clears itself either after the meal flag is older than backlog of 15 minutes or there is not a backlog of insulin to deliver	Insulin meal bolus failed to deliver, please contact the study physician.	20	If refractory period expires	Coordinator will call subject and determine issue and consult with investigator to determine if subject should give bolus open loop.
11	Glucagon pump communication issue	Autoservices if pump communication is restored	Glucagon pump communication issue, please check pump and contact study physician	60 minute initial fire, 10 minute refractory	If refractory period expires during daytime hour of 07:00-22:59 (no nighttime	If refractory period expires two or more times in a row during daytime hour of 07:00-22:59 (no nighttime

					escalation 23:00-06:59)	escalation 23:00-06:59)
12	Sensor calibration due	Calibration detected	Sensor calibration due now, please check blood glucose and calibrate the sensor.	60	If refractory period expires	If refractory period expires two or more times in a row
13	If Alert 4 or 5 was activated, and no BG given in recent 20 minutes	Blood glucose value is entered	Blood glucose check due now.	20	If refractory period expires	If refractory period expires two or more times in a row
14	Cloud is not updating	Cloud connection restored	There is no connection of the phone to the internet. Please move back into cell phone or Wifi range.	20	If refractory period expires	If refractory period expires two or more times in a row
15	User has sent a bolus command to pump when not in "Pause Mode"	NA	Bolus from pump detected when in active mode, please only do this in pause mode	NA	Instantly-coordinator will call subject and determine reason for override and consult with investigator to determine if safety is a concern.	NA
17	Sensor out for > 20 minutes	Autoservices if sensor communication is restored	Sensor has not been acquired in 20 minutes, please check transmitter	20	If refractory period expires	If refractory period expires two or more times in a row

18	Replace Transmitter	Once fires, disables all sensor alarms for 120 minutes.	Please replace the sensor transmitter immediately	NA	NA	NA
19	Sensor Value is Invalid	Autoservices if sensor communication is restored	Sensor value is not reporting correctly. Please check sensor.	20	If refractory period expires	If refractory period expires two or more times in a row
20	Replace Sensor	Once fires, disables all sensor alarms for 120 minutes.	Please replace the sensor immediately.	NA	NA	NA
21	Basal insulin delivery failure	Autoservices if a successful bolus is given	Insulin basal delivery Failure, please contact the study physician	20	If refractory period expires during daytime hour of 07:00-22:59 (no nighttime escalation 23:00-06:59)	If refractory period expires two or more times in a row during daytime hour of 07:00-22:59 (no nighttime escalation 23:00-06:59)
22	Glucagon delivery failure	Autoservices if a successful bolus is given	Glucagon failed to deliver, please contact the study physician	20	If refractory period expires	If refractory period expires two or more times in a row
23	Insulin change due every 72 hours	User must press button to service-every 72 hours	Replace insulin fluid	120	If refractory period expires	If refractory period expires two or more times in a row
24	Glucagon change due every 24 hours	User must press button to service-every 24 hours	Replace glucagon fluid	120	If refractory period expires	If refractory period expires two or more times in a row

26	Insulin delivery has reached 35% of TDIRadj inside a 1 hour period	NA	Max insulin exceeded	60	Immediately then auto-clears	Immediately then auto-clears

Appendix C: PDT Glucose Sensing Cannula Device Description

The Pacific Diabetes Technologies device is able to measure interstitial glucose at the same site of insulin delivery (insulin is delivered via a separate pump that is not a part of this device). Success will be measured by how well the sensor tracks blood glucose changes without being affected by the preservatives in insulin.

PDT's CGM insulin infusion system is composed of four distinct components that function together to meet the intended use of the device. Images of the various components are included in the appendix. The parts are as follows:

Component	Purpose
Sensing Cannula and Housing	The Sensing Cannula sits in subcutaneous interstitial fluid to provide measurement of glucose to an externally worn sensor Housing.
Electronic Module	Attaches to the Sensing Cannula and Housing and stores and transmits a glucose signal to an external location
Insulin Infusion Set	Connects the PDT Sensing Cannula to the separate insulin pump
Insertion Device	Allows accurate and simple insertion of the device into its proper location.

Manufacturing Information: The investigational sensing cannulas/housings and electronic modules are manufactured at PDT's laboratories. All manufacturing and testing is performed in a cleanroom or laminar flow hood. Numerous tests are conducted on all manufactured sensors, throughout the fabrication process, to verify sensor functionality.

Sterilization: The investigational devices have been sterilized by a validated method (electron beam, dose=26 kiloGray). Each sterile study device is packaged in a 50 mL plastic vial (with screw cap) within a cardboard UPS mailing envelope.

Storage Conditions: Sterile sensing cannulas are stored at room temperature, and are not removed from the 50 mL capped plastic tubes before use. A clear adhesive seal, applied between the side of the cap and the side of the tube, safeguards that the tube remains tightly sealed.

Product Labeling: Shown here is a sample of the product labeling that will be displayed on the investigational CGM insulin infusion set. Note that this product label includes the statement "Caution–Investigational Device. Limited by Federal (or United States) Law to Investigational Use." Note that the label also states *"Do not use if package is damaged, or if the seal is broken or missing" (not shown in picture).*

Device Insertion Steps UPDATE for Tslim

NOTE -- the non-sterile devices indicated below will be sanitized with SaniCloth AF-3 wipes prior to use.

Prepare Devices

Physician dons gloves and prepares a sterile field. She carries out the steps listed below.

1. Remove from the sterile 50 mL vial the CGM insulin infusion set. Separate the insulin infusion tubing (Panel 1) from the sensor housing (Panel 2) by pressing the outer arms of the quick connector (Panel 1). Place the insulin infusion tubing on sterile field.
2. Place the sensor housing on the non-sterile loading base being careful to avoid contaminating the sterile cannula.
3. Place the non-sterile insertion device (Panel 5) over the loading base and press down. This action loads the sensor housing into the insertion device.
4. Cock the insertion device and set it aside for later use. Set aside the loading base for later use.

Insert cannula

5. Prepare the skin site with isopropyl alcohol pad(s) in ever-widening circles.
6. Remove the upper and lower liners from the non-woven adhesive patch.
7. Place the non-woven bandage on to the skin surface so that the skin worn device is oriented horizontally (left-right) on the body, not vertically.
8. Align the loaded inserter on to the non-woven bandage, then activate the inserter (insert cannula through skin). Visually verify that the cannula is in the tissue.
9. Remove the inserter and set aside

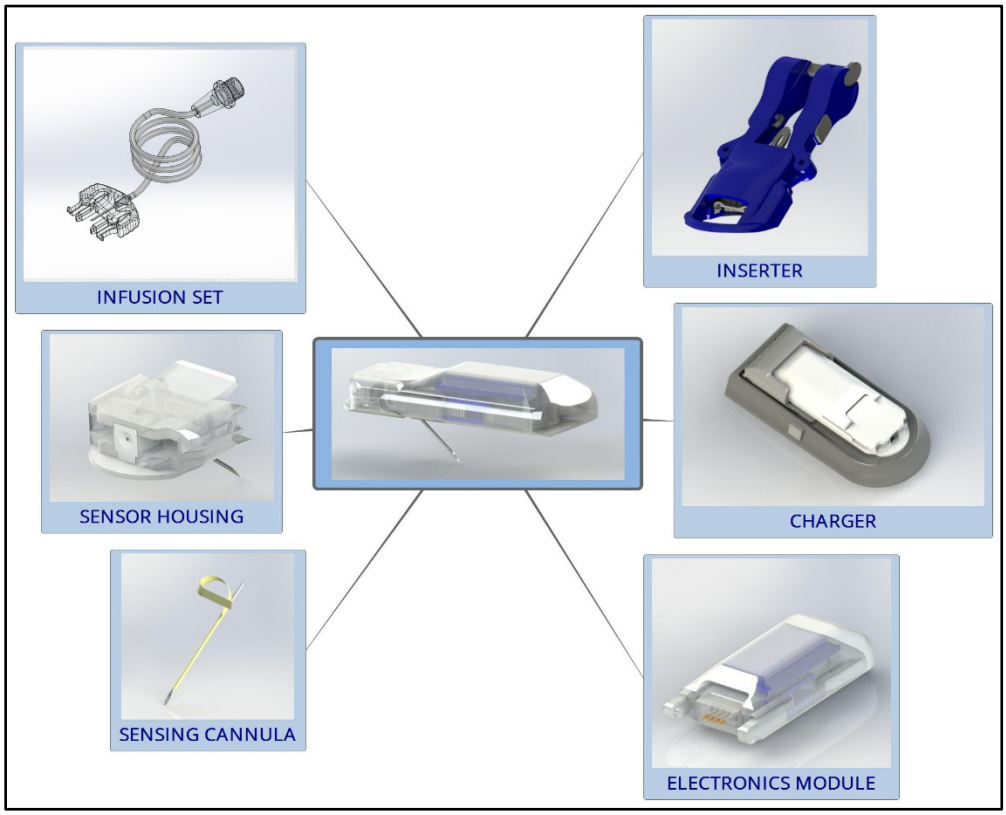
Insert and Anchor Electronic Module

10. Remove the electronic module (Panel 7) from the charger (Panel 6).
11. Using the laptop program, verify connectivity to the Bluetooth electronic module, then connect the electronic module to the sensor housing as shown in Panel 4. The electronic module will automatically start transmitting repeated "Active Status" signals to the laptop computer.
12. Apply polyurethane overbandage (such as Tegaderm), being careful to leave space for mating of quick connector to sensor housing.

Attach Insulin Pump and Fill the Insulin Fluid Path (Prime)

13. Connect reservoir to Tandem t:slim insulin pump. Avoid touching the sterile recessed reservoir-connection needle.
14. Using the pump interface, prime insulin line until insulin liquid is seen dripping through needle on quick connector. Avoid touching the sterile recessed quick connector needle.
15. Attach the quick connector to the sensor housing.
16. Using the pump interface, carry out the needle prime (0.7 units) to fill the cannula with insulin.
17. Now the insulin delivery rates can be programmed and initiated.

COMPONENTS OF CGM/INSULIN INFUSION SYSTEM



APPENDIX D: TOLERABILITY QUESTIONAIRE

APPROXIMATELY 15 MINUTES AFTER INSERTION

1. Did you have any discomfort WHILE THE DEVICES WERE BEING INSERTED?

LEFT	***RIGHT***
○ No discomfort → ***Go to Question #3***	○ No discomfort → ***Go to Question #3***
○ Mild discomfort	○ Mild discomfort
○ Moderate discomfort	○ Moderate discomfort
○ Severe discomfort	○ Severe discomfort

2. The discomfort from the insertion LASTED how long?

LEFT	***RIGHT***
○ Less than 10 seconds	○ Less than 10 seconds
○ 10 seconds to 1 minute	○ 10 seconds to 1 minute
○ 1 to 5 minutes	○ 1 to 5 minutes
○ Longer than 5 minutes	○ Longer than 5 minute

3. Did you have any discomfort that started AFTER insertion?

LEFT	***RIGHT***
○ No discomfort → **Stop here. Don't answer Question #4**	○ No discomfort → **Stop here. Don't answer Question #4**
○ Mild discomfort	○ Mild discomfort
○ Moderate discomfort	○ Moderate discomfort
○ Severe discomfort	○ Severe discomfort

4. The discomfort that started AFTER insertion LASTED how long?

If you currently feel discomfort, please mark "I still feel discomfort"

LEFT	***RIGHT***
○ Less than 10 seconds	○ Less than 10 seconds
○ 10 seconds to 1 minute	○ 10 seconds to 1 minute
○ 1 to 5 minutes	○ 1 to 5 minutes
○ Longer than 5 minutes	○ Longer than 5 minutes
○ I still feel discomfort	○ I still feel discomfort

APPROXIMATELY 2 HOURS AFTER INSERTION

1. **Did you have any discomfort AFTER the first 15 minutes?**

LEFT	***RIGHT***
○ No discomfort → **Stop here. Don't answer Questions #2 and #3**	○ No discomfort → **Stop here. Don't answer Question #2 and #3**
○ Mild discomfort	○ Mild discomfort
○ Moderate discomfort	○ Moderate discomfort
○ Severe discomfort	○ Severe discomfort

2. **How would you describe the discomfort?**

LEFT	***RIGHT***
○ Pain (e.g., stinging)	○ Pain (e.g., stinging)
○ Itching (e.g., burning)	○ Itching (e.g., burning)
○ Other, please describe:	○ Other, please describe:
_____	_____

3. **The discomfort LASTED how long?**

   If you currently feel discomfort, please mark "I still feel discomfort"

LEFT	***RIGHT***
○ 30 seconds or less	○ 30 seconds or less
○ More than 30 seconds but less than 5 minutes	○ More than 30 seconds but less than 5 minutes
○ 5 to 20 minutes	○ 5 to 20 minutes
○ More than 20 minutes but less than 1 hour	○ More than 20 minutes but less than 1 hour
○ 1 hour or more	○ 1 hour or more
○ I still feel discomfort	○ I still feel discomfort

END OF STUDY

OVERALL, did you have any discomfort after the devices were inserted? Please don't include discomfort experienced during the insertion. You can mark as many circles as necessary – For example, from a single device (left or right), you may have felt mild discomfort during part of the study, and moderate discomfort during another part of the study.

LEFT

☐ **NO DISCOMFORT**

☐ **MILD DISCOMFORT**

How would you describe the discomfort?

○ Pain (e.g., stinging) ○ Itching (e.g., burning)

○ Other:

How long did it last?

○ 1 minute or less

○ More than 1 minute but less than 10 minutes

○ 10 minutes to 1 hour

○ More than 1 hour but less than 5 hours

○ 5 hours or more

☐ **MODERATE DISCOMFORT**

How would you describe the discomfort?

○ Pain (e.g., stinging) ○ Itching (e.g., burning)

○ Other:

How long did it last?

○ 1 minute or less

○ More than 1 minute but less than 10 minutes

○ 10 minutes to 1 hour

○ More than 1 hour but less than 5 hours

○ 5 hours or more

☐ **SEVERE DISCOMFORT**

How would you describe the discomfort?

○ Pain (e.g., stinging) ○ Itching (e.g., burning)

○ Other:

How long did it last?

○ 1 minute or less

○ More than 1 minute but less than 10 minutes

○ 10 minutes to 1 hour

○ More than 1 hour but less than 5 hours

○ 5 hours or more

RIGHT

☐ **NO DISCOMFORT**

☐ **MILD DISCOMFORT**

How would you describe the discomfort?

○ Pain (e.g., stinging) ○ Itching (e.g., burning)

○ Other:

How long did it last?

○ 1 minute or less

○ More than 1 minute but less than 10 minutes

○ 10 minutes to 1 hour

○ More than 1 hour but less than 5 hours

○ 5 hours or more

☐ **MODERATE DISCOMFORT**

How would you describe the discomfort?

○ Pain (e.g., stinging) ○ Itching (e.g., burning)

○ Other:

How long did it last?

○ 1 minute or less

○ More than 1 minute but less than 10 minutes

○ 10 minutes to 1 hour

○ More than 1 hour but less than 5 hours

○ 5 hours or more

☐ **SEVERE DISCOMFORT**

How would you describe the discomfort?

○ Pain (e.g., stinging) ○ Itching (e.g., burning)

○ Other:

How long did it last?

○ 1 minute or less

○ More than 1 minute but less than 10 minutes

○ 10 minutes to 1 hour

○ More than 1 hour but less than 5 hours

○ 5 hours or more

APPENDIX E: DRAIZE SCALE

To be completed by the person who removes the devices (PI, Co-I, or clinical coordinator)

Sensing Cannula (LEFT)

DRAIZE SCALE At END OF VISIT	○ 0=No erythema ○ 1=Very slight, barely perceptible erythema ○ 2=Well defined erythema ○ 3=Moderate erythema ○ 4=Severe erythema, Beet redness to slight eschar formation	○ 0=No edema ○ 1=Very slight, barely perceptible edema ○ 2=Well defined edema ○ 3=Moderate edema, raised approx. 1mm ○ 4=Severe edema, raised >1mm and beyond exposure area

Sensing Cannula (RIGHT)

DRAIZE SCALE At END OF VISIT	○ 0=No erythema ○ 1=Very slight, barely perceptible erythema ○ 2=Well defined erythema ○ 3=Moderate erythema ○ 4=Severe erythema, Beet redness to slight eschar formation	○ 0=No edema ○ 1=Very slight, barely perceptible edema ○ 2=Well defined edema ○ 3=Moderate edema, raised approx. 1mm ○ 4=Severe edema, raised >1mm and beyond exposure area

Appendix F: Visual Analog Scale (VAS) for PDT Sensor Site Discomfort

Investigative Site Instructions: The subject should complete the VAS for PDT sensor site 15 minutes and 2 hours after sensor insertion and at the end of the study. The subject completes the VAS by drawing a single vertical line through the scale corresponding to the perceived intensity (severity) of discomfort according to the instructions below. At the 15 minute time point, the goal is for the subject to report the amount of discomfort, if any, associated with needle insertion. For the later time points, the goal is for the subject to report the amount of discomfort, if any, remaining at each time point, as opposed to reporting the transient pain associated with needle insertion.

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

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

Subject Instructions: Please draw a single vertical line through the scale below that corresponds to the intensity (severity) of any discomfort you have felt. At the 15 minute time point after insertion, please describe your pain from the insertion of the sensors. At the 2 hours and end of study time points, please describe any pain you have experienced since the devices were inserted.

Discomfort could include stinging, burning, tingling, throbbing or pain. The further to the right you make your vertical mark, indicates the more intense discomfort you are feeling.

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

No Discomfort Worst Possible Discomfort

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