The Set-Point Study: Evaluating Effects of Changing Glucose Target on Bionic Pancreas Performance

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I. Background and Significance

1.1 Background and Rationale

Maintaining near-normal blood glucose (BG) levels (70--120 mg/dl) is a challenging and critically important task for people with diabetes. The Diabetes Control and Complications Trial (DCCT) Research Group definitively demonstrated that tight BG control can reduce long-term complications in patients with type 1 diabetes (1, 2). The likelihood and severity of nephropathy, retinopathy, neuropathy, macrovascular disease, and skin disorders is reduced in proportion to reductions in glycated hemoglobin (HbA1c), which is closely correlated with long-term average BG levels. Risks for such complications are elevated by three- to five-fold with diabetes. On the other hand, tight BG control through conventional intensive insulin therapy increases the likelihood of episodic hypoglycemia, which carries acute risks, including convulsions, seizures, coma, and death. Conventional therapy also requires a relentless daily effort to count carbohydrates, frequently monitor BG throughout the day and night, and administer a daily insulin regimen.

A more reliable method for achieving consistent BG control consists of an integrated artificial or bionic pancreas (BP) system, consisting of a continuous glucose monitor (CGM), an infusion pump, and a control algorithm that actuates the pump based on CGM glucose data. Such a system can automate and ease the burden of diabetes management and vastly improve glycemic control relative to the current standard of care.

1.2 Bi-hormonal Bionic Pancreas System

We have developed an autonomous, self-learning BP that requires only the subject's weight for initialization, and then autonomously adapts, modestly or dramatically, as needed, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with T1D, and potentially for patients with insulin dependent type 2 diabetes. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

Our core technology is the insulin controller, which orchestrates all subcutaneous (SC) insulin dosing. At its centerpiece is a model-predictive control algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics. We were the first to incorporate insulin pharmacokinetics (PK) into the algorithm, by augmenting it with a mathematical formulation for estimating the concentration of insulin in the blood and predicting its future concentration. It is essential to compensate for the slow absorption rate of SC insulin analogs (peak time in blood of 30--90 min, clearance in 4--8 hr), and to enable the algorithm to refrain from stacking and overdosing insulin. Furthermore, the MPC algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in realtime to different insulin needs between individuals and variable needs within the same individual. Running in parallel with the MPC algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements. Unlike current insulin pumps, and all of the insulin-only control algorithms of which we are aware, the adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her “basal-rate profile”. Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over

a period of hours, days, or weeks (e.g. circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g. hormonal changes that occur during puberty or menopause). Our adaptive meal dose controller obviates the need for the user to set, or even know, his or her "carbohydrate-to-insulin ratios", as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day. Our BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It could occur preemptively even if glucose is above range and it includes a feedback term to account for the pending effects of recent glucagon doses.

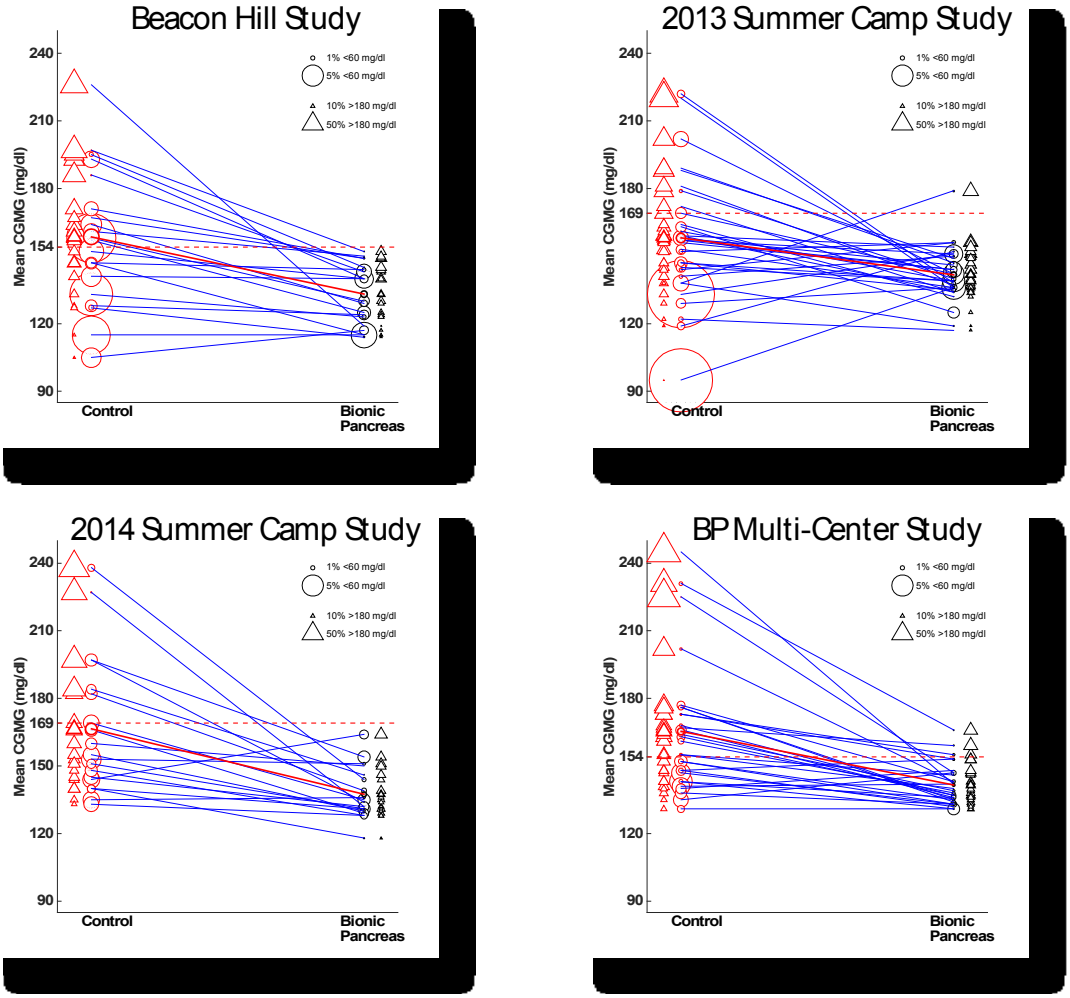
Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge we have met is enabling the technology to remain completely autonomous in managing insulin and glucagon delivery even when the Dexcom CGM is offline. Specifically, when the Dexcom CGM is offline, the BP invokes the high-resolution "basal rate profile" that it had recently learned and stored when the Dexcom CGM was online. On the basis of what the system learned and stored about meal announcements when the Dexcom CGM was online, it is able to respond to meal announcements in the same manner when the Dexcom CGM is offline. Finally, it automatically responds to user-entered BG values when the Dexcom CGM is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the Dexcom CGM was online. Thus, the BP never relies on, or burdens the user with, the determination of subjective dosing decisions, which inevitably vary in quality and reliability among different users. The BP provides a turnkey solution for people with diabetes that comprehensively manages glycemia across a broad range of individual needs and a across a large spectrum of circumstances and challenges to glycemic control.

1.3 Preliminary Studies

Our BP hardware platform has evolved over the years from a laptop-driven system, which we used in all of our inpatient studies (between 2008--2012), to the first truly mobile wearable iPhone-driven platform, which we have used in all of our outpatient studies thus far (between 2013--2015). Using the iPhone-driven BP system, we have conducted >110 outpatient experiments of 5--11 days in duration in each subject (> 800 patient days or > 2 patient years of data), and across subjects ranging in age between 6 and 76 years old and in body mass between 21 and 128 kg. The robust adaptation capabilities of the BP is evident in the fact that the average total daily dose of insulin among these subjects varied by over 13-fold (from 11 to 145 units/day).

The preclinical studies at BU testing the BP in a diabetic swine model of T1D (3-4), and all of the inpatient clinical trials in the Clinical Research Center at MGH testing the BP in adults and adolescents with T1D (5-7) set the stage for the outpatient studies that followed. In November 2012 we obtained FDA approval to conduct our first outpatient study testing our BP in adults 21 years or older with T1D. This study, which we referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1D participated in 5 days on our iPhone-based BP and 5 days of usual care in which they wore a Dexcom CGM with blinded

display and muted alarms. In the BP arm, subjects kept to a three-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to two gyms. Analysis was pre-specified to focus on Days 2--5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1 (8). Results are summarized in the plots and table of Figure 1.



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <'50'mg/dl (%)	Bionic Pancreas (BP) % of CGM glucose levels 70–180'mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM goucose values <'50'mg/dl (%)	Control % of CGM goucose values 70–180'mg/dl (%)	*p*-value (BP versus Control) for: Mean CGM glucose level	*p*-value (BP versus Control) for: % of CGM glucose values <'50'mg/dl	*p*-value (BP versus Control) for: % of CGM glucose values 70–180'mg/dl
Beacon Hill (n=20, 5-day experiments)	≥'21	133	1.5	80	159	3.7	59	<'0.001	0.020	<'0.001
2013 Summer Camp (n=32, 5-day experiments)	12–20	142	1.3	76	158	2.2	65	0.004	0.192	<'0.001
2014 Summer Camp (n=19, 5-day experiments)	6–11	137	1.2	81	168	2.8	58	0.004	0.001	<'0.001
BP Multi-Center (n=29, 11-day experiments)	≥'21	142	0.6	78	165	1.6	61	<'0.001	<'0.001	<'0.001

Figure 1. Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the BP and control arms. Mean CGM glucose levels for each subject under usual care (shown as a red circle on the left) is connected with the subject's mean CGM glucose level on the BP (shown as a black circle on the right). For each subject, the circle diameter is proportional to the percentage of CGM glucose values < 60 mg/dl, and the size of the triangle is proportional to the percentage of CGM glucose values > 180 mg/dl. The horizontal red

dashed line refers to the glucose level corresponding to the ADA therapy goal for each age group tested, which corresponds to 154 mg/dl (HbA1c <7%) for adults and 169 mg/dl (HbA1c <7.5%) for children. Results are summarized in the table below, where the co-primary outcomes (mean CGM glucose level and percentage of CGM glucose values < 60 mg/dl) for the BP are highlighted in red for each of the four studies.

In April 2013, we obtained FDA approval to conduct our first outpatient study testing the BP in adolescents 12--20 years old with T1D. This study, which we referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1D participated in 5 days on the BP and 5 days of supervised camp care in which they wore a Dexcom CGM with blinded display and muted alarms. Subjects were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone-based BP that was used in the Beacon Hill Study. The mean HbA1c of the entire all 32 subjects at baseline (pre-study) was 8.2%, which corresponds to a mean BG of 189 mg/dl. Results are summarized in the plots and table of Figure 1 (8).

In April 2014 we obtained FDA approval conduct our first outpatient study testing the BP in pre-adolescents 6--11 years old with T1D. This study, which we referred to as the 2014 Summer Camp Study, was similar in design to the 2013 Summer Camp Study. Results are summarized in the plots and table of Figure 1. In April 2014, we obtained FDA approval to conduct our first multi-center study, which was also our first home study, to test the BP in adults 18 years or older with T1D. This study, which we referred to as the Bionic Pancreas Multi-Center (BPMC) Study, followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included four medical centers (10 subjects per center), which included MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill.

Preliminary results from an interim analysis of a subset of the data from the BPMC Study are summarized in the plots and table of Figure 1 (unpublished data).

I. d. Rationale and Potential Benefits

Our experiments to date in human subjects with type 1 diabetes have demonstrated the practicality of a wearable automated, bionic pancreas control system for robust glucose regulation using continuous glucose monitoring devices as input to the controller. Despite current technical limitations of the pump and CGM components, we have shown that a bi-hormonal bionic endocrine pancreas is capable of achieving good BG control automatically with minimal hypoglycemia during eleven continuous days in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals).

The bionic pancreas BG control system we have developed is able to provide automatic BG regulation and reduce hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG monitoring, estimating the effects of specific meals and exercise activity on blood glucose levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance. The degree of glycemic control achieved is predicted to dramatically reduce the deleterious and debilitating complications of type 1 diabetes.

A consistent finding in all of our bionic pancreas (BP) studies has been a reduction in both hypoglycemia despite lower mean plasma glucose values, relative to usual care. We have also found no statistically significant difference in the mean total daily dose (TDD) of insulin between the BP and usual pump therapy in both of our 2013 and 2014 Summer Camp Studies, and in our recently completed Multi-Center Study. Nevertheless, some proponents of an insulin-only strategy for automated glycemic control contend that the insulin dosing by the bi-hormonal bionic pancreas is too aggressive, that our BP is too dependent upon glucagon, and that we achieve unnecessarily low mean glucose levels. We note that mean plasma glucagon levels were in the normal fasted range during our inpatient study of the BP more than 60% of the time. That being said, it is true that the BP often achieves mean glucose levels that are lower than necessary to dramatically reduce the long-term risk of diabetes complications; some subjects have had mean CGM glucose values over 11 days of <120 mg/dl. Once an HbA1c of 6.5-7.0% is achieved (estimated average glucose between 140 and 154 mg/dl), incremental reduction in complications with further glucose lowering is very small. It is possible, even likely, that insulin and glucagon usage could both be reduced by raising the mean glucose level without a significant reduction in benefit in these individuals. It may also be possible to achieve substantial improvements over usual care with an insulin-only system with an appropriately high set-point.

The default target glucose used by the BP in our previous studies was 100 mg/dl, which resulted in an average CGM glucose of 133 mg/dl in adults in the Beacon Hill Study, 142 mg/dl in adolescents in the 2013 Summer Camp Study, 137 mg/dl in pre-adolescents in the 2014 Summer Camp Study, and 141 mg/dl in adults in the Multi-Center Study. We hypothesize that shifting the set-point upwards will reduce the amount of insulin delivered, raise the mean glucose level, reduce the amount of glucagon required, and reduce the risk of hypoglycemia. A higher set-point may also allow adequate glycemic control in an insulin-only configuration.

In addition to these considerations, the FDA has asked that we demonstrate glucagon is necessary for the effectiveness of the BP in an in-clinic study using reference quality plasma glucose measurements for outcomes (see attached Meeting Minutes to Pre-Sub Meeting Q150024). These in-clinic studies must be performed after the BP system has adapted in the outpatient setting. Therefore, the in-clinic study will be incorporated into this protocol. The FDA has required that this study be placebo controlled and double-blind, so we will have to use vial blinding devices for placebo vs. glucagon vials during the outpatient and in-clinic portions of the trial. Fortunately, we have already designed and built such blinding devices for a currently running glucagon-only BP trial.

The current study is designed to determine the effect on mean glucose, hypoglycemia, glucagon usage, and insulin usage of adjusting upward the glucose target of the bi-hormonal bionic pancreas, and determine whether there is a target at which adequate glycemic control is achieved by an insulin-only bionic pancreas with minimal hypoglycemia. The design of the study is meant to minimize disruption to the normal routine of subjects while still collecting information critical to comparing the quality of BG control at each glucose target of the bionic pancreas and usual care groups. The overall goal of this study is to determine the default target glucose level for the final pivotal trial of the bionic pancreas that will be required for approval of the bionic pancreas by the FDA, and to provide guidance to users of the bionic pancreas on how to use the glucose target set-point feature. Depending on the performance of the bionic pancreas in the insulin-only configuration, we may decide to proceed with further development of an insulin-

only platform in parallel with the bi-hormonal BP. Such a system could use the same hardware so that it could be upgraded to a bi-hormonal configuration at any time.

Remote, real-time monitoring of both groups will be limited to: 1) monitoring aspects of device function that will not be part of a fully integrated design (e.g. communication between the Dexcom CGM receiver and the iPhone and communication between the iPhone and the pumps), and 2) monitoring to ensure independent confirmation of any events of severe biochemical hypoglycemia (< 50 mg/dl) by BG measurement and to ensure that any true events will not go undetected and untreated, thereby mitigating the risk of injury to subjects.

The bionic pancreas is highly adaptable and is able to automatically adapt to a wide range of insulin requirements. This suggests that it will also be able to automatically manage glycemia for patients with type 2 diabetes who manage their diabetes with insulin injections as well as those with type 1 diabetes.

II. Hypothesis and Specific Aims

We hypothesize that raising the target glucose set-point in the bionic pancreas will reduce the amount of insulin delivered, raise the mean glucose level, reduce the amount of glucagon required, and further reduce the already very low occurrence of hypoglycemia in the bionic pancreas. We further hypothesize that the higher set-points may allow adequate glycemic control in an insulin-only configuration. The specific aims of this study are:

Aim 1. To conduct an outpatient study testing multiple configurations of the bionic pancreas (bi-hormonal and insulin-only at different set-points) in 20 adult (≥ 18 years of age) subjects with type 1 diabetes in a random-order crossover study versus usual care with an insulin pump.

The study will consist of up to 9 3-day (Monday through Thursday) study arms in random order: one usual care, bi-hormonal bionic pancreas with glucose set-points of 100 mg/dl, 110 mg/dl, 115 mg/dl and 130 mg/dl, and insulin only bionic pancreas with glucose set-points of 110 mg/dl, 120 mg/dl, 130 mg/dl and 145 mg/dl. There will be a three day (Friday through Sunday) washout period in between each arm. The only exception to this is during both the 130 mg/dl bi-hormonal and 110 mg/dl bihormonal and insulin only arms, where the study continues until Friday to perform an in-clinic exercise protocol, and the washout period is Saturday and Sunday. The co-primary outcomes will be the mean Dexcom CGM glucose level and time <60 mg/dl, both in the last 2 days of each arms (days 2 and 3) because these will be predictive of outcomes in long-term use. Secondary analyses will include deriving empirical relationships between the set-point and the mean TDD of glucagon and insulin, mean Dexcom CGM glucose, and time < 60 mg/dl.

As of August 2017, this Aim has been completed.

Aim 2. To evaluate the incremental utility of glucagon in the context of automated insulin delivery by the bionic pancreas in preventing hypoglycemia during exercise in the fasted state.

Subjects will fast overnight on Thursday night at the end of the 130 mg/dl and 110 mg/dl insulin-only and bi-hormonal arms (both of which will be run placebo controlled and double-blinding in terms of glucagon exposure), arrive fasted on Friday morning, and exercise on a stationary bike with a heart rate from 120–140 bpm for approximately 30 minutes. BG measurements will be

performed every 10 minutes or every 5 minutes if BG is <80 mg/dl. Carbohydrate will be given for BG <50 mg/dl. Repeat treatments will be given at 15 min intervals if BG remains <50 mg/dl. BG monitoring will continue for 2 hours after exercise. The primary outcome will be the number of subjects discordant for an event with PG <60 mg/dl for more than two consecutive measurements (McNemar test). Secondary endpoints will include the area between the glucose curve and 60 mg/dl and the amount of carbohydrates required to recover from hypoglycemic events.

As of August 2017, this Aim has been completed.

Aim 3. To document the satisfaction of subjects with the bionic pancreas device at different set-points with the goal of optimizing the glucose target level and ascertaining the value of glucagon from the subject point of view.

Questionnaires will be administered at the beginning of the study and the end of each arm to gather data on attitudes towards bionic pancreas BG control, quality of life and treatment satisfaction. This information will be used to make the best choices about how the final version of the bionic pancreas should be configured. We hypothesize that treatment satisfaction with the BP will vary with the set-point. Some subjects may be willing to tolerate more hypoglycemia to maintain a lower mean glucose, while others may prefer to reduce hypoglycemia as far as possible even if that means having a mean glucose > 154 mg/dl. Satisfaction may also be impacted by the use of glucagon itself.

Aim 4. To conduct an outpatient study testing the bionic pancreas in the insulin only configuration at a set point of 100 mg/dl in 10 adult (≥ 18 years of age) subjects with type 2 diabetes in a random-order crossover study versus usual care with multiple or daily injections or an insulin pump.

The study will consist of two 7 day study arms: one usual care, and one insulin-only bionic pancreas at a set point of 100 mg/dl. The co-primary outcomes will be the mean Dexcom CGM glucose level and time <54 mg/dl, both in the last five days of each arm because these will be predictive of outcomes in long term use. The first two days will be excluded to allow for the extended washout of long acting insulins.

Subjects with type 2 diabetes will complete the questionnaires of Aim 3, but will not participate in the Friday exercise visits of Aim 2.

Aim 5. To test the accuracy of the Senseonics implantable CGM vs. the Dexcom G4 CGM in a subset of subjects in this trial (optional for subjects).

Subjects will be offered the option to have a Senseonics implantable CGM device placed. The US pivotal trials for this CE-marked device are fully enrolled and ongoing. It is a tiny device (see figure) that is implanted in the subcutaneous tissue. It is powered externally from the transmitter, which is attached with adhesive or with use of an elastic arm band. The data from the Senseonics sensor will be collected in blinded fashion and will later be compared with reference point-of-care capillary glucose values.

As of August 2017, this aim has been completed.

III. Subject Selection

III. a. Inclusion Criteria

- Type 1 diabetes group: Age ≥ 18 years and have had clinical type 1 diabetes for at least one year managed using an insulin pump for ≥ 6 months
- Type 2 diabetes group: Age ≥18 years and clinical type 2 diabetes managed with:
    - a multiple daily injection insulin regimen that includes NPH insulin and a rapid-acting insulin (insulin lispro, insulin aspart or insulin glulisine),
    - an insulin pump filled with a rapid acting insulin
    - a multiple daily injection insulin regimen that includes Lantus or Levemir and a rapid acting insulin
- Type 2 diabetes group: HbA1c >7%
- Prescription medication regimen stable for > 1 month (except for medications that will not affect the safety of the study and are not expected to affect any outcome of the study, in the judgment of the principal investigator)
- Live within a 60 minute drive-time radius of the central monitoring location
- Willing to remain within a 120 minute drive-time radius of the central monitoring location throughout the study
- Have someone over 18 years of age who lives with them, has access to where they sleep, is willing to be in the house when the subject is sleeping, and is willing to receive calls from the study staff and check the welfare of the study subject if telemetry shows a technical problem or severe biochemical hypoglycemia without subject response and the subject does not answer their telephone (up to two individuals can share this role, but they must be willing to carefully coordinate with each other and the subject so that one of them is clearly designated as having this responsibility at any given time)
- Willing to wear one or two infusion sets and one Dexcom CGM sensor and change sets frequently (at least one new glucagon infusion set daily during bi-hormonal arms, and insulin infusion set every other day throughout the study)
- Have a mobile phone they are willing to keep with them and answer calls from study staff.

No subjects will be excluded on the basis of gender or race. The requirement that type 1 diabetes subjects manage their diabetes using subcutaneous insulin infusion pump therapy is imposed because multiple daily injection therapy involves the use of long-acting basal insulin that would require an extended washout period. The arms for the type 2 diabetes subjects have been extended to allow for the washout period.

The requirement that type 2 diabetes subjects have an A1c > 7% is imposed because blood glucose is generally less liable in patients with type 2 diabetes then in those with type 1 diabetes and the insulin regimens are often less complex. Patients with type 2 diabetes also have less severe hypoglycemia than patients with type 1 diabetes. Therefore, the increased cost of a bionic pancreas could be best justified for those who are not meeting glycemic goals will increase the power of the study to demonstrate a significant difference between the usual care and bionic pancreas arms.

III. b. Exclusion Criteria

- Unable to provide informed consent (e.g. impaired cognition or judgment)
- Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory, unable to speak and read English)
- Current participation in another diabetes-related clinical trial that, in the judgment of the principal investigator, will compromise the results of this study or the safety of the subject
- Pregnancy (positive urine HCG), breast feeding, plan to become pregnant in the immediate future, or sexually active without use of contraception
    - Subjects must use acceptable contraception for the two weeks prior to the study, throughout the study and for the two weeks following the study.
    - Acceptable contraception methods include:
        - Oral contraceptive pill (OCP)
        - Intrauterine Device (IUD, hormonal or copper)
        - Male condoms
        - Female condoms
        - Diaphragm or cervical cap with spermicide
        - Contraceptive patch (such as OrthoEvra)
        - Contraceptive implant (such as Implanon, Nexplanon)
        - Vaginal ring (such as NuvaRing)
        - Progestin shot (such as Depo-Provera)
        - Male partner with a vasectomy proven to be effective by semen analysis
- Need to go outside of the designated geographic boundaries during the study
- Current alcohol abuse (intake averaging > 3 drinks daily in last 30 days), use of marijuana within 1 month of enrollment, or other substance abuse (use within the last 6 months of controlled substances other than marijuana without a prescription)
- Unwilling or unable to refrain from drinking more than 2 drinks in an hour or more than 4 drinks in a day or use of marijuana during the trial
- Unwilling or unable or to avoid use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study (use of beta blockers will be allowed as long as the dose is stable and the subject does not meet the criteria for hypoglycemia unawareness while taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the principal investigator)
- History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g. liver failure or cirrhosis). Other liver disease (i.e. active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the subject if it causes significant compromise to liver function or may do so in an unpredictable fashion.
- Renal failure on dialysis
- Personal history of cystic fibrosis, pancreatitis, pancreatic tumor, or any other pancreatic disease
- Known history of coronary artery disease (CAD) that is symptomatic despite medical management including:
    - Unstable angina
    - Angina that prevents moderate exercise (exercise of intensity up to 6 METS) despite medical management
    - Myocardial infarction within the last 12 months of screening.

- Known history of CAD that is not appropriately medically managed, e.g. not currently treated with ASA or other anti-platelet drug, a statin, and anti-hypertensives if indicated
- Known history of CAD but participant is currently smoking tobacco
- Abnormal EKG consistent with increased risk of malignant arrhythmia including, but not limited to, evidence of active ischemia, prior myocardial infarction, proximal LAD critical stenosis (Wellen's sign), prolonged QT interval (> 440 ms). Other EKG findings, including stable Q waves, are not grounds for exclusion as long as the participant is not exclude according to other criteria. A reassuring evaluation by a cardiologist after an abnormal EKG finding may allow participation.
- Congestive heart failure with New York Heart Association (NYHA) Functional Classification III or IV
- History of TIA or stroke in the last 12 months
- Seizure disorder, history of any non-hypoglycemic seizure within the last two years, or ongoing treatment with anticonvulsants
- History of hypoglycemic seizures (grand-mal) or coma in the last year
- History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    - Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    - Paroxysms of tachycardia, pallor, or headache
    - Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
- History of adrenal disease or tumor
- Hypertension with systolic BP ≥160 mm Hg or diastolic BP ≥100 despite treatment
- Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation.
- Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference
- Unable to completely avoid acetaminophen for duration of study
- History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
- Established history of allergy or severe reaction to adhesive or tape that must be used in the study
- History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight
- History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment
- Type 1 diabetes group: Use of oral (e.g. thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) anti-diabetic medications
- Type 2 diabetes group: Use of oral anti-diabetic medications other than metformin
- Lives in or frequents areas with poor Verizon wireless network coverage (which would prevent remote monitoring)
- Any factors that, in the opinion of the principal investigator would interfere with the safe completion of the study
- For implantation of a Senseonics sensor the following additional exclusion criteria apply. Subjects that are excluded by these criteria cannot have a Senseonics sensor placed,

but can participate in all other aspects of the study.

- A condition preventing or complicating the placement, operation or removal of the Senseonics sensor or wearing of transmitter, including upper extremity deformities or skin condition
- Currently receiving (or likely to need during the study period): immunosuppressant therapy, chemotherapy, anticoagulant/antithrombotic therapy (excluding aspirin), glucocorticoids (excluding ophthalmic or nasal). This does include the use of inhaled and topical glucocorticoids and antibiotics for chronic infection
- A condition requiring or likely requiring magnetic resonance imaging (MRI)
- A known topical or local anesthetic allergy
- A known glucocorticoids allergy
- The presence of any other active implanted device
- The presence of any other CGM sensor or transmitter located in the upper arm (other location is acceptable)
- Hemoglobin < 12 g/dl

III. c. Source of Subjects

Volunteers who fit the selection criteria will be considered as candidates for this study. We will contact individuals who have previously inquired about participation in our studies and have asked us to have their contact information kept on file. In addition, advertisements for the study will be posted at the MGH Diabetes Center and other places, and will be distributed in the weekly broadcast email of research studies seeking volunteers. A letter may be sent to adult endocrinologists in the Boston metropolitan as well as selected nearby endocrinologists informing them of the study and asking them to refer any eligible patients who might be interested. We will post information about the trial along with contact information on our website www.bionicpancreas.org and on www.clinicaltrials.gov.

Prospective subjects may be identified via registry searches (e.g., Diabetes Clinic Patient Registry, RPDR). Study staff will conduct a preliminary pre-screening for basic inclusion and exclusion criteria using the medical records of the potential subjects identified in the registry. If these potential subjects have indicated that they can be contacted directly, an opt-out letter from the principal investigator will be sent to them describing the study and opt-out procedures if they are not interested. If these potential subjects have not indicated that they can be contacted directly, we will use the two-letter approach, where a treating clinician gives permission to contact the patient. Provider permission will be secured by generating a list of potential participants and sending them in a format, with eligibility criteria, where the provider can document yes or no for each patient that may be suitable or unsuitable for the project. After securing provider permission, the potential subject will then be sent a packet including two letters, one non-endorsing, informative letter signed by the clinician stating that they allowed the study team to contact them, and an opt-out letter from the principal investigator describing the study and opt-out procedures if they are not interested. After the opt-out period has ended, a member of study staff will contact all subjects who have not opted out regarding study procedures.
Prospective subjects may also be identified via the Biobank portal of Partners. De-identified prospective subjects are identified via the partners Biobank portal (subject that signed a consent form for re-contact), and Biobank will re-contact the prospective subjects per the requirements of their IRB approval. The recontact letter that will be sent to patients will be co-

signed by the Biobank's PI and the bionic pancreas study's PI. The bionic pancreas flyer and advertisement will be sending to the subject as well.

The Biobank recontact service is detailed on their wiki at:
https://biobankportal.partners.org/mediawiki/index.php?title=Patient_Recontact

IV. Subject Enrollment

IV. a. Number of Subjects

It is expected that we will have up to 6 subjects complete the test run and 20 subjects complete the type 1 diabetes study with a consistent protocol. It is expected that we will have 10 subjects complete the type 2 diabetes study with a consistent protocol. We expect that the experiments can be accomplished over a period of 6-18 months. Up to 46 subjects with type 1 diabetes will be enrolled and up to 20 subjects with type 2 diabetes will be enrolled. The upper bound is based on the expectation that some volunteers will be excluded after the screening visit and the possibility that some experiments may have to be discontinued before completion (due to, for instance, intercurrent illness or subject withdrawal).

For each subject with diabetes there will be an adult who lives with them who will also be considered a participant in the study, because they will receive some training regarding treatment of hypoglycemia and will consent to be a designated contact for the study participant. Up to two individuals may share this role, but they must be willing to carefully coordinate with each other and the subject so that one of them is clearly designated as having this responsibility at any given time, both must consent, and both must complete the required training. These designated contacts are also enrolled in the study, bringing the total enrollment to 132 subjects.

We may enroll up to 10 subjects in “test runs” that may be performed before the start of the main study in each subject group (type 1 diabetes group vs. type 2 diabetes group). The test run may include up to 4 out of the 6 total arms in the type 1 diabetes group and up to all the 4 total arms in the type 2 diabetes group. These test runs may be conducted with 4 subjects at a time, and up to three test runs. The goal of these test runs is to make sure all methods, procedures, CRFs, and communication protocols are working properly, and to guide us in finalizing the set-point feature configuration and decide on the final set points. Subjects who participate in the test run are eligible to participate in the full study.

IV. b. Enrollment Procedures

Prospective participants and designated contacts will be briefed by a study staff member by phone or e-mail regarding the study procedure and the inclusion and exclusion criteria. Potential subjects and contacts will be sent an informed consent document by mail, fax, or email.

IV. c. Consent Procedures

Once potential subjects have had time to review the consent document, they will meet with a study provider in-person (MD or NP) that will explain the study, answer any questions, and administer informed consent. In the event that a volunteer is a patient of one of the study MDs

or NPs, another staff MD or NP will answer questions and administer consent. Prior to consent, their designated contact will have to meet in person or over the phone with a study provider to hear what will be required of them if the subject participates in the study. Designated contact participants must have their own telephone in order to participate-either a personal cell phone or a household phone. If an NP is administering the consent, subjects and/or their designated contacts will be offered the chance to speak with a study MD if they wish. A licensed physician investigator will be available to speak with the subjects during the consent process. There will be separate consent documents for the subject and the designated contact.

Study staff will answer any questions that the subjects and designated contacts may have during their participation. They will share any new information in a timely manner that may be relevant to the subject's willingness to continue participating in the trial. The subjects or designated contact may choose to discontinue their participation at any time. If the designated contact chooses to discontinue their participation, another contact must be available or the subject will have to discontinue their participation.

V. Study Procedures

V. a. Screening data

- Age
- Sex
- Race and ethnicity
- Date of last menstrual period in female volunteers
- Date of diabetes diagnosis
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria
- Medications (prescription and non-prescription) and date of last change in medication regimen
- Duration of insulin pump use
- Type of insulin
- Average total daily dose of insulin in the last 30 days (from pump history in type 1 diabetes subjects or subject report for MDI users) – for comparison with insulin dosing during the usual care and bionic pancreas arms of the study
- History of insulin types used (beef insulin, pork insulin, regular human insulin, NPH insulin, ultralente insulin, insulin aspart, insulin lispro, insuline glulisine, insulin detemir, insulin glargine)
- Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Height and weight
- Blood pressure
- EKG (if applicable)
- Urine HCG (pre-menopausal females)
- Hemoglobin A1c
- Fractionated plasma metanephrines (if testing is indicated by history)
- Stimulated glucose, insulin, and C-peptide 90 minutes after a mixed meal challenge not pre-treated with a bolus of insulin
- Hemoglobin (if consented to Senseonics sensor)

V. b. Drugs

The study involves subcutaneous administration of insulin lispro (Humalog, Lilly), or insulin aspart (Novolog, Novo Nordisk) Both are commercially available by prescription and are indicated for patients with diabetes, but not for use in a bionic pancreas. Subjects will be provided with and use whichever analog of rapid acting insulin they usually use during all arms of the study. If subjects use insulin glulisine as part of their usual care, they will be given either Humalog or Novolog, as insulin glulisine is not compatible with use in the t:silm pump. The study also involves subcutaneous administration of glucagon for injection (Eli Lilly) which is indicated for the treatment of severe hypoglycemia, but not for use in a bionic pancreas.

The control system can administer bolus doses of each drug up to every five minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose [30 µl] and a single meal-priming dose, which is triggered by the user, will not exceed 12 units [120 µl]. A single bolus of glucagon will not exceed 80 µg [80 µl]. The insulin pumps can administer as little as 0.5 µl (0.05 units of U-100 insulin or 0.5 µg of 1 mg/ml glucagon) in single programmable bolus doses.

It is expected that the total daily dose of glucagon will be < 1.0 mg daily as in previous studies. The mean daily glucagon dose in our previous 11 day outpatient study was 0.51 mg/day (range 0.20-0.90 mg/day). The recommended dose of glucagon for adult patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in our previous inpatient studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of subjects is expected to be modest. We expect that glucagon exposure will decrease with each increase in the glucose set-point of the bionic pancreas.

V. c. Devices

Infusion sets: Subjects will wear up to two FDA approved commercially available infusion sets, one for insulin infusion and one for glucagon infusion, when applicable. Infusion sets that are compatible with the Tandem t:slim insulin pump (leur lock connection) will be provided during all bionic pancreas arms that are similar to the infusion sets they use during usual care. If an infusion set falls off or is clinically suspected of failing, it will be replaced with a new one. The insulin infusion set will be changed at least every 48 hours; the glucagon infusion set will be changed every 24 hours.

Continuous glucose monitors: One transcutaneous glucose sensor for the DexCom G5 will be inserted in the subcutaneous tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the G5 application running on a mobile device. If the G5 sensor fails for any reason during the experiment it will be replaced promptly.

For subjects who opt to participate in the optional Senseonics sensor insertion, one transcutaneous glucose sensor for the Senseonics Continuous Glucose Monitor System will be inserted in the subcutaneous tissue of the upper arm. The sensor is approximately 3.3 mm in diameter and 15.7 mm long. It contains a ring that elutes the steroid dexamethasone and core electronics that are potted in epoxy within a poly-methylmethacrylate (PMMA) encasement. The glucose indicating copolymer, which is grafted onto the PMMA surface, is fluorescent and

changes in intensity in response to changes in glucose concentrations. That intensity data is transmitted to a battery-powered transmitter that is worn on the upper arm over the insertion site of the sensor. The transmitter is a reusable device that powers the sensor and collects information about glucose levels. It is secured over the sensor insertion site with a transmitter strap or adhesive patch. The transmitter communicates via Bluetooth Low Energy (BTLE) to a Mobile Medical Application (MMA) installed on a smartphone or other handheld device. This MMA can display glucose information and allows for calibration of the sensor. The glucose information will be blinded during this study, but subjects will use the MMA to calibrate the sensor twice a day at the same time and with the same glucose value as they calibrate the Dexcom CGM.

Bionic Pancreas Control Unit: The Beta Bionics mobile application that runs the control algorithm and the Dexcom G5 app are both installed on a stock iPhone 6s running iOS 10. The Betabionics app receives the CGM glucose values that are captured by the Dexcom G5 app.

The control algorithm app has a graphical user interface (GUI) that displays the current Dexcom CGM glucose, a graphical history of the Dexcom CGM glucose, and doses of insulin and glucagon delivered by the control algorithm. The GUI can also be used to input meal announcements, designating the size of the meal as larger than typical, typical in size, smaller than typical, or just a bite, and the type of meal as breakfast, lunch, or dinner. This will trigger a partial meal-priming bolus the size of which will adapt during the course of the trial to meet a target of 75% of the insulin needs for that size and type of meal.

The target glucose level in the bionic pancreas will be programmed by the study engineers prior to the start of each experiment. This will be locked for each arm of the study; the subject will be unable to accidentally change or tamper with this setting. Subjects will be aware of what their glucose target is each week.

The user will have the option during the bi-hormonal bionic pancreas arms to trigger the administration of a glucagon dose, intended to be used prior to device disconnection (e.g. for a shower or swimming). The size of the glucagon dose will be automatically determined by the bionic pancreas based on the subject's body mass and will be between 40 and 80 micrograms. This option will provide a means for subjects to raise their BG if they anticipate they will be at risk for hypoglycemia during a period of disconnection, based on their glucose level and glucose trend at the time.

The GUI can also be used to manage meal boluses and correction boluses during periods when the Dexcom CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated. During these times the control algorithm will determine and direct the administration of insulin basal rates either based on the subject's weight early in the course of the experiment, or on the average of adaptively determined basal rates for that time of day once sufficient experience has been accumulated (i.e. 24 hours or more) by the control algorithm. The controller will also administer insulin and/or glucagon as appropriate in response to any entered BG values, just as if they were Dexcom CGM values.

The GUI also displays local audio and visual alarms if communication is dropped between the Dexcom CGM transmitter and the bionic pancreas control unit or between the control unit and the two insulin pumps. It also displays an alarm associated with an audio signal when the Dexcom CGM glucose crosses a low (50 mg/dl) threshold. In addition, the Dexcom has it's own

hard coded alarm when the CGM glucose drops below 55 mg/dl.

The iPhone communicates wirelessly via the Bluetooth Low Energy (BTLE) protocol with up to two Tandem t:slim insulin pumps to deliver insulin and glucagon.

The bionic pancreas control unit can be used with two Tandem pumps, one for insulin and the other for glucagon, to make up the bi-hormonal bionic pancreas. It can also be used with one Tandem pump to deliver insulin, as in the insulin-only bionic pancreas arms. It can also be used on its own to record blinded Dexcom CGM data and allow remote telemetry of Dexcom CGM data. In all configurations, if communication failures between the Dexcom CGM and the bionic pancreas or the bionic pancreas and the cloud are not resolved within 20 minutes they trigger alerts to study staff who will then make contact with the wearer according to study protocol. If communication failure between the bionic pancreas and pumps is not resolved within 20 minutes this triggers and alert to study staff who will make contact with the wearer. Also in both configurations, if the Dexcom CGM glucose drops below 50 mg/dl and the user does not enter a BG into the bionic pancreas GUI within 15 minutes, this will trigger an alert to study staff, who will then make contact with the wearer according to the study protocol.

Tandem t:slim Pumps: These pumps are FDA approved insulin pumps with reservoirs capable of holding 300 units (3 ml) of insulin or 3 ml of a glucagon solution. The pumps have a mechanical dosing resolution of 1/120 (0.00833) unit and can deliver liquids at a maximal rate of ~ 33 µl per minute (2 ml per hour). They are slave to the bionic pancreas control unit and are controlled wirelessly via the BTLE protocol by the iPhone 4S.

Nova Biomedical StatStrip Xpress Glucose Meter: The StatStrip Xpress glucose meter is an FDA approved glucose meter that is commercially available. Blood glucose measurements for CGM calibration will be obtained via fingerstick with the StatStrip Xpress in both study arms. This meter will be used to calibrate both the Dexcom sensor and the Senseonics sensor if applicable.

Yellow Springs Instrument (YSI) 2300 STAT PLUS: The YSI Model 2300 STAT PLUS Glucose and Lactate Analyzer is a laboratory instrument that is intended for use in clinical care. It provides quick measurements of glucose in whole blood, plasma or serum and will be used as to measure plasma glucose during the Day 5 exercise visit. This device will be stored at the Diabetes Research Center when not in use, and study staff will follow proper maintenance and quality assurance procedures.

Exercise bike: the study will utilize a stationary exercise bike (ergometer) for the Day 5 exercise visit. This bike will be stored at the Diabetes Research Center when not in use.

MetriaIH1 Activity Monitor: The MetriaIH1 is a patch that attaches to the skin and contains a 3-axis accelerometer, skin temperature sensor, and a skin galvanic response sensor. The device is a patch that is worn on the back of the left arm that requires no input from the wearer. It collects data passively every minute for 7 days. It then stores the data for 3 weeks. The data is retrieved by connecting the patch to a computer through a microUSB-USB interface. The data is analyzed using validated software to provide calorie expenditure and METS within 10% of indirect calorimetry studies, activity duration within 5% of actual time of activity directly observed, steps taken within 9% vs. Omron pedometer, lying down and sleep duration and sleep quality metrics within 10% of polysomnogram data.

V. d. Experimental Procedures and Data Collection

V. d. 1. Screening Visit

- All subjects will have a screening visit to confirm eligibility. Subjects will arrive at this visit having fasted since 10:00 PM.
- The subject will be interviewed and the case report form will be completed by study staff to establish whether the subject is eligible to continue with the screening.
- A urine pregnancy test will be performed in female volunteers. If the test is positive the volunteer will be informed of the result and the visit will be ended.
- Height, weight and blood pressure will be measured. An EKG will be performed in subjects who are either ≥50 years of age or who have had diabetes for ≥20 years.
- If the volunteer is not excluded based on historical criteria, blood pressure, EKG or urine pregnancy test, a mixed meal tolerance test (MMTT) will be performed. The volunteers will drink an amount of a liquid meal replacement product (Boost High Protein or similar equivalent to Sustical) sufficient to provide 30% of their caloric requirement (30% of 30 kcal/kg for males and 25 kcal/kg for females) or 8 fluid ounces (237 ml) providing 240 calories, whichever is less. They will be asked not to pre-bolus with insulin for the meal. Blood will be drawn 90 minutes after the meal is consumed for glucose, insulin, C-peptide, and hemoglobin A1c. Plasma fractionated metanephrines may be obtained if indicated by history.
- **Subjects with type 2 diabetes who have a history of CAD will also complete the Seattle Angina Questionnaire-7 at the time of screening to assess their risk for another cardiac event. A study provider will review the results of this questionnaire and will also remind the subjects of the risks, and possible symptoms of a cardiac event. Subjects will be instructed to report these symptoms and seek emergency medical care immediately, and that the study will be stopped.**
- Once all of the laboratory results have been returned, a study MD or NP will review the case report form to determine subject eligibility. If subjects are not eligible to continue in the study the results of abnormal tests will be reported to the subjects and to a health care provider of their choosing.
- Subjects who have been screened and are eligible can participate without having to be re-screened for a period of one year. The study staff should verbally confirm that there have been no health events that would make them ineligible if the interval between screening and participation is longer than 3 months.

V. d. 2. Randomization of Visit Order: Once the subject has been enrolled and eligibility of subjects has been established, subjects with type 1 diabetes will be randomized to one of 20 visit-order schedules that randomize the visit orders while at the same time arranging the schedule so that no more than 4 subjects are due for in-clinic sessions on any given Friday (pseudo-randomized visit order). The 110 mg/dl set-point arms will be performed after the completion of the other arms, with the insulin-only and bihormonal arms performed in random order. The 120 mg/dl insulin only set point arm will be completed after all other study arms, and will not be randomized in any way. The subjects with type 2 diabetes will be randomized to perform their visits in random order.

V. d. 3. Training Visit: A training visit will take place within approximately one week of the scheduled start of the first arm of the study. It must be attended by both the subject and their designated contact (or contacts). Subjects will be trained in the use of the Dexcom CGM, the

bionic pancreas, the t:slim pump and on study policies and procedures. The designated contact will be trained on the study policies and procedures, on how to recognize the symptoms and signs of hypoglycemia, how to test BG using a glucometer, how to treat hypoglycemia (including treating severe hypoglycemia with glucagon), and the correct procedures for contacting emergency personnel, if needed. Study staff will verify that the subjects and their designated contacts have understood the material and are competent to participate safely in the study.

V. d. 4. General Study Policies For Both Study Arms:

- Subjects will remain at all times within a geographic boundary established on the basis of 120 minutes drive time from the designated base for study personnel.
- Subjects and their designated contact will sleep at home. If the subject is sleeping at home, the designated contact (or one of the designated contacts, if two individuals are sharing the job) must also be at home.
- Subjects and their designated contact will keep a charged mobile phone on their person (or at their bedside) at all times and will answer calls from the study staff.
- Subjects will test their blood glucose with the Stat Strip Express meter before driving and treat their glucose with appropriate carbohydrates as they would do normally before driving. They will text or call the study monitor on call before they begin driving and the alert glucose threshold on the realtime data monitoring dashboard will be raised to 60 mg/dl for 1 hour. Therefore, the monitor will contact the provider on call if the Dexcom CGM glucose is <60 mg/dl rather than <50 mg/dl. If the subject is driving for more than 1 hour then they should inform the study monitor of this fact and the alert glucose threshold will be raised to 60 mg/dl for an additional hour. When a provider calls the subject regarding an event with Dexcom CGM glucose <60 mg/dl the on-call provider will inquire whether the subject is driving. If they have finished their trip and are no longer driving the provider will inform the monitor to lower the threshold back to 50 mg/dl.
- Subjects and their designated contact will not drink more than two alcoholic drinks in one hour or more than four drinks in one day. This policy is in place because excessive alcohol consumption may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, and hinder appropriate decision-making. It may also reduce the effectiveness of glucagon in preventing or treating hypoglycemia.
- Subjects and their designated contact will not use any recreational drugs or drugs of abuse, other than alcohol. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the site principal investigator.
- Subjects may not take acetaminophen during either study arm due to potential interference with CGM sensing.
- Subjects will not tamper with the bionic pancreas device in any way, including changing any settings.
- During the experiment the bionic pancreas or the Dexcom CGM will be worn by the subject or kept nearby (such as when sleeping) at all times to ensure good radio-frequency signal reception.
- Subjects will keep their bionic pancreas charged, which will require charging when sleeping and likely during one other period during the day.
- The bionic pancreas is not water resistant and therefore must be removed for showering. Subjects are urged to take appropriate precautions when they are disconnected from the

bionic pancreas, including frequent BG checks and having carbohydrate readily available. Subject may give a glucagon bolus prior to disconnecting.

- The accelerometer subjects may wear cannot be submerged in water, so they will be asked to avoid swimming.
- Subjects may not remove the bionic pancreas for more than 1 hour at a time (e.g. for bathing) and may not remove it for more than 2 hours total in any 24 hour period.
- Study subjects will keep a StatStrip Xpress glucometer easily accessible at all times in case a calibration is needed, and they will do all calibrations with this meter. They will keep a glucometer, fast-acting carbohydrates, and a glucagon emergency kit easily accessible at home in case their designated contact needs to use it.
- Any medical advice needed by the subjects during their participation, which is not directly related to BG control during the experiment, should be obtained by them in the usual manner with their primary care physician or endocrinologist.
- If subject develops an illness during the experiment, they can seek medical care as usual. As long as the subject is not hospitalized, the study can be continued. If the subject is unable to eat for a period exceeding one day, they must notify study staff so that the medical staff can assess the safety of continuing in the study.
- Subjects may participate in any activities that they wish, as long as they abide by the policies above.
- There are no restrictions of any kind on diet or exercise, although subjects should attempt to maintain similar dietary habits and exercise habits during each arm of the study. The bionic pancreas must be kept dry during exercise. We may use an accelerometer to accurately compare activity level in each arm of the study.
- Subjects are encouraged to check their BG at least four times a day, before meals and before bedtime. They will also be encouraged to check before exercise and at intervals during exercise, and for any symptoms of hypoglycemia. There are no restrictions on additional checks and subjects should check as often as they wish to maintain adequate control of glycemia and safety in the usual care arm, and to confirm the accuracy of the Dexcom CGM and for safety in the bionic pancreas arms. However, they should use the study provided glucose meter for all checks.
- Subjects who normally wear a CGM are encouraged to do so during their usual care period.
- If subjects use non-insulin injectable drugs to manage their diabetes (e.g. GLP-1 agonist drugs such as exenatide and liraglutide, or the amylin analog pramlintide), they will be encouraged to do so during the usual care period. However, they are not allowed to use them during the bionic pancreas arms of the study. They will be instructed to stop taking them at least 24 hours before their bionic pancreas periods begin.
- The 60 and 120 minute drive-time boundary maps may be found in Appendix XII. A.
- Subjects may choose to withdraw from the study at any time. If they withdraw from the study, they should contact a provider immediately. If they are wearing the bionic pancreas, a provider will help them transition to their own insulin regimen safely.
- While wearing the Senseonics sensor, subjects must abide by the following additional rules:
    - No massage therapy near the sensor placement site
    - Do not use a damaged or cracked Transmitter
    - Do not exchange a Transmitter with another person wearing a Senseonic sensor
    - Use only the provided power supply with the Transmitter
    - Do not immerse the transmitter in water, as this may result in electric shock.

Remove the transmitter before bathing or swimming.
    - Carry a Senseonic Sensor identification card
    - Remove the transmitter if the sensor feels warm and contact the study physician
    - Avoid close contact with Electromagnetic Interference (theft detectors, CB radio antennae, electric arc welding equipment, linear power amplifiers, and industrial equipment that generates high levels of electromagnetic interference)
    - Avoid the following medical therapies:
        - Lithotripsy or High-output Ultrasound
        - Diathermy
        - Electrocautery
        - Radiation therapy
        - Steroid use
        - MRI, CT or x-ray

V. d. 5. Remote Monitoring During All Study Arms

- A central monitoring station will be staffed 24 hours a day. There will be at least one provider (MD or NP) on call at all times in addition to the staff member monitoring for alarms. Additional study staff members may assist with on-call duties. A study staff member will make contact with subjects as necessary and help them troubleshoot any issues that may arise, leaving the monitor free to focus on identifying alarms and communicating them to the runners.
- The system will generate an alarm to the subject for low (<50 mg/dl) threshold Dexcom CGM glucose values. If the Dexcom CGM glucose is <50 mg/dl and the subject does not enter a blood glucose value into the bionic pancreas control unit within 15 minutes, this will generate an alarm at the central monitoring station.
- The system also generates alarms to the subject and the monitoring center if the wireless connection between the Dexcom CGM transmitter and the bionic pancreas has been lost and has not spontaneously reconnected (after 20 minutes, all study arms) or if the wireless connection between the bionic pancreas control unit and a Tandem pump has been lost and has not spontaneously reconnected within 20 minutes (bionic pancreas arms).
- When an alert for a missed alarm comes to the monitoring station, a study staff member will contact the volunteer on any of the provided phone numbers. If staff remains unable to contact the subject they will call the designated contact on any of the provided phone numbers.
- In the case of a low threshold alarm with no response from the subject and no success in locating them, the site principal investigator will be immediately informed.
- If there is a technical problem with the bionic pancreas that cannot be resolved over the phone, a member of study staff may be dispatched to the location of the subject to provide in-person assistance. The subject may be asked to come to the Diabetes Research Center or study staff may meet them in another public place. If this is not possible or would be too disruptive (i.e. in the middle of the night) the subject will be asked to take over their own glycemic control using their insulin pump until such time as a meeting can be arranged for in-person inspection of the device. This should occur in most cases within 12 hours. Staff will not go into subjects' houses or other non-public places, nor will they go to any place to meet the subject that is not public or where they do not feel safe.
- Remote monitoring for severe lows and device connectivity is only possible when the

subject has Verizon network coverage and data can be transmitted to the cloud service. There may be times when a subject enters an area where Verizon coverage is not available. We may provide subjects with WiFi boosters for their homes or WiFi hot spots to carry with them in order to improve data throughput. We may also encourage subjects to connect to public but secure wireless networks if they are having trouble connecting to cellular service.

- If we are unable to monitor a subject remotely for greater than 20 minutes, a study staff member will contact the subject to check that the bionic pancreas is functioning properly and to resolve problems with network coverage. If there are no indications of device malfunction as the cause for lost connectivity, the glucose level is in safe range, and a subject chooses to remain in an area with poor network coverage, we will instruct the subject to check the bionic pancreas display at least every 30 minutes for alert icons and to be aware that we are unable to monitor for severe lows at this time. We will call the subject every 2 hours to check on safety and device function until remote monitoring is restored. The same rules will be used for checking in when the subject in in the usual care and bionic pancreas arms.

V. d. 6. Visit Procedures

Day 0 visit: Senseonics sensor insertion

All Study Arms (optional)

- The Senseonic sensor insertion will take place 10 days before the bionic pancreas study arm is scheduled to start to allow the sensor insertion site to heal and the sensor to acclimate to the surrounding tissue.
- A urine pregnancy test will be performed in female volunteers prior to the sensor insertion. If the test is positive, the volunteer will be informed of the result, the visit will be ended and the sensor will not be inserted.
- The temperature of the subject will be documented. Study staff will ask about any recent fever or vomiting, in addition to other adverse events or changes to medications. If the subject has a temperature greater than 100.4 degrees F, or has had one in the previous 24 hours, the visit will be ended and the sensor will not be inserted.
- The subject's skin will be numbed using a local anesthetic (i.e. lidocaine without epinephrine). The study physician will make a small incision in the skin between the shoulder and the elbow using the Insertion Templates provided by Senseonics to mark in the incision site.
- Senseonics will provide sterile, one-time use tools for placing the sensor. The Blunt Dissector is used to create the subcutaneous pocket for insertion of the sensor, and has guide marks to assist in determining the correct pocket length. The Insertion Tool is used in combination with the Sensor Holder to transfer the sensor, and has guide marks on the cannula to assist in proper placement in the subcutaneous pocket. See the Investigator Brochure (Appendix B) for details on sensor insertion.
- The sensor will be inserted at least three inches away from any infusion or injection sites.
- Once the sensor is inserted, the incision will be closed using surgical tapes or a suture and a bandage. Blood loss during the procedure is expected to be minimal (between 1-3 ml)
- During this visit, subjects will be trained on how to use the Senseonics Transmitter and when to call the study physician for any issues at the sensor insertion site.

Day 1 visits:

- On arrival to the first study visit, the subject will complete the beginning questionnaires.
- The body weight of the subject will be documented.
- A urine pregnancy test will be performed in female volunteers at the start of the first arm. If the test is positive the volunteer will be informed of the result and the visit will be ended. The date of the last menstrual period will also be documented, along with usual cycle length, for female subjects.
- Study staff may place an accelerometer on the subject's left arm to collect activity data during each week.
- The subjects will place a Dexcom G5 sensor and study staff will confirm they are doing it properly.
- Study staff will provide supplies and review the study procedures again. For all bionic pancreas arms, study staff will supervise the setup of the insulin and/or glucagon pumps and infusion sets.
- The control algorithm will be initialized only with the subject's weight. Diagnostics will be performed to ensure that the Dexcom CGM device is appropriately calibrated and that all of the components of the bionic pancreas (Dexcom G5, iPhone running the control algorithm, infusion pump(s) if applicable) are in good communication with each other.
- Study staff will assess the Senseonic sensor insertion site and will assist with calibrating the Senseonics sensor if applicable.
- In the bionic pancreas arms, the subject's own insulin infusion pump (if applicable) will be stopped and disconnected, and its infusion set will be removed. Subjects with type 2 diabetes in the bionic pancreas arm will take no further insulin injections after the bionic pancreas session is started.
- The staff will start the bionic pancreas as close as possible to a minute divisible by 5 minutes (i.e. on a 5-minute mark) and before 6:00 PM. Study staff will verify that data streaming is working prior to the subject leaving the Diabetes Research Center.
- Subjects with type 2 diabetes will follow a slightly different visit schedule. Their study periods will be seven days long, allowing two days of washout of long acting insulin prior to the 5 days of analysis.

During the Outpatient Study:

All Study Arms

- The subjects will calibrate the G5 Sensor and the Senseonics sensor if applicable twice daily, at the same time and preferably using the same glucose value from the StatStip Xpress meter, preferably before breakfast and supper, using the StatStrip Xpress.
    - Subjects will be advised to delay calibration if there is a steep rise or fall in the blood glucose (>2 mg/dl/min), or if they suspect a steep rise or fall while in blinded mode, there has been carbohydrate intake in the last 30 minutes, or there has been a glucagon dose in the last 15 minutes. In the immediate aftermath of carbohydrate intake or glucagon dosing it is possible for the BG to be rising without a change in interstitial fluid glucose. If a calibration is delayed for any of these reasons, it will be performed at the next opportunity.
    - Subjects may perform additional calibrations if the Dexcom CGM is inaccurate relative to a BG measurement as long as they do not calibrate within 30 minutes of food intake or 15 minutes of glucagon dosing. Subjects will be discouraged from performing extra calibrations if the Dexcom CGM is within 15 mg/dl when the BG is ≤ 75 mg/dl and within 20% if the BG is >75 mg/dl at times when the rate of change is low. They will also be trained to understand that the apparent error

can be higher than this when the BG is changing rapidly, and that it is typical for the Dexcom CGM to underestimate BG when the trend is upward and to overestimate BG when the trend is downward as a result of physiologic lag. Errors in these directions should typically not prompt extra calibrations unless they are very large (≥ 50%).
    - Subjects will be instructed to calibrate the Senseonics sensor if applicable every time they calibrate the Dexcom G5 sensor using the same blood glucose from the StatStrip Xpress meter.
- The Senseonics sensor will be blinded to the subjects and study staff in all study arms until the bionic pancreas study arm is complete. Study staff will download the transmitter at the end of each of the study arms.
- Subjects will be able to tell whether BG data is streaming based on an onscreen indicator and the subject will be contacted if streaming is interrupted for more than 20 minutes. If the sensor has been lost, it will be replaced promptly. If there is a technical fault that is preventing streaming or connection of the pumps, study staff will troubleshoot this with the subject. If necessary, a staff member will meet the subject to assist with troubleshooting. This meeting may be delayed until morning if the problem occurs overnight. If necessary, the bionic pancreas control unit may be replaced.
    - When meeting subjects in an off-site location, the principal investigator will always be notified. A member of the clinical team (MD, NP or RN) will be dispatched if the problem is clinical in nature. If the principal investigator determines the problem to be purely technical, a trained engineer will be dispatched to assist the subject with troubleshooting their device.
- If the subject cannot be reached at night, then the designated contact will be called and asked to wake the subject so that troubleshooting can be performed.
- Alarms will sound and a visual alert will appear on the iPhone screen of the bionic pancreas control unit if the Dexcom CGM glucose is less than 50 mg/dl. Subjects will test their BG and enter the results into the bionic pancreas in response to such an alarm. If they do not enter a BG within 15 minutes of such an alarm, this will trigger an alert to the central monitoring station and the subject will be called. In the case of a low alarm with no response from the subject and no success in locating them, the site principle investigator will be immediately informed.
- Subjects will be trained on troubleshooting for various scenarios that could lead to a low threshold alarms. For instance, a threshold alarm could be due to true hypoglycemia, poor Dexcom CGM calibration, or a compression artifact at the site of the sensor.
    - The first step for all low glucose-related alarms will be to perform a fingerstick BG measurement.
    - If the BG measurement is not consistent with the fact that a threshold alarm has occurred: the subject will assess the possibility of a compression artifact (they will be trained in the causes and recognition of these events). If a compression artifact is suspected, they will take steps to relieve the pressure on the transmitter. If compression is not suspected, they will calibrate the Dexcom CGM as long as there has been no food or carbohydrate intake in the last 30 minutes. If a calibration is delayed for this reason, it will be performed at the next opportunity.
    - If the BG measurement is consistent with a low threshold alarm: the subject will treat hypoglycemia with carbohydrate ingestion according to their usual practice.

- Subjects will be asked to change their insulin infusion set and reservoir at least every two days during every arm in the study.
- Subjects will remove the Senseonics transmitter before bathing or swimming, and will replace the adhesive patch used to secure it daily.
- Subjects will be asked to report all hypoglycemia, carbohydrate interventions, any nausea and/or vomiting, any other adverse events, time spent exercising, and any unscheduled infusion set changes, alcohol use, and other questions through a daily email survey. Subjects will also be asked to report any irritation at the Senseonics sensor insertion site.

Usual Care Arm

- In the usual care arm, subjects will continue to manage their own BG according to their usual practice. If they routinely use a CGM, they will be encouraged to continue to use it during the usual care period.
  Subjects will be trained in the appropriate use of the CGM, but advised not to make any changes to their diabetes care, activity level or diet during this study based on CGM readings. Subjects will be trained to respond to hypoglycemia and hyperglycemia according to their usual practice and best practice recommendations.
- Subjects with type 2 diabetes using multiple daily injections will keep a log in which they record all insulin doses and they will be asked for this information as a part of the daily email survey.

Bionic Pancreas Study Arms (bi-hormonal and insulin only):

- Subjects will be able to tell whether BG data is streaming based on the bionic pancreas display and subjects will be contacted if Dexcom CGM streaming or the Bluetooth connection to the pump(s) is interrupted for more than 20 minutes. If the Dexcom sensor has been lost, it will be replaced. If there is a technical fault that is preventing streaming or connection of the pumps, the monitor will troubleshoot this with the subject. If necessary, a staff member will meet the subject to assist with troubleshooting. This meeting may be delayed until morning if the problem occurs overnight - in this case, the subject will use their own pump until a meeting is possible. If necessary, the bionic pancreas device may be replaced.
- Subjects will be trained on troubleshooting for various scenarios that could lead to hyperglycemia. For instance, hyperglycemia could be due to true hyperglycemia or poor Dexcom CGM calibration.
  - The first step in responding to hyperglycemia according to the CGM will be to perform a fingerstick BG measurement.
  - If the BG measurement is not consistent with the CGMG: the subject will calibrate the Dexcom CGM as long as there has been no carbohydrate intake in the last 30 minutes and there is no steep rise or fall in glucose (>2 mg/dl/min). If a calibration is delayed for this reason, it will be performed at the next opportunity.
  - If the BG measurement is consistent with the CGMG: the subject will investigate their insulin infusion site and consider replacing it.
- If there is a complete failure of bionic pancreas operation and it is anticipated that restarting it will take more than an hour, subjects may take over their own BG control using their own insulin pump or with insulin injections until the bionic pancreas can be brought back online with the help of study staff. During the day, this should be rare. If the failure occurs at night, every effort should be made to correct the problem as soon as possible, which should almost always be possible within 12 hours.
- If a Dexcom CGM sensor fails during the course of an experiment the system will provide

basal insulin based on past requirements and will allow announcement of meals and entry of fingerstick BG measurements, which will be treated as Dexcom CGM data and may result in administration of insulin and/or glucagon. The Dexcom CGM sensor will be replaced as soon as possible and normal bionic pancreas control will resume when the new sensor is calibrated.

- Subjects will be asked to announce the three major meals of the day, but not snacks, to the bionic pancreas. The meal announcement will consist of choosing the type of meal (breakfast, lunch, dinner) and the size of the meal relative to typical meals for that subject (snack, smaller than typical, typical, larger than typical).
- The glucagon reservoir will be replaced every day during bi-hormonal arms. Each reservoir will be filled with two vials of freshly reconstituted Lilly glucagon. The glucagon infusion set will be changed daily with the reservoir change. We have received an IND exemption from the FDA for use of glucagon in this application for up to 27 hours.
- During the 130 and 110 mg/dl bi-hormonal and insulin only set point arms, the glucagon used will be double-blinded. Subjects and study staff will know that their glucose set point is 130 or 110 mg/dl, but will not be told whether they are receiving glucagon or placebo that week.
    - The blinding of this arm has been agreed with the FDA CDER. The rationale is that these two arms will continue to the in-clinic exercise study designed to evaluate the incremental benefit of glucagon in a setting with reference plasma glucose values used to determine the outcome (hypoglycemia).
    - We will use custom built vial blinding devices. For the bi-hormonal arm the vial blinding devices will contain vials of Eli Lilly glucagon (lyophilized) and the subjects will inject the Eli Lilly diluent to reconstitute the glucagon. For the insulin only the blinding device will contain an empty sterile vile and the subjects will inject the Eli Lilly diluent.
    - The clinical research pharmacy at MGH will blind the vials and maintain documentation of this until it is released to the investigators for analysis.
    - We have already completed a study using this blinding strategy and found that subjects were able to use the blinding devices effectively and there were no unusual infusion site reactions in this trial, demonstrating that infusion of the diluent is benign, as expected.
    - At the end of these two arms, subjects will continue to wear the bionic pancreas through day 4 and will not come in for the scheduled day 4 visit. Instead, they will come in for a day 5 exercise visit, described below.

Bi-hormonal Bionic Pancreas Arms Only

- On days when both the insulin and glucagon reservoirs will be changed, subjects will be asked to change them at different times in the day, separated by at least one hour. They will label the infusion sets and tubing with supplied labels to avoid confusion or cross connection.
- When investigating suspected or persistent hypoglycemia, subjects will also be trained to investigate the glucagon infusion set and consider replacing it.

End of each arm:

- This visit is only for subjects in the usual care arm, 100 mg/dl, 115 mg/dl, 120 mg/dl and 145 mg/dl set point arms.
- At the end of the 4 or 6 day period they will return the bionic pancreas and answer the final questionnaires for the study arm.
- Glucose meters, personal CGM if applicable and the insulin pump in the usual care arm

will be downloaded. The Dexcom G5 transmitter will be cleaned using the validated cleaning and disinfecting procedures after each use.

- The Senseonics transmitter will be downloaded, if applicable
- The accelerometer will be collected and downloaded, if applicable.
- A provider (MD or NP) will review the last several hours of insulin and or glucagon dosing for subjects in the bionic pancreas arms and assist the subject in resuming their usual care. For subjects with type 1 diabetes and subject with type 2 diabetes using a pump, this will involve restarting the basal rate of the pump. For subjects with type 2 diabetes using multiple daily injections, this will typically involve resuming their normal injection regimen at the next scheduled injection time after the end of the bionic pancreas session, although a study provider will review with them when this will occur and will provide recommendations if some treatment at the time of disconnection from the bionic pancreas (e.g. an injection of basal or rapid-acting insulin to provide coverage until the next scheduled injection) is warranted
- If all study arms are completed, the Senseonics sensor will be removed. The senseonic sensor will never be worn by a subject for more than 90 days. This procedure is similar to the sensor insertion. The skin near the sensor is numbed using a local anesthetic, a small incision is made in the skin using the Removal Template provided by the sponsor, and the sensor is removed. The incision will be closed using surgical tape or a suture, and covered with a bandage.

Type 2 Diabetes End of each arm:

- At the end of the 7-day study period, subjects will return to the DRC and answer the post questionnaires for the study arm.
- The body weight of the subject will be documented.
- The bionic pancreas, glucose meters, personal CGM if applicable, and the insulin pump in the usual care arm will be downloaded. The Dexcom G5 transmitter will be cleaned using the validated cleaning and disinfecting procedures after each use.
- A new Dexcom sensor will be placed and calibrated.
- The memory of the bionic pancreas will be wiped and it will be re-initialized with the subject's current weight. Diagnostics will be performed to ensure that the Dexcom CGM device is appropriately calibrated and that all of the components of the bionic pancreas are in good communication with each other.
- Study staff will provide supplies and review the study procedures.
- For all bionic pancreas arms, study staff will supervise the setup of the insulin pump and infusion set.
- If the participant is switching from usual care to bionic pancreas, the subject's own insulin will be stopped. A study provider will review the subject's insulin regimen and assist them in transitioning.
- If the participant is switching from bionic pancreas to usual care, a provider (MD or NP) will review the last several hours of insulin and/or glucagon dosing for subjects in the bionic pancreas arms and assist the subject in resuming their usual care.
- The staff will start the bionic pancreas as close as possible to a minute divisible by 5 minutes (i.e. on a 5-minute mark). Study staff will verify that data streaming is working prior to the subject leaving the Diabetes Research Center.

Type 2 Diabetes End of Study Visit:

- At the end of the 7 day period, subjects will return to the clinic and answer the post questionnaires for the study arm. Subjects with type 2 diabetes with a history of CAD will complete the Seattle Angina Questionnaire-7 at the end of the study, and a study

provider will review their results and any changes from baseline. Subjects will be instructed to contact their medical team and study staff if they have any cardiac events after the study is completed.

- The body weight of the subject will be documented
- The bionic pancreas, glucose meters, personal CGM if applicable, and the insulin pump in the usual care arm will be downloaded. The Senseonics transmitter will be downloaded. The Dexcom G5 transmitter will be cleaned using the validated cleaning and disinfecting procedures after each use.
- The Dexcom CGM and all bionic pancreas infusion sites will be removed.
- A provider (MD or NP) will review the last several hours of insulin dosing for subjects in the bionic pancreas arms and assist the subject in resuming their usual care.

Day 5 Exercise Visit:

- Subjects in the 130 and 110 mg/dl bi-hormonal and insulin only bionic pancreas arms will continue to wear their bionic pancreas and not attend the scheduled day 4 visit. These subjects will come in to the Diabetes Research Center on Friday morning, day 5, having fasted since 10:00 PM the night before. We will ask subjects to avoid certain skin care products that will interfere with sweat sample collection on the day of the visit.
- They will answer the final questionnaires for the study arm.
- Their glucose meters will be downloaded.
- The Senseonics transmitter will be downloaded.
- The body weight of the subject will be documented.
- A 20 gauge or smaller peripheral I.V. will be placed.
- Subjects will exercise on a stationary bike with a heart rate from 120-140 beats per minute (bpm) for a total of 4,000 heart beats (approximately 30 minutes). Subjects will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.
- BG measurements using the YSI will be obtained off of the IV line every 10 minutes. If the BG is < 80 mg/dl, BG measurements will be obtained off of the IV line every 5 minutes.
    - Carbohydrates will be given for any BG < 50 mg/dl according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15g
    - Repeat treatments will be given at 15 minute intervals as long as BG remains < 50 mg/dl.
- Study staff will collect samples of sweat from the subject's underarm and will ask subjects to exhale into a breath collection device at the beginning of, at intervals during and at the completion of exercise, with increased frequency during any episodes of hypoglycemia. These samples will be collected, de-identified and shipped out to collaborators at the MITRE Corporation (an non-profit research corporation) for analysis of the relationship between volatile organic compounds in breath and sweat and hypoglycemia. BG monitoring off of the IV line will continue for 2 hours after the exercise is completed. After the exercise is complete, if the BG is > 120 mg/dl then the interval between BG measurements using the YSI may be increased to 20 minutes.
- Once the 2 hours post-exercise are complete and the subjects blood glucose is stable, they will be discharged off of the bionic pancreas and will resume their usual care, following the typical Day 4 protocol.
- If all study arms are completed, the Senseonics sensor will be removed. The senseonic sensor will never be worn by a subject for more than 90 days. This procedure is similar

to the sensor insertion. The skin near the sensor is numbed using a local anesthetic, a small incision is made in the skin using the Removal Template provided by the sponsor, and the sensor is removed. The incision will be closed using surgical tape or a suture, and covered with a bandage.

Final visit: Senseonic sensor site assessment
All Study Arms (optional)

- 10 days after the Senseonic sensor has been removed, the subject will return to the Diabetes Research Center. Study staff will assess the sensor insertion site for proper healing and any signs of infection or other adverse events.
- This visit will be repeated every 10 days if any complications are noted at the sensor insertion site until the study physician determines the site is properly healed.
- These follow up visits are mandatory for every subject that participates in the Senseonics sensor portion of the study.

V. d. 7. Test Run

We may perform “test runs”, consisting of up to 10 subjects and up to 4 arms. The test runs may include 4 subjects at a time, for up to three total test runs. Data from these test runs will be excluded in the final analysis, but used for guiding the investigators in finalizing the set point configurations for the study. Once finalized, the exact same experimental protocol and conditions will be applied to the cohorts of 20 subjects (type 1 diabetes) and 10 subjects (type 2 diabetes).

V. d. 8. Response to Hypoglycemia

- Subjects in all study arms are encouraged to check their BG for any symptoms of hypoglycemia.
- Subjects are encouraged to treat hypoglycemia according their usual practice or according to the rule of 15s: take 15 grams of rapid acting carbohydrate and recheck in 15 minutes, then repeat as needed.
- During bi-hormonal bionic pancreas arms, subjects will be instructed to check their glucagon infusion site and their bionic pancreas for normal operation any time hypoglycemia occurs. If there is any suspicion of glucagon infusion set malfunction, the site should be replaced.
- The designated contact will be trained in the signs and symptoms of hypoglycemia and the protocols for treating it. They will also be trained in the use of the glucagon rescue kit. If they should find the subject unresponsive they are to use the glucagon rescue kit and call 911.
- If a subject experiences a seizure or unconsciousness associated with hypoglycemia in a bionic pancreas arm, his or her participation in the study will be discontinued. If a subject experiences a seizure or unconsciousness associated with hypoglycemia in the usual care arm, the PI will make a determination regarding whether it will be safe to allow them to continue in the study.
- If a subject has > 5% of the time < 60 mg/dl on days 2-3 of any bionic pancreas arm of the study (either insulin-only or bi-hormonal) they will not participate in any further arms of the study with that configuration (insulin-only or bi-hormonal) at a lower set-point. In other words, if a subject has > 5% of the time < 60 mg/dl on days 2-3 of the insulin-only arm with a target of 145 mg/dl they will not participate in the insulin-only 130 mg/dl set-

point arm. We do not anticipate the need for any discontinuation in the bi-hormonal arms because all of our previous studies have been done with the lowest set-point to be tested in this study, and no subject had time < 60 mg/dl of ≥ 5%. There were subjects in the usual care arms of previous studies that did have time < 60 mg/dl of ≥ 5%.

V. d. 9. Response to Hyperglycemia

- Subjects will be instructed to check their insulin infusion site and their pump or bionic pancreas for normal operation any time BG is greater than 300 mg/dl. If there is any suspicion of insulin infusion set malfunction, the site should be replaced.
- Subjects may contact a study provider (MD or NP) for advice at any time, and may contact the troubleshooting support team, as they wish. During the bionic pancreas arms they will be assisted in checking the bionic pancreas for any malfunction and correcting and problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the bionic pancreas system, an entirely new backup bionic pancreas system may be brought to the subject's location by study staff.
- If a subject experiences diabetic ketoacidosis requiring hospitalization during a bionic pancreas arm of the study, his or her participation in the study will be discontinued. If a subject experiences a diabetic ketoacidosis requiring hospitalization in the usual care arm, the PI will make a determination regarding whether it will be safe to allow them to continue in the study.

V. d. 10. Response to Nausea/Vomiting

If significant nausea, nausea that prevents the subject from eating normally, or any vomiting occurs during either arm of the study subjects will be encouraged to contact a study provider (MD or NP). They will document the report of nausea or vomiting. If this occurs during the bi-hormonal bionic pancreas arms, they may assist the subject in troubleshooting, such as checking the BG and the calibration of the Dexcom CGM (excessive glucagon dosing may occur if the Dexcom CGM is reading lower than the true BG). If a subject experiences persistent nausea and vomiting thought to be related to glucagon dosing, his or her participation in the study will be discontinued.

V. d 11. Response to Other Medical Needs

If the subject experiences any non-emergent medical concerns outside the scope of diabetes care, he or she will see their personal physician. If the subject experiences urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they should visit a walk-in clinic or emergency room, or if necessary call 911.

V. d. 12. Monitoring of Bionic Pancreas Performance

Collaborators (and bionic pancreas inventors and developers) Edward Damiano, Firas El-Khatib and/or an engineer trained by them will be readily available by phone for consultation at all times during the course of each experiment They will have the capability of viewing diagnostic information regarding the connection of the Dexcom CGM with the bionic pancreas,

the functioning of the bionic pancreas, and the connection of the bionic pancreas with the insulin and glucagon pumps remotely during the experiment, in order to monitor and assist in any needed troubleshooting. The connection will be secure and password protected, and will be set up so that only viewing of the screen is possible - no input or changes to the controller can be made remotely. For privacy reasons, no audio or video connection will be made to the iPhone.

V. d. 13. Supervision by Study Staff

A study provider (MD or NP) will be on call at all times during the course of each experiment. All trained staff will have the capability of remotely viewing diagnostic information to facilitate phone troubleshooting with subjects and decide about whether additional assistance is needed.

VI. Biostatistical Analysis

VI. a. Data Collected

VI. a. 1. Prior to start of experiment:

- Age
- Sex
- Race and ethnicity
- Date of last menstrual period in female subjects
- Date of diabetes diagnosis
- Type of diabetes (type 1 vs. type 2)
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria
- Medications (prescription and non-prescription) and date of last change in medication regimen
- Duration of insulin pump use (if applicable)
- Type of insulin used in pump (if applicable)
- Insulin regimen (basal rate for pump users, NPH, Lantus or Levemir doses for MDI users, sensitivity factor, and carbohydrate ratio)
- Average total daily dose of insulin in the last 30 days as available
- Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Height and weight
- Blood pressure
- EKG if applicable
- Hemoglobin A1c
- Urine HCG (pre-menopausal females)
- Fractionated plasma metanephrines (if indicated by history)
- Stimulated glucose, insulin, and C-peptide 90 minutes after a mixed meal challenge not pre-treated with a bolus of insulin
- Hemoglobin (if wearing Senseonics)

VI. a. 2. During Both the Usual Care and Bionic Pancreas Arms:

- CGMG (CGM glucose) every five minutes from the DexCom CGM and Senseonics CGM
- All fingerstick BG measurements taken by the subject (meter download)

- Information collected from the daily email survey and phone calls including hypoglycemia, carbohydrate interventions, any nausea and/or vomiting, diarrhea, any local skin reactions at infusion sites, and other rash, any other adverse events, time spent exercising each day, exercise intensity, and exercise exposure (time X intensity), any unscheduled infusion set changes or Dexcom CGM sensor changes, and alcohol intake.
- Insulin total daily dose (from the bionic pancreas, insulin pump download, or a log of insulin dosing for subjects with type 2 diabetes using multiple daily injections)
- Glucagon total daily dose (in the bi-hormonal bionic pancreas arms)
- Timing of meal announcements and size of meals announced (in the bionic pancreas arms)
- Timing and doses of glucagon boluses
- Data from a questionnaire about attitudes and expectations regarding the bionic pancreas on the first day and the last day of each arm.
- Time subjects were not under bionic pancreas control during the bionic pancreas arms
- Time without Dexcom CGM monitoring data during the usual care arm
- List of technical faults associated with the bionic pancreas including cause and resolution
- Date of last menstrual period
- MetriaIH1 download at the end of each study arm if applicable

VI. a. 3. During the Day 5 Exercise Visit:

- Plasma BG measurements every 10 minutes, every 5 minutes when BG < 80 mg/dl, or every 20 minutes when exercise is complete and BG > 120 mg/dl
- Time from start of exercise to first glucose measurement < 60 mg/dl
- Grams of oral carbohydrates given to the subject to treat hypoglycemia
- Timing of exercise and duration
- Volunteer reported Borg scale score for exercise intensity every 5 minutes during exercise
- Heart rate during exercise from Polar heart rate monitor every 5 minutes

VI. b. Study Endpoints

VI. b. 1. Primary endpoint analyses

Outpatient Study – Type 1

Both of these metrics will be generated from the DexCom CGM data during the bionic pancreas and usual care arms:

- Mean CGMG during days 2 and 3 of each arm
- Fraction of time spent with CGMG < 60 mg/dl during days 2 and 3 of each arm or days

In-clinic Exercise Study – Type 1

- Number of subjects discordant for reaching a BG < 60 mg/dl (measured with YSI) for > 2 consecutive plasma glucose measurements

Outpatient Study – Type 2

Both of these metrics will be generated from the DexCom CGM data during the bionic pancreas and usual care arms and will only be analyzed over the last 5 days, allowing for the extended washout of long acting insulin over the first two days.

- Mean CGMG
- Fraction of time spent with CGMG < 54 mg/dl

VI. b. 2. Secondary endpoint analyses – Type 1 and Type 2 Diabetes:

- All of following metrics will be generated from the DexCom CGM data during the bionic pancreas and usual care arms. Each of these measures will be calculated for the entire period and separately for the daytime and nighttime, for day 1, each individual day, and the duration of the study arm after the washout (days 2-3 in type 1 diabetes, or days 3-7 in type 2 diabetes)
    - Mean Dexcom CGMG
    - Fraction of time spent within each of the following glucose ranges:
        - < 50 mg/dl
        - < 60 mg/dl
        - < 70 mg/dl
        - 70-120 mg/dl
        - 70-180 mg/dl
        - >180 mg/dl
        - >250 mg/dl
    - Percentage of subjects with mean Dexcom CGMG < 154 mg/dl (estimated average glucose corresponding to an A1c of 7%)

In-Clinic Exercise Study:

- Area between the glucose curve and 60 mg/dl calculated from BG measurements
- Area between the glucose curve and 60 mg/dl calculated from Dexcom CGM data
- Time from start of exercise to first BG measurement < 60 mg/dl
- Time from start of exercise to first Dexcom CGM measurement < 60 mg/dl

In-Clinic Exercise Study:

- Grams of oral carbohydrates given to the subject to treat hypoglycemia
- Total glucagon dosing by bi-hormonal bionic pancreas from the start of exercise until the end of the visit

VI. b. 3. Secondary endpoint analyses – Monitoring for possible adverse events

- Episodes of nausea and nausea index (sum of number of episodes times severity from VAS) on day 1, days 2-3 or days 5-6, and each individual day 2-3 or days 5-6.

VI. b. 4. Other outcomes

- Correlation between the bionic pancreas target and the mean Dexcom CGM glucose
- Correlation between the bionic pancreas target and time < 60 mg/dl
- Number of hypoglycemic event (< 70 mg/dl, < 60 mg/dl, <50 mg/dl); a series of hypoglycemic measurements is defined as a single event until there is a break of ≥ 30 minutes between measurements below the defined threshold)
- CGM Reliability index, calculated as percent of possible values actually recorded by CGM (for both Dexcom and Senseonics CGMs)
- Correlation between mean Dexcom CGMG and mean number of meal announcements per day

- Mean Dexcom CGM glucose at the time of user initiated glucagon doses
- CGM MARD from Dexcom G4 CGM versus time-stamped BG values from meter downloads (any other BG values will not be considered)
- CGM MARD from Senseonics CGM versus time-stamped BG values from meter downloads

BG

- All of following metrics will be generated from any fingerstick data available (downloaded from the subjects meter) during the bionic pancreas and usual care arms.
    - Mean number of daily BG measurements
    - Number of hypoglycemic events as determined from all BG measurements (hypoglycemia defined as < 70 mg/dl < 60 mg/dl, and < 50 mg/dl; a series of hypoglycemic measurements is defined as a single event until there is a break of ≥ 30 minutes between hypoglycemic measurements)

Non-glycemic

- Fraction of days that CGM was used by participants as part of their usual care
- Number of severe hypoglycemic events (subject unable to self-treat, requiring the assistance of another person)
- All of following metrics will be generated during the bionic pancreas and usual care arms. Each of these measures will be calculated for the entire period and, as appropriate, separately for the daytime and nighttime (based on self-reported sleep time and wake times self-reported on daily questionnaire), for day 1, days 2-3 or 5-6, and each individual day 2-3 or 5-6.
    - Glucagon total daily dose in bi-hormonal bionic pancreas arm (TDD)
    - Insulin total daily dose (TDD)
    - Correlation between bionic pancreas target and mean insulin dosing by the bionic pancreas (TDD)
    - Correlation between bionic pancreas target and mean glucagon dosing by the bionic pancreas (TDD)
    - Number of episodes of symptomatic hypoglycemia (reported daily by subjects)
    - Number of reported carbohydrate interventions for hypoglycemia (reported daily by subjects)
    - Total grams of carbohydrate taken for hypoglycemia (reported daily by subjects)
    - Fraction of time bionic pancreas off-line or not functioning properly (e.g. due to system crash, communication problem between Dexcom CGM and bionic pancreas, communication problem between bionic pancreas and pumps, pump malfunction)
    - METS, calories expended, steps, time in different exercise zones (mild, moderate, vigorous), time sedentary, time lying down, sleep efficiency.
    - Correlation between periods of exercise and hypoglcemia
    - Correlation between nighttime hypoglycemia, nighttime mean glucose, nighttime time in glucose ranges, and nighttime glycemic variability, and sleep efficiency.
- Fraction of subjects using a GLP-1 agonist during usual care
- Fraction of subjects using pramlintide during usual care
- Fraction of subjects with type 2 diabetes using metformin during the study
- All of following metrics will be generated during the bionic pancreas and usual care arms. Each of these measures will be calculated for the entire period and, as appropriate,

separately for the daytime and nighttime (based on self-reported sleep time and wake times self-reported on daily questionnaire), for day 1, days 2-3 or 5-6, and each individual day 2-3 or 5-6.
    - Number of user initiated glucagon doses
    - Fraction of user initiated glucagon doses followed within 15 minutes by a period of Dexcom CGM connection loss (i.e. when the feature was used as intended)
    - Correlation between the number of user initiated glucagon doses and number of reported carbohydrate interventions for hypoglycemia
    - Correlation between the number of user initiated glucagon doses and total grams of carbohydrate taken for hypoglycemia (reported daily by subjects)
    - Mean daily basal insulin dose
    - Mean daily bolus insulin dose
    - Correlation between number of user initiated glucagon doses and insulin dosing by the bionic pancreas (TDD)
    - Correlation between number of user initiated glucagon doses and overall glucagon dosing by the bionic pancreas (TDD)
- Fraction of time bionic pancreas disconnected by the subject for bathing or swimming (self-report on daily questionnaire)
- Number of unscheduled infusion set replacements
- Number of unscheduled Dexcom CGM sensor changes
- Time without Dexcom CGM monitoring data during the usual care arm
- List of technical faults associated with the bionic pancreas including cause and resolution
- Alcohol intake (mean drinks per day)
- Relative risk of hypoglycemia in periods following alcohol intake vs. the matched periods on days without alcohol intake (period starts with first drink and extends two hours after last drink – if a new drink is consumed before the end of the 2-hour period the period is extended until 2 hours after the last drink)
- Relative risk of hypoglycemia on nights following days with alcohol intake vs. nights following days without alcohol intake
- Correlation between mean alcohol intake and risk of hypoglycemia per subject
- Exercise duration
- Exercise exposure (duration X intensity)
- Relative risk of hypoglycemia in the nights following bouts of exercise vs. nights without exercise in the preceding day.
- Correlation between exercise exposure and risk of hypoglycemia
- Complications at Senseonic sensor insertion site including but not limited to infection, bruising, swelling, excessive bleeding, poor wound healing, prolonged pain or discomfort, nerve damage, skin irritation, redness, discoloration or erosion, device migration, allergic reaction to device components, difficulty in removing the device or other adverse events.
- Number of Senseonic device failures, requiring premature removal of the sensor
- Systemic reactions to the Senseonic sensor including but not limited to infection, allergic reaction, and other systemic adverse events.

The primary analysis of the designated endpoints will be calculated on an intention-to-treat basis, including data from periods when the bionic pancreas was not in use, if available (Dexcom CGM data may not be available in some failure modes). In cases where an arm was not completed we will use the available data from that arm in the data analysis. We will only

include arms that were started by the subject. We will also perform secondary, exploratory analyses excluding bionic pancreas down-time, since this may better represent the performance possible with a fully integrated system. We will calculate percentages, means, standard deviations, and ranges in descriptive analyses. We will use paired t-test for comparison of means. In a secondary analysis we will look for any period effect and any interaction between treatment and period, although no such interaction is predicted and there is probably insufficient power to identify a small interaction. We may, in exploratory analyses, also stratify subjects for secondary analyses of the pre-specified endpoints by the following characteristics: sex, age, usual care insulin total daily dose, body mass index, phase of menstrual cycle (follicular vs. luteal), baseline A1c, and use of CGM in usual care.

The purpose of the test run is only to test the operating procedures of the study, so this data will not be reported as part of the final dataset.

VI. c. Power Analysis

Outpatient Glycemic Control

We do not have data that allows us to predict with confidence the differences we expect to see in mean glucose and time < 60 mg/dl with different set-points. However, we do have some data on what to expect with regard to mean glucose in subjects with type 1 diabetes. In a previous inpatient study lasting 2 days we compared the mean glucose when we compared announcing all meals so that adaptive meal-priming boluses (AMB) were delivered vs. no meal announcements (NMB). In that study there were 6 adult and 6 adolescent subjects in each group and the age groups were analyzed separately (n=12 for each age-group). In the adult group, the difference in mean glucose was 14 mg/dl ($p = 0.03$) and in adolescents the difference in mean glucose was 13 mg/dl ($p = 0.01$). Therefore, we were able to see statistically significant differences with a nominal mean difference similar to what might be expected with shift of the set-point by 15 mg/dl, which is the increment between set-points in the proposed study. Notably, the previous study used a parallel design, and we would expect higher power if each subject served as their own control, as they do in the current study. In the present study 20 subjects will participate instead of the 12 subjects studied in the previous trial. Therefore, we anticipate more than sufficient power to detect differences in the mean glucose between the set-points.

With regard to hypoglycemia, if we assume that the mean hypoglycemia rate in the lowest set-point arm (100 mg/dl) is 1.8% with SD=1.5% (consistent with past experience at this set-point) and the mean hypoglycemia rate in a higher target arm (either 115 mg/dl or 130 mg/dl) is 0.9% with SD=0.75 (~50% reduction), and then calculate the statistical power of detecting a difference in mean hypoglycemia rate using one-sided paired t-test with 5% type 1 error we get the following power for n = 20 (assuming a range of within-subject correlation coefficients):

Correlation coefficient	Power
0.1	78%
0.2	81%
0.3	84%
0.4	88%
0.5	91%

Based on previous datasets 0.2-0.3 is a reasonable and conservative assumption for the correlation coefficient, so we have at least 80% power to detect a difference in hypoglycemia between arms in the current design.

We do not have preliminary data in subjects with type 2 diabetes upon which to base a power calculation. We expect that subjects with type 2 diabetes will have less hypoglycemia than subjects with type 1 diabetes in the usual care arm, thereby making it less likely that we will be able to detect a reduction in hypoglycemia with the bionic pancreas. The bionic pancreas has the ability to adapt to the insulin needs of the individual. Based on our experiments with adolescents in our previous Summer Camp study, many of whom had insulin requirements on a per kg basis of the same magnitude as patients with type 2 diabetes, we are confident that the bionic pancreas will be able to achieve similar mean glucose values in subjects with type 2 diabetes as we have seen in subjects with type 1 diabetes. Our ability to detect Our ability to detect an improvement in mean glucose will therefore be dependent on the mean glucose of subjects during the usual care arm. This is part of the rationale for requiring that subjects with type 2 diabetes have an A1c > 7% as part of the eligibility criteria. Given this criterion, we believe that 10 subjects will provide sufficient power to detect a different in mean glucose. However, the study in type 2 subjects is primarily a feasibility analysis, and we will consider the study a success as long as the mean glucose and time < 60 mg/dl are non-inferior in the bionic pancreas arms relative to the usual care arms.

Analysis of the Effect of Glucagon During the In-clinic Experiment

We will assess the incremental effect of glucagon in the context of automated insulin delivery by the bionic pancreas in preventing hypoglycemia during exercise in the fasted state. We will compare the proportions of patients having at least one hypoglycemia event between the bi-hormonal and insulin-only bionic pancreas arms. A hypoglycemia event is defined as an event with PG <60 mg/dl for more than two consecutive measurements.

In the crossover design, each subject will serve as own control and the hypoglycemia event is considered to be correlated within the same patient. We will apply a two-sided exact McNemar's test to compare hypoglycemia rates between the bi-hormonal and insulin-only bionic pancreas arms. We use a conservative threshold for p-value <0.025 as indication of statistical significance.

To avoid making assumptions on missing data mechanism, the primary comparison will only include data from those randomized patients with complete data on the in-clinic hypoglycemia endpoint from both the bi-hormonal and insulin-only treatment periods.

Power calculations

From our clinical experience, we expect the hypoglycemia rate to be around 25% in the bi-hormonal arm and around 75% in the insulin-only arm, corresponding to a difference of 50 percentage points.

The table below provides power calculations of a two-sided exact McNemar's test with 2.5% type I error under varying degrees of within-subject correlations.

Based on our clinical experience with bi-hormonal bionic pancreas, patients who develop hypoglycemia using bi-hormonal bionic pancreas are highly likely to also develop hypoglycemia when not given glucagon. We expect 5% of patients who develop hypoglycemia with glucagon will have no hypoglycemia when glucagon is not given. If our expectation is correct, our planned

sample size of 20 patients will provide ≥90% statistical power to detect a difference in hypoglycemia rates between the two arms. If this proportion is three times as big as we expect (15%), we will still have 82% power to detect the difference.

Statistical power of two-sided exact McNemar's test with 2.5% type 1 error, assuming a difference of 50% (25% vs. 75%) in hypoglycemia rate between two arms. Crossover design, N=20.

Proportion discordant (higher value corresponds to lower correlation between two arms)	Proportion of those having hypoglycemia with glucagon that do not have hypoglycemia when glucagon is withdrawn	Statistical power
0.625†	25%	75%
0.6	20%	78%
0.575	15%	82%
0.55	10%	86%
0.525	5%	90%
0.505	1%	93%

†corresponding to independence between two arms

VI. d. Criteria for Success of the Study

The main criteria for the success of the outpatient portion of the study will be that we see significant differences in the primary outcomes measures between the different set-points.

The criteria for success of the in-clinic portion of the study is that there is a reduction in hypoglycemic event in the bi-hormonal arm relative to the insulin-only arm. If we do not see a difference at a set-point of 130 mg/dl, as we may see a significant difference at the lower set-point of 110 mg/dl.

VII. Risks and Discomforts

Subjects may experience mild discomfort associated with the insertion of the infusion sets and Dexcom sensor into the SC tissues. In subjects with type 1 diabetes, the risk of discomfort due

to insertion of infusion sets and Dexcom sensors may to be greater than in their lives outside the trial because more infusion sets will be inserted and a Dexcom CGM sensor will be inserted, which may not be used in usual care. In subjects with type 2 diabetes, the risk of discomfort due to insertion of infusion sets and sensors may be greater than in their lives outside the trial because insulin pump and CGM use is less common in patients with type 2 diabetes.

There are additional risks associated with the Senseonics sensor insertion, removal and/or use of the CGM system. The risks are greater than in the lives of people with diabetes outside this trial, as the Senseonics system is not approved for consumer use. In studies using the Senseonics CGM system to date, no device related serious adverse events have been reported, and only a few device related averse events have been reported. Of those, most were predominately expected local skin reactions to the insertion and/or the local anesthesia provided during this procedure, which all recovered without residual damage after short time periods. Study staff will examine the insertion site at each study visit and make appropriate notes that will be relayed back to the sponsor. Subjects will be instructed to contact study staff immediately upon any sign of extreme irritation or discomfort.

There is a potential risk of hypoglycemia, since exogenous insulin will be administered. Due to remote monitoring of severe biochemical hypoglycemia, the risk is expected to be reduced relative to during the subjects' lives outside the trial. In the bionic pancreas arms, this risk is expected to be further reduced relative to the risk during the subjects' lives outside of the trial based on data from earlier trials in subjects with type 1 diabetes. The set-points not previously tested are all higher than previously tested, and are therefore likely to be associated with even less hypoglycemia. Having never tested an insulin-only version of the bionic pancreas we cannot predict the hypoglycemia rate with accuracy. We have chosen to raise the set-points in the insulin-only arm relative to those in the bi-hormonal arm to reduce the risk. The rate and severity of hypoglycemia will be closely monitored and interim analyses will be performed to assure the safety of continuing with those arms of the study.

There is a risk of hyperglycemia. In the usual care arm, this risk is expected to be of the same nature and magnitude as during the subjects' lives outside of the trial. In the bi-hormonal bionic pancreas arms, this risk is expected to be less than the risk during the subjects' lives outside of the trial based on data from earlier trials in subjects with type 1 diabetes. In the insulin-only arms we expect the risk to be similar to or less than the risk during subjects' lives outside the trial based on the nature of the insulin-only dosing algorithm.

There is a risk of headache, nausea, or vomiting in subjects due to the administration of exogenous glucagon. There is a possible risk of skin rash due to administration of exogenous glucagon. There may be risks of daily, low-level glucagon administration that have not become apparent during trials lasting up to 11 days. One possible risk is weight loss although no changes in weight has been observed in trials lasting up to 11 days. Others may include changes in blood chemistries or blood counts. The magnitude of the other possible risks due to daily administration of small amounts of glucagon are unknown, but are not expected to be high because mean glucagon levels have been in the normal fasted range in previous trials and there have be no other adverse events in previous bionic pancreas trials lasting up to five days. Of note, the risk of nausea or vomiting has been low in prior studies.

There are additional risks for subjects with type 2 diabetes who have a history of coronary artery disease. Risks to subjects with prior CAD in our study are cardiac events including myocardial

infarction, arrhythmia and sudden cardiac death. In order to monitor these subjects, we will ask them to monitor for symptoms in both study arms. These symptoms of possible arrhythmia or MI include chest pain or discomfort, pain radiating from the chest to the shoulders, arms or upper back, sudden nausea or vomiting, lightheadedness, sudden heavy diaphoresis, or new palpitations. Should these symptoms arise at any point they are to call us and immediately present to the emergency department. Should they report any of the symptoms listed above and require medical intervention, we will stop our study immediately and refer them to the proper medical care. In order to assess any increased cardiovascular risk we will also use the Seattle Angina Questionnaire -7. This questionnaire has been validated to predict cardiovascular outcomes in patients with stable CAD. We will have our subjects fill out a questionnaire at the beginning and at the end of our study and compare the cumulative scores. By including subjects who have stable CAD and are appropriately medically managed, and with improved glycemic control while using the bionic pancreas, we believe the risk of another cardiac event to be minimal.

VIII. Potential Benefits

Based on evidence from previous trials of the bionic pancreas and the design of this trial, subjects enrolled in the study may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose during the bionic pancreas arms. They may also benefit from a reduction in risk of severe hypoglycemia in the usual care arm due to monitoring for severe events.

Subjects are expected to benefit in all arms of the study from the formal involvement of a designated contact who will serve as a backup to respond to any overnight threshold alarms to which the subject does not respond.

The data derived from this study will allow us to evaluate the robustness and effectiveness of the bionic pancreas control system. The data obtained may be used to further improve the bionic pancreas by identifying the best default target glucose level.

The anticipated use of the Senseonics sensor as a CGM could ultimately provide a major improvement in overall safety and convenience for patients with diabetes by helping to reduce the number of potentially life-threatening hypoglycemic and hyperglycemic events while reducing the burden of CGM use on the wearer. The Senseonics sensor could be an alternative to the Dexcom sensor as the source of CGM data for the bionic pancreas.

This study is a necessary step in preparing the bionic pancreas to become available to people with type 1 and type 2 diabetes. Wide availability of the bionic pancreas could improve the care adults and children with diabetes.

Subjects will be financially compensated for participating in the study.

IX. Data and Safety Monitoring

IX. a. Monitoring of Source Data

During the experiment, Dexcom CGM data will be collected in various ways. Dexcom CGM data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored

in the bionic pancreas device (from which it will be downloaded at intervals) and wirelessly streamed to the cloud where it will be stored to provide redundancy in data storage and mitigate the risk of data loss. Daily emails will be sent to the subject to document contemporaneously hypoglycemia, adverse events, and estimated exercise duration. All of the data will be combined in a single database that will be compared against the primary data files for integrity. The computer database will be backed up at least monthly and the backup media stored in a secure location. Senseonics sensor data will be blinded throughout the study and downloaded that the completion of the study arms. Sensor data and analysis will be shared with the sponsor Senseonics and stored in the same computer database.

Study staff will be encouraged to raise any concerns they may have or problems they have identified at any time. The PI, in consultation with the co-investigators, will decide a course of corrective action, and resolution or progress will be assessed no later than the next meeting.

An audit of procedures, regulatory documentation, and a sample of subject files will be performed by a member of the Diabetes Research Center at least biannually. The audit will be conducted by a staff member who is not directly involved in the conduct of the study. This audit will include a review of regulatory documentation, such as IRB and FDA correspondence, and a review of subject files, including a review of consents, case report forms, and other data from study visits.

A numeric code will be substituted for the subjects personal identifying information in the study database, which will be password protected. The key linking the medical record number of the subject with the numeric code, along with case report forms, and all information that is personally identifiable, will be kept in a locked filing cabinet in an investigator's locked office. All electronic records will be kept in a password protected computer database. All printed computer data will be disposed of confidentially when no longer needed. Only the study staff will have access to the study database. Subjects may not withdraw from the de-identified database, but they may elect to have the key linking their medical record to the de-identified database destroyed.

The study data may be shared with collaborators at Boston University, at the MITRE Corporation (a non-profit research corporation), and at Senseonics, Inc. but only in a form in which all personally identifiable information has been removed (e.g. combined database including BG values, record of insulin and glucagon delivered by the device, and blood insulin and glucagon levels). Shared data will be in the form of a database in which only a number identifies subjects.

Subjects may not withdraw their data, as it will be stored in non-personally identifiable form.

IX. b. Safety Monitoring

This study is considered moderate risk. An external Data and Safety Monitoring Board will oversee the conduct of the study and review its results on a regular basis. Additionally, the DSMB will be informed in the event of any severe or unexpected adverse events. The DSMB will be informed if there are any changes to the study protocol that could significantly impact the safety or scientific validity of the study. A final DSMB meeting will convene after the completion of the study. Safety and efficacy data will also be reported to the FDA in compliance with applicable regulations.

As noted above, the participation of individual subjects in the bionic pancreas arm of the study will be discontinued if they experience:

- Diabetic ketoacidosis requiring hospitalization during a bionic pancreas arm
- Seizure or unconsciousness associated with hypoglycemia in a bionic pancreas arm
- Persistent nausea and vomiting thought to be related to glucagon dosing in a bi-hormonal bionic pancreas arm
- For subjects participating in the Senseonics CGM portion of the study, the following additional stopping rules will be followed:
    - Infection at the Senseonics sensor insertion site that does not resolve in three days. The sensor will be removed and not replaced. The bionic pancreas portion of the study can continue.
    - A serious adverse event related to the Senseonics device or procedures. The sensor will be removed and not replaced. The bionic pancreas portion of the study can continue.

If more than 2 subjects must be withdrawn from either the type 1 or type 2 diabetes portion of the study for these reasons, the study will stop and a vote of the DSMB will be required to restart it. All serious and unexpected events will be reported to the DSMB within 72 hours. If more than 2 subjects must be withdrawn from the Senseonics CGM portion of the study for either of the above reasons, no more Senseonics sensors will be placed. Participation in the bionic pancreas visits will not be stopped.

Note that subjects may discontinue participation at any time and subjects may be removed from the trial for other reasons, for instance failure to comply with study procedures or intercurrent illness that is unrelated to the bionic pancreas but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

IX. c. Adverse Event Reporting Guidelines

The PI and co-investigators will review any adverse events after each experiment. Any serious or unexpected but possibly related adverse events will be communicated to the PI as soon as possible and within 48 hours of the time they are detected. Adverse events will be reported promptly to the Partner's IRB and to the BU IRB. Collaborator Ed Damiano is the sponsor of the Investigational Device Exception (IDE) for the bionic pancreas to be used in this trial. Reports of adverse events will be made to the FDA in compliance with the terms of IDE. Adverse events will also be promptly reported to the sponsor Senseonics, Inc as related to the use of their investigational device.

X. Subject Compensation

Financial compensation will be provided to all subjects who complete the screening visit.

Subjects will be paid $50 for completing the screening visit whether or not they are eligible to participate in the study.

Study participants with type 1 diabetes will be compensated $950 for completing the first 6 arms of the study. Thus the total compensation for a subject who completed the first 6 arms of the study would be $1,000. Of this compensation, $10 a day will be contingent on completing the daily survey, which is expected to take < 5 minutes to complete on a smartphone, tablet, or computer, in a timely manner (e.g. between 6:00 PM and 12:00 PM on the following day). Thus, a total of $180 of the total possible compensation of $1,000 will be contingent on timely completion of the daily survey. Subjects will receive reminders and it our intention that making a relatively small amount of the payment conditional on timely survey completion. Subjects who are unable to complete the study or chose to stop participation will receive prorated compensation at a rate of $50 per completed day.

Designated contacts for subjects with type 1 diabetes will be compensated $50 to complete the screening/consent visit. They will be compensated $100 for completing the study. Thus, the total compensation for a designated contact would be $150.

Subjects who complete the 110 mg/dl arms (bihormonal and insulin-only) will be compensated $300. Designated contacts will be compensated an additional $50 for participation in the 110 mg/dl arms.

Subjects who complete the 120 mg/dl insulin only arm will be compensated $150. Designated contacts will be compensated an additional $25 for participation in the 120 mg/dl arm.

Study participants with type 2 diabetes will be compensated $325 for completing the study. Thus the total compensation for a subject who completed the study would be $375. Of this compensation, $10 a day will be contingent on completing the daily survey, which is expected to take < 5 minutes to complete on a smartphone, tablet, or computer, in a timely manner (e.g. between 6:00 PM and 12:00 PM on the following day). Thus, a total of $140 of the total possible compensation of $375 will be contingent on timely completion of the daily survey. Subjects will receive reminders and it our intention that making a relatively small amount of the payment conditional on timely survey completion. Subjects who are unable to complete the study or chose to stop participation will receive prorated compensation at a rate of $50 per completed day.

Designated contacts for subjects with type 2 diabetes will be compensated $50 to complete the screening/consent visit. They will be compensated $50 for completing the study. Thus, the total compensation for a designated contact would be $100.

Subjects who participate in the test run will be compensated at a rate of $50 per arm. Subjects who participate in the test run will also be eligible to participate in the full study.

Designated contacts who participate in the test run will be compensated $20. The total compensation available to a designated contact participating in both the test run and the full study could be up to $120.

Subjects who consent to wearing a Senseonics sensor will receive an additional $50 for the insertion visit and $50 for the removal visit.

XI. References

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XII. Appendices

XII. a. Appendix A. Maps of Boundaries

60 Minute and 120 Minute Drive Time Boundaries