The Monitoring Study: Evaluating the Effect of Remote Monitoring For Hypoglycemia on Bionic Pancreas Safety and Efficacy

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TABLE OF CONTENTS

I. Background and Significance

1.a. Background

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.

I.b. 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.

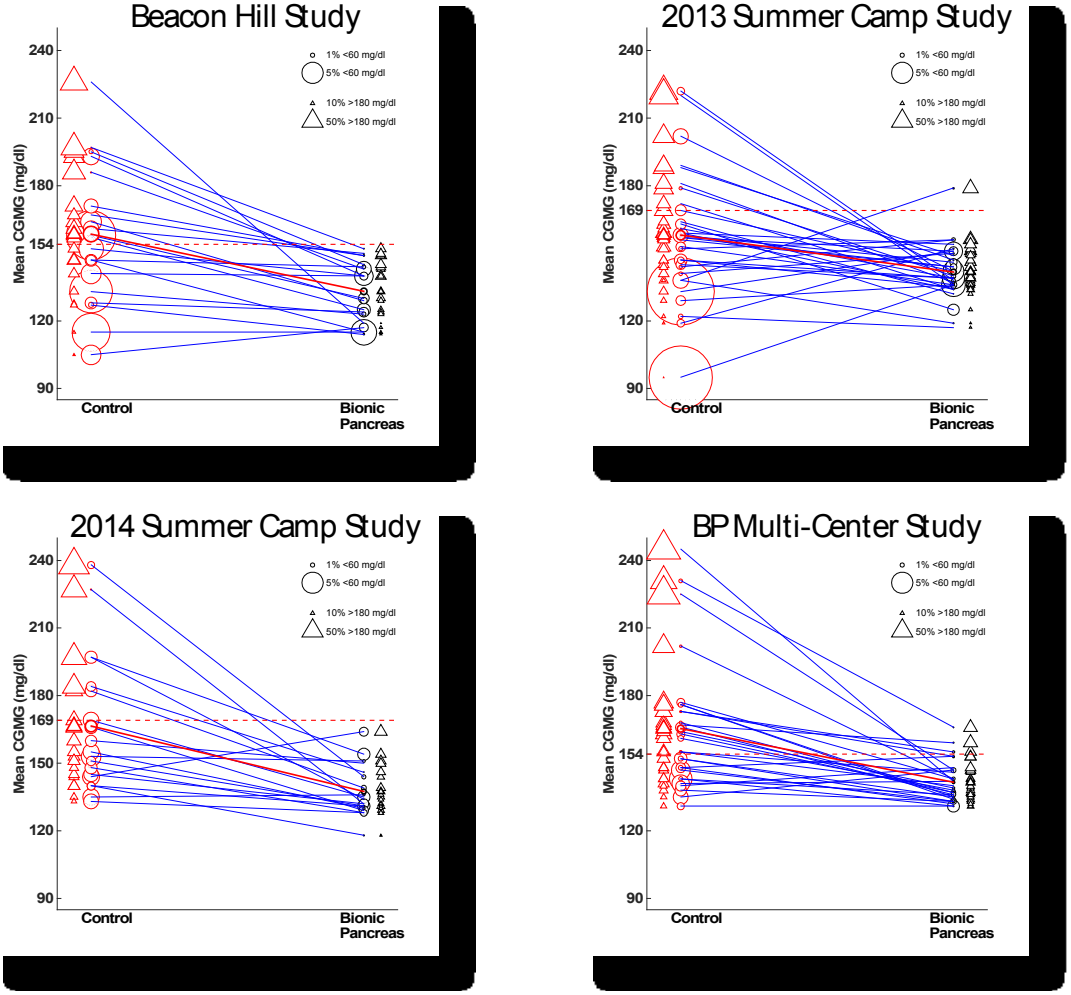
Our core technology is the insulin controller, which orchestrates all subcutaneous (SC) insulin dosing. At its centerpiece is a model-predictive control algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics. We were the first to incorporate insulin pharmacokinetics (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.

I.c. 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--2016). 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 glucose 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 to 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).

The mean CGM glucose levels obtained by the bihormonal BP from our 2013 and 2014 Summer Camp Studies and the Bionic Pancreas Multicenter Study, were 141 ± 10 mg/dl in adults, 142 ± 12 mg/dl in adolescents, and 137 ± 11 mg/dl in pre-adolescents. Based on these mean CGM glucose levels, we projected what the bihormonal BP would achieve in terms of HbA1c in the three populations we studied. In adults, we expect an HbA1c of 6.5 ± 0.4%, in adolescents we expect an HbA1c of 6.6 ± 0.4%, and in pre-adolescents we expect an HbA1c of 6.4 ± 0.4%. It is important to note that the BP was able to achieve mean CGM glucose levels below the American Diabetes Association (ADA) goal for therapy in all three populations in nearly all subjects tested while simultaneously eliminating almost all hypoglycemia. On the BP, CGM glucose levels fell below 60 mg/dl only 0.6% of the time in adults, 1.3% of the time in adolescents, and 1.2% of the time in pre-adolescents. A summary of results from each of these studies is included in Figure 2.

The BP can also operate in an insulin-only configuration. During operation in this mode, all other features of the BP operate as usual except that glucagon is not given. In the insulin-only configuration, the quantity of glucagon that would have been given (virtual glucagon) is also tracked and feeds back to reduce the aggressiveness of the insulin controller. This effect is typically stronger in the insulin-only configuration, since, in the absence of a prompt anti-hypoglycemic response, more virtual glucagon is given. In addition, the lowest glucose target that can be chosen by the user is increased from 100 mg/dl in the bihormonal system to 110 mg/dl in the insulin-only system. These two mechanisms combine to significantly reduce the aggressiveness of insulin dosing in the insulin-only system, with the aim of keeping the amount of hypoglycemia low at the expense of raising the mean glucose level achieved by the insulin-only system.

In addition to conducting four outpatient studies testing our BP in the bihormonal configuration, we have also conducted two home-use outpatient studies testing our iPhone-based BP system in the insulin-only configuration and targeting different glycemic set-points. These studies were conducted by our clinical collaborators at Stanford and at MGH. In the study conducted by our Stanford team, 16 adults with T1D compared our BP in the insulin-only configuration with insulin pump therapy in one-week experiments at work and at home (with a glucose target of ~ 130 mg/dl). In the study conducted by our MGH team, 20 adults with T1D compared our BP in the insulin-only configuration at a set-point of 130 mg/dl, with our BP in the bihormonal configuration at glucose set-points of 100, 115, and 130 mg/dl, and with insulin pump therapy in 3-day experiments at work and at home. (Note, the glycemic set-point that was used in the Beacon Hill Study, the 2013 and 2014 Summer Camp Studies and the Bionic Pancreas Multi-Center Study shown in Figure 2 targeted 100 mg/dl.)

The mean CGM glucose levels obtained by the insulin-only BP with a glycemic set-point of 130 mg/dl was 161 ± 9 mg/dl in our Stanford Insulin-only Study and 160 ± 17 mg/dl in our MGH Set-Point Study, with CGM glucose levels falling below 60 mg/dl only 0.9% and 0.8% of the time, respectively. Based on these mean CGM glucose levels, we project that our insulin-only BP would achieve an HbA1c in adults of ~ 7.2 ± 0.5%, while simultaneously limiting CGM glucose levels below 60 mg/dl to less than 1% of the time. Thus, we project that the insulin-only configuration of our BP would result in HbA1c levels that are ~ 0.7% higher than would be expected from our BP in the bihormonal configuration. A summary of results from these two studies is included in Figure 2.

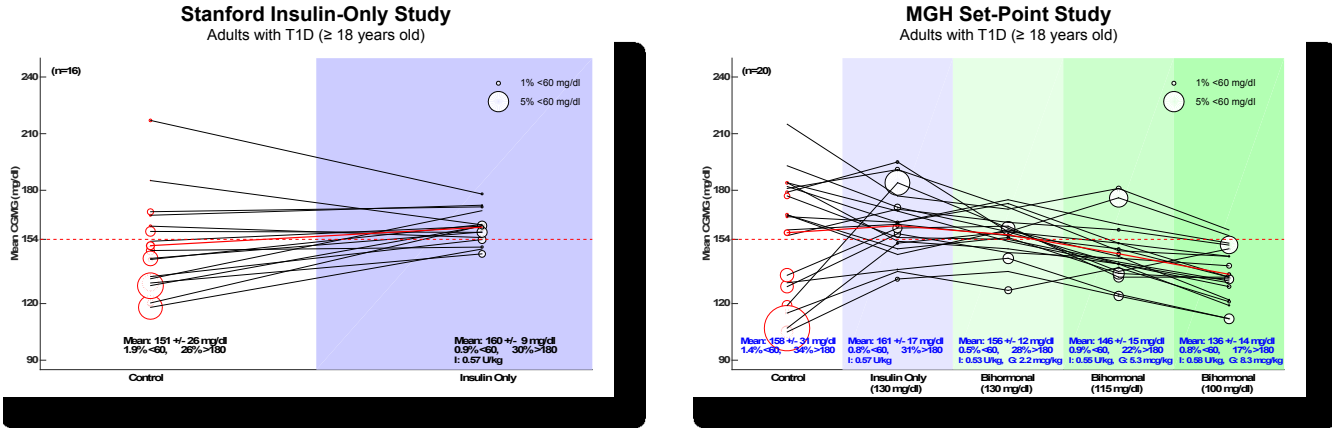


Figure 2. Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the bihormonal, insulin-only, and control arms from the BP studies at MGH and Stanford. *Left*: Mean CGM glucose levels for each subject under usual care (red circles) is connected with the subject's mean CGM glucose level using the insulin-only configuration of the BP (black circles). *Right*: Mean CGM glucose levels for each subject under usual care (red circles) is connected with the subject's mean CGM glucose levels (black circles) using (1) the insulin-only configuration of the BP with a set-point of 130 mg/dl, (2), the bihormonal configuration of the BP with a set-point of 130 mg/dl, (3) the bihormonal configuration of the BP with a set-point of 115 mg/dl, and (4) the bihormonal configuration of the BP with a set-point of 100 mg/dl. As in Figure 2, the diameters of the circles shown are proportional to the percentage of CGM glucose values < 60 mg/dl that were experienced by each subject during the control and intervention arms, and the horizontal red dashed line refers to the glucose level corresponding to the ADA therapy goal, which corresponds to 154 mg/dl (HbA1c of 7%) for adults. Summary results showing the co-primary outcomes (mean CGM glucose level and percentage of CGM glucose values < 60 mg/dl) for the control and intervention arms are superimposed on the plots.

In all of our previous outpatient studies using the bihormonal bionic pancreas, we have done remote monitoring for severe biochemical hypoglycemia. Data was sent from the device to the cloud every 5 minutes and if the CGM glucose was <50 mg/dl for more than 3 consecutive measurements (a minimum of 15 minutes) then a study staff member was notified and they called the subject to ensure their wellbeing. If study staff were unable to contact the subject they would contact the designated contact, someone who lives with the subject and has agreed to be contacted in such a situation. Subjects were instructed that if they were aware of a hypoglycemic event or received an alarm from the bionic pancreas they were to enter a BG measurement into the bionic pancreas. Any such entered measurements were transmitted to the cloud; this would reset the 15 minute clock for calling a study staff monitor. It is important to note that the same monitoring was performed in the bionic pancreas arms and the comparator, usual care arms. This was critical because it meant that differences in hypoglycemia between the two arms were not due to the monitoring, but rather to the effect of the bionic pancreas itself.

The remote monitoring was done to mitigate the risk of a severe hypoglycemic event and was mandatory in the first outpatient trial of the bihormonal bionic pancreas, the Multicenter Study, because we had no prior experience with how it would perform in this setting. We also performed remote monitoring in the Set-point Study because it was the first study to test an insulin-only configuration of the bionic pancreas. We found in the Multicenter Study that the percentage of time <60 mg/dl was substantially lower in the bihormonal bionic pancreas arm than in the usual care comparator arm (0.6±0.6% vs. 1.9±1.7, p<0.0001) and the difference was even larger at the lower threshold of <50 mg/dl (0.1±0.2 versus 0.6±0.6%, p<0.0001). In the Set-point Study we found that the percentage of time <60 mg/dl was nominally lower in all three set-points using the insulin-only bionic pancreas arm (145 mg/dl: 0.96±1.5%, 130 mg/dl: 0.79±1.4%, 110 mg/dl: 1.34±1.3%) than in the usual care comparator arm (1.38±2.6) although the difference were not statistically significant. Therefore, our data support the safety of allowing subjects to use the bionic pancreas without monitoring because the risk appears to be lower than in usual care with the bihormonal bionic pancreas and equivalent to usual care with the insulin-only bionic pancreas. However, we don't know how much remote monitoring for severe hypoglycemia affected the outcomes of these studies. Although calls to subjects for severe hypoglycemia were rare, they did occur. Each call that resulted in a subject taking action sooner than they otherwise would have reduced the amount of hypoglycemia. We don't know how much hypoglycemia was reduced, nor do we know whether the amount of hypoglycemia reduction due to monitoring was similar in the two arms. Since hypoglycemia was more common in the comparator usual care arm than in the bihormonal bionic pancreas arms, it seems likely that monitoring reduced hypoglycemia more in the usual care arm and therefore reduced the effect size associated with use of the bionic pancreas.

We have done only one study without remote monitoring for severe hypoglycemia, the Glucagon-only Study. This study assessed the effectiveness of a glucagon-only bionic pancreas for reducing hypoglycemia when subjects controlled their own insulin delivery via an insulin pump. In this study subjects wore the glucagon-only bionic pancreas for two continuous weeks during which time they used their insulin pump as usual. Each day they filled the bionic pancreas with glucagon or placebo from a vial-blinding device. They did not know whether they would receive glucagon on any given day and therefore could not rely on it to prevent hypoglycemia. We asked subjects to complete a brief questionnaire each day and found that blinding was effective; subjects correctly guessed whether they were receiving glucagon or placebo only 42% of the time. Since they were managing their insulin dosing as usual, and since we told them to take all of their usual precautions to prevent hypoglycemia and to treat hypoglycemia as they usual would, their risk of hypoglycemia was not increased by participation in the trial and we did not have to perform remote monitoring. We found that the percentage of time <60 mg/dl was dramatically reduced on glucagon days vs. placebo days (1.27±0.91% vs. 5.80±4.81%, p=0.0001). However, the notable finding in this context is how high the hypoglycemia was in the usual care arm without monitoring for severe hypoglycemia. The time <60 mg/dl in the usual care arm of this unmonitored trial (5.8%) was much higher than that in the usual care arms of our trials with remote monitoring for severe biochemical hypoglycemia (1.9% in the Multicenter Study and 1.4% in the Set-point Study). This difference could be due to the fact that inclusion criteria for the Glucagon-only Study required that participants have at least partial hypoglycemia unawareness (at least sometime finding their BG <50 mg/dl without symptoms) and report at least two episodes of hypoglycemia a week. However, these criteria are commonly met by many patients with type 1 diabetes, and we don't know that they wouldn't have been met by the subjects in the Multicenter and Set-point Studies. Therefore, there remains uncertainly regarding how much hypoglycemia to expect in both the usual care and bionic pancreas arms of unmonitored studies. This information is important for powering studies to detect differences in hypoglycemia between bionic pancreas and usual care.

In addition to gaining important information about the role of remote monitoring in affecting the outcomes of bionic pancreas studies, we can have additional questions that can be answered in the context of a new study. First, it is important to know if and how bionic pancreas technology affects food intake, activity, weight, and body composition. There is very little information available regarding any of these issues. As we go forward into longer trial we will need to know how to power sub-studies to gain this information. Second, new

continuous glucose monitoring technology is nearing approval in the United States. It is important to take advantage of the best glucose measurement technology to achieve the best outcomes with the bionic pancreas. We had previously chosen the best CGM device to drive the bionic pancreas. We now wish to test new CGM devices with an eye to potentially using them as alternative sources of glucose information for the bionic pancreas.

I. d. Rationale and Potential Benefits

The rationale for this study is to measure the safety of eliminating the glycemic monitoring that we have done in all of our previous outpatient studies under both insulin only and bihormonal bionic pancreas control. We are planning to transition our outpatient studies to an integrated bionic pancreas, the iLet, in the near future. The intended use of this device does not include remote monitoring, which would not be feasible on a commercial scale. Therefore, in this trial we will test the effects on hypoglycemia of eliminating blood glucose related monitoring. In addition, we will perform a pilot trial testing the effects of the bionic pancreas on food intake, exercise, weight and body composition. The primary purpose of this pilot is to assess the feasibility of performing these measurements in the context of a larger trial and to collect data that can be used to power sub-studies of pivotal trials looking at these outcomes. Finally, we will test the accuracy of two new CGM devices to see if they have sufficient accuracy to provide glucose data to the bionic pancreas. If so, this would provide new options for users who may have difficulties with the only currently validated CGM for this purpose, the Dexcom G4 AP / G5 platform.

II. Hypothesis and Specific Aims

We hypothesize that the amount of hypoglycemia (% time <60 mg/dl) on the bionic pancreas will be less than or equal to the amount of hypoglycemia during the usual care arm both with and without monitoring for severe biochemical hypoglycemia (<50 mg/dl for >15 minutes). Furthermore, we hypothesize that the difference in hypoglycemia between the bionic pancreas and usual care arms in the absence of remote monitoring for hypoglycemia will be equal to or larger than the difference in the presence of such monitoring. The specific aims of this study are:

Aim 1. To conduct an outpatient study testing two configurations of the bionic pancreas (bi-hormonal and insulin-only) with and without remote monitoring of hypoglycemia in 24 adult (≥ 18 years of age) subjects with type 1 diabetes in a random-order crossover study versus usual care with an insulin pump with and without remote monitoring of hypoglycemia.

The study will consist of six 7-day study arms in random order: two usual care arms, two bi-hormonal bionic pancreas arms, and two insulin only bionic pancreas arms. Each BP arm and the usual care arm will be completed twice in random order, once with 24 hour remote monitoring for device connectivity and severe biochemical hypoglycemia, and once with 24 hour remote monitoring solely for device connectivity with no monitoring for hypoglycemia. The primary outcome will be the time <60 mg/dl.

Aim 2. 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.

Aim 3. To test the accuracy of the Senseonics implantable CGM vs. the Dexcom G5 CGM vs. the Freestyle Libre Pro factory calibrated CGM.

Subjects will wear two blinded CGMs in addition to the Dexcom G5 CGM that runs the bionic pancreas. The Senseonics implantable CGM 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. It requires twice daily calibration and performs CGM glucose measurements every 5 minutes for up to 90 days. The Freestyle Libre Pro uses a subcutaneous sensor and an external plastic transmitter connected to the sensor base, similar to the design of the Dexcom. It is factory calibrated and therefore does not require calibration, and performs and stores CGM glucose measurements every 15 minutes for up to 14 days. The data from the Senseonics sensor and the Freestyle sensor will be collected in blinded fashion and will later be compared with reference point-of-care capillary glucose values. Data from the Dexcom G5 CGM will be collected in an unblinded fashion and will later be compared with reference point-of-care capillary glucose values. The primary outcome for this aim will be the mean absolute relative difference (MARD) of the three CGM systems. Because the Freestyle CGM only takes a reading every fifteen minutes, for every reference glucose meter reading we will compare it with the Freestyle CGM reading that is nearest in time, as long as it is within 10 minutes. We will then chose the Dexcom and Senseonics CGM readings that are closest to the Freestyle reading (as long as there is a reading with 5 minutes), and compare all three to the same meter glucose.

Aim 4. To test the feasibility of determining whether there are differences in activity, caloric intake, types of foods consumed, and weight associated with use of the bionic pancreas, either in the insulin-only or bihormonal configurations, as compared to conventional insulin pump therapy.

Subjects will wear an Actigraph activity monitor daily during each arm of the study. They will also participate in a 24 hour diet and activity recall twice before the study to determine a baseline and twice at the end of each study arm. They will also have weight and body composition documented at the beginning and the end of each study arm.

The data derived from this Aim may show significant differences, but if not it will provide data that can be used to power follow-on investigations.

III. Subject Selection

III. a. Inclusion Criteria

- Age ≥ 18 years and have had clinical type 1 diabetes for at least one year managed using an insulin pump for ≥ 6 months
- 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 120 minute drive-time radius of the central monitoring location
- Willing to remain within a 250 mile radius of the central monitoring location throughout the study. No air travel will be allowed due to the inability to remotely monitor patients while they are flying.
- 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)
- Willing to wear two additional CGM sensors that must be placed in the upper arm
- Have a mobile phone they will have access to at all times throughout the study for making contact with

study staff
- Have used a CGM for at least one cumulative month over the last 12 months

No subjects will be excluded on the basis of gender or race. The requirement that 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.

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
- Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary

artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)

- Abnormal EKG consistent with coronary artery disease or 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). Non-specific ST segment and T wave changes are not grounds for exclusion in the absence of symptoms or history of heart disease. A reassuring evaluation by a cardiologist after an abnormal EKG finding may allow participation.
- Congestive heart failure (established history of CHF, lower extremity edema, paroxysmal nocturnal dyspnea, or orthopnea)
- History of TIA or stroke
- 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
- The presence of any other active implanted device
- Unable to completely avoid acetaminophen for duration of study
- Unable to completely avoid ascorbic acid (Vitamin C) for duration of study
- Unable to completely avoid salicylic acid (used in some pain relievers such as Aspirin and some skin care products)
- 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
- Use of oral (e.g. thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) or non-insulin injectable (GLP-1 agonists, amylin) anti-diabetic medications
- 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
- 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), Computed Tomography (CT) scan, or high-frequency electrical heat (diathermy)
- A known topical or local anesthetic allergy
- A known glucocorticoids allergy
- The presence of any other CGM sensor or transmitter located in the upper arm (other location is acceptable)
- Hemoglobin < 11 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 may be posted at the MGH Diabetes Center and other places, and may 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.

IV. Subject Enrollment

IV. a. Number of Subjects

It is expected that we will have 24 subjects complete the study with a consistent protocol. We expect that the experiments and analysis can be accomplished over a period of 6-12 months. Up to 48 subjects 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 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 as many as 150 subjects.

IV. b. Enrollment and Consent 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 e-mail.

Once potential subjects have had time to review the consent document, they will meet with a study provider (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. Their designated contact will also have to meet with a study provider to hear what will be required of them if the subject participates in the study. Designated contact consent will be obtained in person or over the phone. Designated contact participants must have their own telephone in order to participate-either a personal cell phone or a household phone. If the designated contact's consent is obtained over the phone, two copies of the consent form will either be mailed or sent electronically to the designated contact (one to keep and one to return) and he/she will have the form in front of him/her during the phone consent process. The

designated contact will return the signed consent form to the study staff either by mail or electronically, and the person obtaining informed consent will sign the document upon receiving it. There will be separate consent documents for the subject and the designated contact. A licensed physician investigator will be available to speak with the subjects during the consent process in the event of an NP administering consent.

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 used in pump
- Average total daily dose of insulin in the last 30 days (from pump history in type 1 diabetes subjects) – for comparison with insulin dosing during the usual care and bionic pancreas arms of the study
- 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. If this test has been previously administered and the results are available and were negative (no detectable c-peptide), then it does not need to be repeated.
- Hemoglobin

V. b. Drug*s*

The study involves subcutaneous administration of insulin lispro (Humalog, Lilly), insulin aspart (Novolog, Novo Nordisk), or insulin glulisine (Apidra, Sanofi Aventis). All 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. 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.

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 72 hours; the glucagon infusion set will be changed every 24 hours.

Continuous glucose monitors: Subjects will wear three continuous glucose monitors throughout the study: the Dexcom G5 CGM, the Senseonics CGM, and the Freestyle Libre Pro CGM.

One transcutaneous glucose sensor for the DexCom G5 (9) 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. The whole assembly is held to the skin with an adhesive patch and communicates wirelessly via Bluetooth Low Energy 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.

One subcutaneous glucose sensor for the Senseonics Continuous Glucose Monitor System will be inserted in the subcutaneous tissue of the upper arm. The insertion is an office procedure that takes approximately 5 minutes. The insertion requires local anesthesia and a sterile field, and is done 10 days prior to the first measurements to allow the insertion site to heal. The sensor is currently approved in Europe for use up to 90 days after which is removed in a brief office procedure under local anesthesia. 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. The MMA will be installed on an iPod touch or iPhone. It will not interact with the Bionic Pancreas in any way.

One transcutaneous glucose sensor for the FreeStyle Libre Pro Flash Glucose Monitoring System will be inserted in the subcutaneous tissue of the upper arm. The sensor measures and stores glucose readings when worn on the body and automatically records glucose level every 15 minutes. The sensor is powered by the battery within the transmitter and the whole assembly is held to the skin with an adhesive patch. The sensor communicates wirelessly with the FreeStyle Libre Pro reader when activated. The reader will be stored at the

Diabetes Research Center, and the sensor data will be downloaded at the end of each arm. If the FreeStyle sensor fails for any reason during the experiment it will be replaced promptly. The glucose data from the sensor will be blinded during this study. It will not be installed on the Bionic Pancreas or interact with it in any way.

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 staff 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 as usual, and will administer correction boluses in response to entered BG values, 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. The Dexcom CGM also has its own hard-coded alarm distinct from the bionic pancreas when the CGM glucose crosses below 55 mg/dl. These alarms may be configured so that they require the entry of a code to dismiss.

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.

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 15 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 15 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 in the study arms with hypoglycemia monitoring, who will then make contact with the wearer according to the study protocol. Monitoring will be the same in all study arms with the exception of the hypoglycemia alarm, which will only be monitored in the hypoglycemia monitoring study arms.

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.

Actigraph Activity Tracker: Study subjects will be provided with an activity monitor that is FDA approved and designed for use in research studies. The Actigraph uses a validated, solid state 3-axis MEMS accelerometer and digital filtering technology to continuously record high resolution physical activity and sleep/wake information. It can be worn on the subject's right hip or wrist and requires no input from the user. The battery can last up to 25 days, and it can store data for up to 180 days.

V. d. Experimental Procedures and Data Collection

V. d. i. Screening Visit

- All subjects will have a screening visit to confirm eligibility. Subjects will arrive at this visit having fasted since 10:00 PM if they need to complete the mixed meal tolerance test.
- 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) component 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, hemoglobin, and hemoglobin A1c. Plasma fractionated metanephrines may be obtained if indicated by history. If the subject has had the test performed in the past and was negative (no detectable C-peptide) then it does not need to be repeated.
- 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. ii. Randomization of Study Visit Order: Once the subject has been enrolled and eligibility of subjects has been established, subjects will be randomized to one of the possible 6 visit-order schedules that randomize the visit orders while at the same time arranging the schedule so distribution across the arms is even each week (pseudo-randomized visit order).

V. d. iii. General Study Policies for all Study Arms:

- Subjects will remain at all times within a geographic boundary established on the basis of 250 miles from the designated base for study personnel and will avoid any air travel.
- 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. If the subject is traveling within the geographic boundary, the designated contact must go with them.
- 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.
- 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.
- 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 use their own CGM during their usual care period.
- Subjects will test their blood glucose with the Stat Strip Xpress meter before driving and treat their glucose with appropriate carbohydrates as they would do normally before driving. If they are in a hypoglycemia monitored arm, 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 (a study is currently ongoing to determine if this is the case).
- 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 principal investigator.
- Subjects may not take acetaminophen, ascorbic acid, salicylic acid or aspirin (acetylsalicylic acid) during all study arms due to potential interference with CGM sensing. Acetaminophen is known to interfere with the accuracy of the Dexcom CGM. Very high doses of salicylic acid and aspirin (doses of greater than 2 grams per day) are known to interfere with the accuracy of the Senseonics CGM. Very

high doses of salicylic acid and aspirin (doses of greater than 2 grams per day) and high doses of acetaminophen may interfere with the Abbott CGM although it is much more resistant to interference from acetaminophen than the Dexcom CGM.

- Subjects will not tamper with the bionic pancreas device in any way, including changing any settings. Subjects will not use the bionic pancreas iPhone for anything beyond its intended purpose in this study.
- During the experiment the bionic pancreas 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 at least once per 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. Subjects may give a glucagon bolus prior to disconnecting in bihormonal bionic pancreas arms.
- The Dexcom CGM transmitter is water resistant and can be left on for bathing and swimming. The Senseonics transmitter should be removed prior to bathing or swimming. The Senseonics transmitter contains a rechargeable battery that should be recharged during bathing.
- 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.
- 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 a 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 will use an accelerometer to accurately compare activity level in each arm of the study.
- 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. iv. Remote Monitoring

Local Alarms

- The system will generate the following local alarms to the subject:
  - Low threshold audio alarm of 50 mg/dl Dexcom CGM glucose values on the bionic pancreas
  - The Dexcom CGM app also has a low threshold audio and vibrating alarm of 55 mg/dl
  - Audio and visual alarms on the bionic pancreas for pump disconnections after 10 minutes, and then every 5 minutes following that until the disconnection is resolved
  - Audio and visual alarms on the bionic pancreas for Dexcom G5 disconnections after 10 minutes, and then every hour following that until the disconnection is resolved
- Subjects will be trained in recognizing and responding to all of these alarms. They will also be told if they are randomized to monitoring or no monitoring that week, but we will explain that they need to keep their behavior and vigilance to local alarms the same in all study arms.
- The Senseonics and Freestyle CGMs have no alarms.

Remote Monitoring

- 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 study staff.
- Only half of the study arms will be monitored for hypoglycemia. The subjects will be randomized so that they participate in their usual care arm and each bionic pancreas arm both with and without hypoglycemia monitoring. All subjects will be monitored for device connectivity in each arm.
- All remote monitoring is of the Dexcom G5 CGM and the Bionic Pancreas function. There is no remote monitoring of the Senseonics or Freestyle CGM in any arm.
- The system generates the following alarms to the monitoring center:
  - if the Dexcom CGM has been disconnected and has not spontaneously reconnected (after 15 minutes, all study arms)
  - if the wireless connection between the bionic pancreas control unit and a Tandem pump has been lost and has not spontaneously reconnected within 15 minutes (bionic pancreas arms)
  - CGMG less than 50 mg/dl for 15 minutes for half of the study arms
  - No internet connectivity (either through cellular or WiFi), and therefore unable to monitor, for 15 minutes
- When an alert 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 CGMG alarm, in a monitored arm, with no response from the subject or their contact and no success in locating them, the site principal investigator will be immediately informed.
- Remote monitoring 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.
  - In the monitoring arms, if we are unable to monitor a subject remotely for greater than 15 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 with the subject regardless of what study arm they are in.

- 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.

V. d. v. Visit Procedures

Visit 0: Senseonics sensor insertion

All Study Arms

- The Senseonic sensor insertion will take place before the first 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 (less than 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.

Visit 1: First Day 1 Visit

All Study Arms

- Prior to starting their first study arm, subjects will complete a structured phone interview with collaborators about their baseline dietary habits. To optimize the accuracy of the assessment of dietary intake data, we will conduct 24-hour dietary recalls using the USDA multi-pass method administered by trained diet recall technicians. Participants will self-report on intake of the previous day. Diet recalls will be conducted in English and will last 20-30 minutes. Dietary data will be entered and analyzed using NDS-R software (Nutrient Data System for Research, St. Paul, MN). Study participants will also be asked to complete Previous Day Activity Recall as part of the 24-hr Dietary Recall. These telephone

recalls will collect information about physical activity from the previous 24-hour period. The physical activity recalls will take 5-10 min, added onto the dietary recalls. To increase precision of short-term usual dietary intake and physical activity, interviews will be conducted twice to cover two days within a four day period leading up and including the baseline visit day (one day per interview).

  - Telephone recalls will be completed by the UNC Diet, Physical Activity, and Body Composition Team in the NIH/NIDDK funded UNC Nutrition Obesity Research Center. Study site staff will provide UNC with participant contact information including name, contact phone number, as well as best times to contact in order to conduct the diet/physical activity recalls via telephone.

- The body weight of the subject will be documented.
- 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. The date of the last menstrual period will also be documented, along with usual cycle length, for female subjects.
- The subjects will place a Dexcom G5 sensor and study staff will confirm they are doing it properly.
- The subject will complete the beginning questionnaires regarding their general health and well being, quality of life, diabetes management and dietary habits.
  - We will administer two questionnaires to understand impulsivity and eating behavior, including the short version of the Barratt Impulsivity Scale (BIS-15) will be used to assess trait impulsivity (15 items, 2-3 minutes) (10) and the full Dutch Eating Behavior Scale (33 items, 10 minutes) (11) to measure three different eating behaviors: emotional eating (eating in response to emotional arousal states such as fear, anger or anxiety), externality (eating in response to external food cues such as sight and smell of food), and restrained eating behavior/cognitive restraint (conscious efforts to limit and control dietary intake) (11).
    - **General Impulsivity (BIS-15; 15 items 2-3 minutes) (**10**).** The short version of the Barratt Impulsivity Scale (BIS-15) will be used to assess trait impulsivity. Subjects report the extent to which various descriptions regarding impulsivity apply to them using a response format ranging from 1 = rarely/never to 4 = almost always/always (10). This scale has shown internal consistency (α = .79 - .83), 2-week test-retest reliability (r = .88), and discriminates between psychiatric patients and controls (10). The Barratt Impulsiveness Scale (10) has been described as a gold-standard measure that has been influential in shaping current theories of impulse control, and has played a key role in studies of impulsivity and its biological, psychological, and behavioral correlates (12). The15-item short form of the BIS (BIS 15) has been shown to retain the 3-factor structure (nonplanning, motor impulsivity, and attention impulsivity), as well as maintain good reliability and validity (13).
    - **Dutch Eating Behavior Scale (33 items, 10 minutes) (11).** The Dutch Eating Behavior Questionnaire (DEBQ) was developed to measure eating styles that may contribute to or attenuate the development of overweight. It comprises three scales that measure three different eating behaviors: emotional eating (eating in response to emotional arousal states such as fear, anger or anxiety), externality (eating in response to external food cues such as sight and smell of food), and restrained eating behavior/cognitive restraint (conscious efforts to limit and control dietary intake) (11). The norms and Cronbach's alpha coefficients of the scales and also the Pearson's correlation coefficients to assess interrelationships between scales indicate that the scales have a high internal consistency and factorial validity (11).
    - **Low Blood Sugar Survey (33 items, 10 minutes).** Fear of hypoglycemia is a common deterrent to physical activity in Type 1 diabetes. The Low Blood Sugar Survey may predict behavior on automated insulin systems. Questions will be self-administered and consist of 33 questions on behavior and worry.
- Study staff will place an accelerometer in a belt on the subject's right hip or on the subject's wrist,

according to their preference, to collect activity data during each week.

- Study staff will place a FreeStyle Libre Pro sensor and activate it. Study staff will assess the Senseonic sensor insertion site and will assist with calibrating the Senseonics sensor.
- Study staff will provide supplies and review the study procedures. 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 are in good communication with each other.
- In the bionic pancreas arms, the subject's own insulin infusion pump will be stopped and disconnected, and its infusion set will be removed.
- 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.

Days 1-7:

All Study Arms

- The subjects will calibrate the Dexcom CGM and the Senseonics CGM twice daily, preferably before breakfast and supper, using the StatStrip Xpress. Ideally the Dexcom and Senseonics CGMs will be calibrated at the same time with the same glucose value. The calibrations must be completed within 5 minutes from the time the glucose measurement is taken. The Freestyle Libre Pro sensor does not need to be calibrated.
    - Subjects will be advised to delay calibration if there is a steep rise or fall in the blood glucose (>2 mg/dl/min), 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 every time they calibrate the Dexcom G5 sensor using the same blood glucose from the StatStrip Xpress meter. All calibrations must be completed within 5 minutes of the glucose measurement. If this cannot be accomplished then another glucose measurement must be performed.
- The Senseonics sensor will be blinded to the subjects in all study arms. Study staff will download the transmitter at the end of each of the study arms.
- The FreeStyle Libre Pro sensor will be blinded to the subjects in all study arms. Study staff will download the transmitter at the end of each of the study arms.
- Subjects will be contacted if Dexcom CGM streaming is interrupted for more than 15 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 other day 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.
- Subjects will complete structured phone interviews about their dietary and physical activity habits during this arm. In addition to assessment at baseline, this includes 24 hour Dietary Recall and Activity Recall on the 6th and 7th day of each arm, as outlined previously.

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. They will be asked not to modify their insulin regimen based on the CGM readings over these two weeks without consulting their own endocrinologist.
- Subjects will be trained to respond to hypoglycemia and hyperglycemia according to their usual practice and best practice recommendations.

Bionic Pancreas Study Arms

- 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 15 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).

Bi-hormonal Bionic Pancreas Arms Only

- 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.
- 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.

Visits 2, 3, 4, 5 and 6: Day 7/Day 1

All Study Arms

- At the end of the 7 day period, subjects will return to the clinic 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 Senseonics transmitter will be downloaded. The FreeStyle Libre Pro sensor will be read. The accelerometer will be downloaded, and saved with the participant ID and monitor number so that data can be linked for analysis.
- If the Freestyle sensor has been in place for two study arms, it will be removed and a new sensor will be placed and activated. The Freestyle Libre sensor will never be worn by a subject for more than 14 days.

- Study staff will assess the Senseonic sensor insertion site and will assist with calibrating the Senseonics sensor.
- A new Dexcom sensor will be placed and calibrated.
- Study staff will place an accelerometer in a belt on the subject's right hip or on the subject's wrist, according to their preference, to collect activity data during each week.
- 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 and/or glucagon pumps and infusion sets. Participants will need to fill pumps with new reservoirs and place new infusion sets if they are switching from a bionic pancreas arm to another bionic pancreas arm.
- If the participant is switching from usual care to bionic pancreas, the subject's own insulin infusion pump will be stopped and disconnected, and its infusion set will be removed.
- 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.

Visit 7: Final Day 7 Visit

All Study Arms

- At the end of the 7 day period, subjects will return to the clinic 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 Senseonics transmitter will be downloaded. The FreeStyle Libre Pro sensor will be read. The accelerometer will be downloaded, and saved with the participant ID and monitor number so that data can be linked for analysis.
- The Freestyle and Dexcom CGMs and all bionic pancreas infusion sites will be removed.
- 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 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.

Visit 8: Final visit - Senseonic sensor site assessment

All Study Arms

- Approximately 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 approximately 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.

V. d. vi. 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.

V. d. vii. 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. viii. 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 ix. 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. x. Monitoring of Bionic Pancreas Performance

Engineers familiar with the operation of the bionic pancreas 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. xi. 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. i. Prior to start of experiment:

- Age
- Sex
- Race and ethnicity
- Date of last menstrual period in female subjects
- 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 used in pump
- Insulin regimen
- 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. If the subject has had the test performed in the past and was negative (no detectable C-peptide) then it does not need to be repeated.
- Hemoglobin

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

- CGMG (CGM glucose) every five minutes from the DexCom G5 CGM and Senseonics CGM
- CGMG every fifteen minutes from the FreeStyle Libre Pro 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 or insulin pump download)
- 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 (in the bi-hormonal bionic pancreas arms)
- Timing and glucose values at calibrations of Dexcom and Senseonics CGM
- Data from a questionnaire about attitudes and expectations regarding the bionic pancreas at baseline and on day 7 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
- Body weight after each arm
- 24 Hour dietary and activity recalls at baseline and after each arm
- Actigraph activity monitor data

VI. b. Study Endpoints
VI. b. i. Primary endpoint analyses

Bionic Pancreas Performance
The primary outcome for bionic pancreas performance will be the fraction of time spent with Dexcom CGMG < 60 mg/dl. This will be generated from the DexCom G5 CGM data during the bionic pancreas and usual care arms, both monitored and un-monitored.

CGM Comparison
The primary outcome for the third aim of the study, comparing the accuracy of the Dexcom, Senseonics and Freestyle CGMs, will be the MARD compared to the Nova Biomedical Statstrip Xpress meter, using CGM readings every fifteen minutes. Because the Freestyle CGM only takes a reading every fifteen minutes, we will chose the closest meter glucose reading that pairs with a Freestyle CGM reading. We will then chose the Dexcom and Senseonics CGM readings that are closest to the Freestyle reading, and compare all three to the same meter glucose.

VI. b. ii. Secondary endpoint analyses
Bionic Pancreas Performance:
- All of following metrics will be generated from the DexCom G5 CGM data during the bionic pancreas and usual care arms, both monitored and un-monitored. Each of these measures will be calculated for the entire period and separately for the daytime and nighttime (11 pm to 7 am), for days 2-7, and each individual day 2-7.
    - Mean Dexcom CGMG
    - Fraction of time spent within each of the following glucose ranges:
        - < 50 mg/dl
        - < 60 mg/dl
        - < 70 mg/dl
        - 70-180 mg/dl
        - >180 mg/dl
        - >250 mg/dl
    - Number of episodes of symptomatic hypoglycemia (reported daily by subjects)
- Percentage of subjects with mean Dexcom CGMG <154 mg/dl (estimated average glucose corresponding to an A1c of 7%)

CGM Comparison:

- CGM Reliability index, calculated as percent of possible values actually recorded by CGM (for Dexcom, FreeStyle, and Senseonics CGMs)
- A two-way comparison of MARDs, comparing Dexcom and Senseonics CGM, using CGM readings measured every 5 minutes and the meter download
- The same two-way comparison of MARDs, comparing Dexcom and Senseonics CGM in the following ranges:
    - Meter BG <70 mg/dl
    - Meter BG 70-180 mg/dl
    - Meter BG >180 mg/dl
- The three-way comparison of MARDs that is specified as the primary outcome comparing the Dexcom, Senseonics and Freestyle CGM, using CGM readings measured every 15 minutes and the meter download in the following ranges:
    - Meter BG <70 mg/dl
    - Meter BG 70-180 mg/dl
    - Meter BG >180 mg/dl

VI. b. v. Other outcomes

CGM

- Correlation between mean Dexcom CGMG and mean number of meal announcements per day
- Fraction of days that CGM was used by participants as part of their usual care
- All of following metrics will be generated during the bionic pancreas and usual care arms, both monitored and un-monitored. Each of these measures will be calculated for the entire period and, as appropriate, separately for the daytime and nighttime (11 pm to 7 am), for days 2-7, and each individual day 2-7.
    - Glucagon total daily dose in bi-hormonal bionic pancreas arm (TDD)
    - Insulin total daily dose (TDD)
    - 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)

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, both monitored and un-monitored.
    - Mean number of daily BG measurements
    - Number of hypoglycemic measurements < 70 mg/dl < 60 mg/dl, and < 50 mg/dl
- Number of severe hypoglycemic events (subject unable to self-treat, requiring the assistance of another person)

Non-glycemic

- Mean nausea severity from VAS
- All of following metrics will be generated during the bionic pancreas and usual care arms, both monitored and un-monitored. Each of these measures will be calculated for the entire period and, as appropriate, separately for the daytime and nighttime (11 pm to 7 am), for days 2-7, and each individual day 2-7.
    - Mean daily basal insulin dose
    - Mean daily bolus insulin dose
- 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
- Alcohol intake (mean drinks per day)
- Exercise duration
- Exercise exposure (duration X intensity)
- 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.
- Change in weight and body composition after each arm
- Dietary data from 24 hr dietary recalls will be entered and analyzed using NDS-R software (Nutrient Data System for Research, St. Paul, MN). We will obtain detailed data on foods and nutrients to evaluate whether, and to what extent dietary behaviors change in relation to use of the BP, particularly intake of carbohydrate and calories, and overall dietary quality. We will assess whether baseline eating behaviors and impulsivity ascertained at baseline predict dietary response to use of the BP.
- Mean daily caloric intake
- Collection of raw acceleration data will allow outcomes to be computed and summarized at multiple epoch (example minute by minute, hourly, daily). Accelerometer data will be used to calculate minutes of moderate and vigorous activity, as well as sedentary time, using appropriate analytic techniques and cut points (16). Physical activity recall data will be paired with accelerometry data to determine behavioral patterns for type of activities in which the participants engage.
- Mean daily calories expended

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 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 may look for any period effect and any interaction between treatment and period. We may, in exploratory analyses, also stratify subjects for secondary analyses of the pre-specified endpoints by subject characteristics including: sex, age, use of CGM in usual care, baseline C-peptide in the context of a mixed meal stimulation test, baseline A1c, usual care insulin total daily dose, body mass index, phase of menstrual cycle (follicular vs. luteal).

VI. c. Power Analysis

In Aim 1 of this study our goal is to test the hypothesis that the amount of hypoglycemia (% time <60 mg/dl) on the bionic pancreas will be less than or equal to the amount of hypoglycemia during the usual care arm both with and without monitoring for severe biochemical hypoglycemia (<50 mg/dl for >15 minutes). A secondary hypothesis is that the difference between the bionic pancreas and usual care arms in % time <60 mg/dl in the unmonitored arms will be greater than or equal to the difference in the monitored arms. In order to adequately power the study, we need a sample size that is sufficient to detect a clinically meaningful increase in hypoglycemia. In our previous outpatient studies less than 1% of the time was spent with CGM glucose <60 mg/dl. In the study most comparable to this design, the Set-point Study, the mean time <60 mg/dl was 0.88 ± 1.32% in the bionic pancreas groups. A clinically meaningful increase in hypoglycemia would be an absolute increase of time <60 mg/dl of 1%, which would represent more than doubling of the predicted amount of hypoglycemia in the bionic pancreas group, and an increase of time <60 mg/dl of 14.4 minutes per day.

The standard deviation of the difference will depend on the within-subject correlation r in this crossover study design. If we assume that the standard deviation of both groups would be the same (1.32%) the following table shows the sample size needed to detect a difference of 1% with an alpha of 0.05 and a power of 0.8 for different values of r.

Effect size	SD of each arm	r	SD of difference	Sample size 1-β=0.8)
1	1.32	0.001	1.87	23
1	1.32	0.01	1.86	23
1	1.32	0.05	1.82	22
1	1.32	0.1	1.77	21
1	1.32	0.2	1.67	19
1	1.32	0.3	1.56	17
1	1.32	0.4	1.45	15
1	1.32	0.5	1.32	13

In previous outpatient studies there has been very little correlation between the amount of hypoglycemia in the usual care group and the bionic pancreas group; the r value varied from 0.012 to 0.15. Therefore, a sample size of 23 subjects is predicted to give an 80% power to detect an increase of 1% in the time <60 mg/dl in the group without monitoring for hypoglycemia relative to the group with monitoring for hypoglycemia. Therefore, we will target an enrolment of 24 subjects to provide a margin of safety in the event that some subjects are unable to complete the study.

VII. Risks and Discomforts

Subjects may experience mild discomfort associated with the insertion of the infusion sets, the Dexcom sensor and the Freestyle sensor into the SC tissues. The risk of discomfort due to insertion of infusion sets and sensors may to be greater than in their lives outside the trial because more infusion sets and sensors than are used in usual care.

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. In our own experience with the Senseonics sensor, 4 sensors were implanted and removed without any unexpected or serious adverse events. 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 risk of hypoglycemia. 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 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. All of our previous studies have shown, albeit with monitoring, that hypoglycemia is significantly reduced in all configurations of the bionic pancreas when compared with usual care. Based on our experience, we believe that the risk of hypoglycemia in study arms without remote monitoring for severe biochemical hypoglycemia will be less than or equal to the risks that they are exposed to on a daily basis while living with type 1 diabetes outside

of the trial.

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 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.

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 have 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.

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.

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 allowing us to increase patient independence and move towards a more outpatient device without monitoring.

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. Both the Senseonics and Freestyle sensors 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 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 and Freestyle 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.

24 Hour dietary and activity recall information will be stored in the Sheps Integrated Research System (SIRS), a secure online database, developed and maintained by the UNC Cecil Sheps Center for Health Services Research. Access to the participant information within the online database will only be available to approved study site staff and trained UNC interviewers. All system login procedures and data submissions will be encrypted via the Secure Sockets Layer (SSL). Sheps Center programmers and research staff who work with sensitive data are required to complete appropriate HIPAA training with periodic updates, complete Sheps Center internal training, comply with the UNC IT Security Policies, and agree to the provisions of the Sheps Center's Rules of Behavior and Sanction Policy. The Sheps Center strives to implement reasonable security controls guided by FISMA, HIPAA, and OMB Circular A-130. The Actigraph saves timestamped acceleration. During data collection no identifying information is stored or collected with the activity monitor.

The study data may be shared with collaborators at Boston University 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
- Infection at the Senseonics sensor insertion site that does not resolve in three days. The sensor will be removed and not replaced.
- A serious adverse event related to the Senseonics device or procedures. The sensor will be removed and not replaced.

If more than 2 subjects must be withdrawn from 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 $50 for completing each study visit. Thus the total compensation for a subject who completed the screening visit, Senseonics sensor insertion visit, the additional 7 scheduled study visits (1 initial day 1 visit, 5 day 7/day 1 visits, and 1 final day 7 visits), and the Senseonics sensor removal site follow-up visit would be $500.

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.

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