The Summer Camp Study: Feasibility of Outpatient Automated Blood Glucose Control with a Bi-Hormonal Bionic Endocrine Pancreas in a Pediatric Population at the Clara Barton Diabetes Camps

Principal Investigator:
Steven J. Russell, M.D., Ph.D.1

Co-Investigators:
Edward R. Damiano, Ph.D.2
Firas H. El-Khatib, Ph.D.2
Manasi Sinha, M.D., M.P.H.1
Mary M. Lee, M.D.3
David M. Nathan, M.D.1

1Massachusetts General Hospital, Boston, Massachusetts.
2Department of Biomedical Engineering, Boston University, Boston, Massachusetts
3University of Massachusetts Medical School, Worcester, Massachusetts

Address correspondence to Steven J. Russell, M.D., Ph.D., MGH Diabetes Center, 50 Staniford Street, Suite 340, Boston, MA 02214, email: sjrussell@partners.org, phone: 617-726-8722, fax: 617-726-8524, page: 617-726-2066

NCT: NCT01833988
Date: February 12th, 2014

I. Background and Significance

I. a. Historical Background

Diabetes is a chronic, life-threatening disease that can result in serious acute and chronic deleterious consequences. Hypoglycemia may result in acute complications including convulsions, seizures, and coma, while chronic hyperglycemia can cause several long-term complications including cardiovascular disease (CVD), renal complications, vision disorders, nerve degeneration, and skin disorders. The risk of CVD alone is elevated by three- to five-fold with diabetes and the diabetes-specific complications (retinopathy, nephropathy and neuropathy) many fold more (1,2,3). Owing to the epidemic growth of diabetes in the past 30 years, diabetes-related morbidity and mortality are rapidly increasing. In the U.S.A., over 22 million individuals (>7% of the population) are afflicted with diabetes (~ 90% of these have type 2), despite about one third being unaware of it. Total diabetes health care costs in the US are above $170 billion annually and are steadily increasing. Diabetes causes over 200,000 deaths annually in the U.S.A. alone.

I. b. The Current Standard of Care

Prior to the discovery of insulin by Banting and Best in 1921 and its subsequent purification by Collip and Macleod (4,5), type 1 diabetes was an inescapably fatal disease. The availability of insulin transformed type 1 diabetes into a chronic disease, now managed by frequent blood glucose (BG) tests and administration of insulin to treat or prevent excursions of BG outside the normal range. The process was facilitated by hand-held BG meters capable of measuring glucose concentration very quickly from small blood samples, and more recently by continuous glucose monitors (CGM) that measure the glucose in the sub-cutaneous interstitial fluid and, once calibrated, provide an estimate of the blood glucose as often as once every minute. Flexibility in administration of insulin has been facilitated by small, precise insulin pumps that administer insulin into the subcutaneous space either continuously to supply basal requirements or as boluses to treat or prevent hyperglycemia from consumed carbohydrates. Analogs of human insulin have been developed that are absorbed more rapidly from the subcutaneous space into the blood, allowing patients to match their insulin dosing to food intake rather than planning meals to match the insulin taken hours earlier.

Even with modern tools, maintaining the blood glucose as close to the normoglycemic range as possible while avoiding hypoglycemia is a very challenging task. The importance of this task to the long term health of people with diabetes was demonstrated by the Diabetes Control and Complications Trial (DCCT), which compared the progression of complications in a group of subjects with type 1 diabetes under intensive BG control with another group under conventional therapy. The intensive control group achieved a mean hemoglobin A1c (HbA1c) of ~7% (mean BG of 154 mg/dl) while the control group achieved a mean HbA1c of ~9% (mean BG of 212 mg/dl). The reduction in mean BG with intensive therapy reduced the development of retinopathy, neuropathy, and nephropathy by as much as 76% relative to the control group (1). A followup study on the progression of cardiovascular disease in some DCCT subjects showed that intensive therapy also had long-term beneficial effects on the risk of cardiovascular disease (2).

The DCCT established that maintaining BG as close to normoglycemic range as safely possible reduced long-term complications of type 1 diabetes and that the tighter this control was, the fewer and less severe were the complications. The drawbacks to tight control include the technical demands of carbohydrate counting, frequent BG monitoring, frequent dosing of insulin via a syringe or insulin pump, and the requirement of making frequent calculations and decisions regarding insulin dosing.

The continuous demands of intensive therapy are challenging and painstaking for even the most diligent, motivated, and educated individual, and can be daunting for average individuals due to the training and self-management skills required. Intensive management is also more expensive in the short term, albeit less expensive when morbidity and mortality are considered. Most importantly, individuals who diligently keep their BG in near physiologic range are more prone to severe hypoglycemia, which can be life threatening.

Although intensive therapy is not a cure for type 1 diabetes and does have costs and drawbacks, it was the single most important technological breakthrough in the management of complications of the disease. Short of islet-cell or pancreas transplantation procedures, exogenous insulin administration, either through injection therapy or continuous subcutaneous (SC) insulin infusion therapy is the only method available for maintaining near normoglycemia in type 1 diabetes patients.

With the recent emergence of practical continuous glucose monitoring (CGM) technologies approved for home use and the increasingly widespread use of insulin infusion pumps, the stage is set for the realization of automated closed-loop BG control. Achieving this goal requires the coordination of three main components into an integrated system; a CGM device, a continuous drug infusion system, and a controller or modulating unit. We have recently completed two clinical studies of a closed-loop BG control device using algorithm-controlled infusions of insulin lispro (Humalog, Lilly) and glucagon (6,7– See Appendices A and B).

I. c. Past Pre-clinical and Clinical Studies

Research efforts to develop closed-loop BG control systems have been ongoing for decades, the Biostator design of Clemens being one of the earliest (8). Like most glucose-control systems (9-12), the Biostator assumed the intravenous (IV) route for drug infusion, and, like most dual-infusion systems (13-15), it used dextrose as the counter-regulatory agent to insulin. While IV infusion results in faster drug bioavailability than SC infusion, its associated risks of infection, embolism, or thrombosis, and the challenge of maintaining permanent IV access, render the SC route more practical for ambulatory usage (16-17).

The SC route poses an additional challenge due to the delayed and attenuated absorption of the infused drug into the blood stream (6,18-19 – see Appendix A). Delays in absorption create the possibility of excessive insulin accumulation in the SC tissue, which can result in delayed hypoglycemia (17), an event that must be safeguarded against in any practical glucose control system. One preventative measure is to use the naturally occurring hormone glucagon as the counter-regulatory agent (20-22). Unlike dextrose or other fast-acting sugars, exogenous glucagon mimics (23) a physiologic process deficient in people with type 1 diabetes (24), in which mobilization of the body's own glucose reserves raise BG. Another measure to prevent hypoglycemia is to have the control algorithm keep track of, and act in light of, the estimated accumulation of SC insulin based on its in vivo pharmacokinetics. Our closed-loop algorithm utilizes both of these strategies. Unlike any other BG control algorithm of which we are aware, our algorithm only requires the subject's weight (for the purpose of initialization only) and regularly-sampled BG for online operation (6-7,21 – see Appendices A and B), without any additional input, such as carbohydrate counting, physical activity, or other user feed-forward information, that is required by other systems (25-27). In essence, it is the only existing BG control system that is truly self-running and self-tuning. We performed pre-clinical studies of this system in a swine model of type 1 diabetes (28) and showed that automated, bi-hormonal, closed-loop control of blood glucose was feasible (21).

To date, we tested the control algorithm in three successful clinical trials. The first of these trials used frequent measurements of venous BG and the SC infusion of insulin and glucagon to achieve and maintain normoglycemia in subjects with type 1 diabetes (6 – see Appendix A). These experiments were 27 hours in duration during which the subjects consumed 3 standardized meals. The only input to the control algorithm was the subject weight and venous BG measurements every 5 minutes. The key conclusion from these experiments was that the control system was able to achieve near-normal mean BG (aggregate mean BG 140 mg/dl, equivalent to a HbA1c of 6.5%) with negligible hypoglycemia in 6 subjects with relatively rapid absorption of insulin lispro. In 5 other subjects with delayed lispro absorption, modifying the insulin pharmacokinetic assumptions of the control algorithm was required to prevent hypoglycemia, and this increased the aggregate mean BG achievable by the control system (mean BG 164 mg/dl, equivalent to a HbA1c of 7.4%). These results demonstrated the feasibility of a bi-hormonal artificial endocrine pancreas. However, the use of venous BG as the input to the algorithm limited the applicability of the system tested to the inpatient setting. In order to develop a system suitable for outpatient use, the BG input to the system need to be obtained using a less invasive method. In the same study we also compared the accuracy and reliability of three commercially available continuous glucose monitors (CGMs) in each subject. We found that one device (Abbott Diabetes Care FreeStyle Navigator) was sufficiently reliable and provided estimated BG measurements that were sufficiently accurate to be used as input for our closed-loop control algorithm. This finding suggested that closed-loop control could be achieved using CGM as the input, potentially making a closed-loop device for outpatient use feasible.

The first clinical trial and pre-clinical studies in diabetic swine suggested additional avenues of investigation and additional challenges that the controller must be able to meet if it is to be validated for outpatient use. In our first study subjects were entirely sedentary due to the requirement of maintaining two intravenous lines for automated BG measurements every 5 minutes and blood sampling for measurement of insulin and glucagon levels every 10 minutes. Exercise can pose a significant challenge to BG control, potentially causing hyperglycemia or hypoglycemia acutely as well as delayed hypoglycemia. Studies including exercise are therefore required to establish the safety and utility of the system in outpatient use. We realized future studies also needed to test the ability of the control system to regulate BG for longer periods of time and to see if there are any differences in BG regulation under prolonged closed-loop control. Finally, our first clinical trial identified delayed absorption of insulin lispro as a key problem for closed-loop control. There are several potential solutions to this problem. More rapidly absorbed insulin is predicted to improve BG control and might potentially reduce inter-subject and intra-subject variability in insulin pharmacokinetics. If a more rapid-acting insulin analog becomes available we will wish to test it in the closed-loop system. However, an approach that can be implemented immediately is delivering a partial pre-bolus for meals delivered through the controller when the meal is presented. This will allow a portion of the insulin to start working earlier and be better matched to carbohydrate absorption. This is important because a fully closed-loop controller is entirely reactive, and can only respond to hyperglycemia once it has occurred; delivery of insulin to the blood is delayed by the subcutaneous route, inevitably resulting in a period of post-prandial hyperglycemia until the controller is able to “catch up”. By limiting the size of the partial meal-priming bolus to only a portion of what is anticipated to be required, a margin of safety is maintained against hypoglycemia that might result from an overestimation of the insulin requirement and/or an interruption of the meal. Delivering a partial meal-priming bolus through the controller allows the insulin delivered to be tracked by the controller so that “insulin stacking” i.e. duplicate administration of insulin for the same glycemic excursion can be avoided.

Based on the our results from the first human study and preclinical studies in diabetic pigs, we hypothesized that glycemic control could be achieved in humans with type 1 diabetes using glucose

values from one of these CGMs as the sole input to the controller. The second phase of the our closed-loop controlled trials included testing this hypothesis in experiments more than two days in length that included six high-carbohydrate meals and a period of exercise as challenges to glycemic control (7 – see Appendix B). Subcutaneous dosing of glucagon and insulin were controlled by an algorithm requiring only the subject's weight for initialization. Six subjects with type 1 diabetes and no endogenous insulin secretion each participated in two 51-hour experiments. Blood glucose was managed with a bionic endocrine pancreas controlling subcutaneous delivery of insulin and glucagon with insulin pumps. The only input signal was data from the Freestyle Navigator (Abbott Diabetes Care), an FDA-approved interstitial fluid continuous glucose monitor (CGM). A partial meal-priming bolus of insulin was also given at the beginning of each meal. Blood glucose control was evaluated with a reference quality measurement on venous blood every 15 minutes. Results showed the overall mean blood glucose (BG) was 158 mg/dl, with 68% of BG values in the 70–180 mg/dl range. Hypoglycemia (BG < 70 mg/dl) was rare, with 8 incidents during 576 hours of closed-loop control (0.7% of total time). During 192 hours of nighttime control, mean BG was 123 mg/dl with 93% of BG values in the 70–180 mg/dl range and only one episode of mild hypoglycemia (minimum BG, 62 mg/dl).

The period of exercise markedly increased glucose clearance and was associated with increased glucagon dosing and levels during and immediately following the exercise period. However, no difference was observed in overall glycemic control between the nights preceding and following the period of exercise, in contrast to a previous report that found a lower mean glucose and more hypoglycemia during nights under closed-loop control following a period of structured exercise conducted under open-loop therapy. This apparent difference between our findings may be explained by the lack of a counter-regulatory capability in the insulin-only system used in the previous report.

The second trial of our closed-loop experiments showed that the bi-hormonal bionic endocrine pancreas achieved excellent glycemic control with minimal hypoglycemia over two days of continuous use despite high-carbohydrate meals and exercise. We concluded that a trial testing a wearable version of the system under free-living conditions is thus justified.

Between our second and third trials, we learned that our control system that performed so well in an adult population could not achieve mean glucose levels in adolescents that were substantially different from the standard of care in that population (although with less hypoglycemia). Our early attempts at increasing the aggressiveness of the control algorithm lowered the mean glucose levels in adolescent subjects, but at the cost of significantly more hypoglycemia in adults. After substantially redesigning the algorithm to include methods which allowed the algorithm to adapt robustly online, we sought U.S. Food and Drug Administration (FDA) approval to begin testing our new control system in a cohort that included both pediatric and adult subjects.

Our third trial was designed to test this new ability of our control algorithm to adapt robustly online to the broad range of insulin needs of individual subjects. These new capabilities not only automatically adapted the aggressiveness of the insulin controller, it also allowed the control system to adapt the size of the meal priming bolus based on the amount of additional insulin that was required for previous meals. In this trial participants were randomized to closed-loop control with no meal priming bolus or closed-loop control with adaptive meal priming boluses. Otherwise, the trial was conducted with the same protocol as our second trial, where the closed-loop system used the Navigator CGM as the input in experiments that lasted more than two days, included six meals, and included a 30–40-minute period of exercise. BG was lower in the adaptive meal-priming bolus vs. fully reactive group in both adults (132 vs. 146 mg/dl, $p = 0.03$) and pediatric subjects (162 vs. 175 mg/dl, $p = 0.01$). Although

carbohydrate intake was similar, mean BG was lower in adult subjects in both adaptive and fully reactive groups ($p < 0.001$) despite 64% higher insulin usage in pediatric subjects ($p < 0.005$). The fraction of BG measurements < 70 mg/dl was not statistically different with or without adaptive meal-priming boluses in either adult (5.1% vs. 3.6%, $p = 0.7$) or pediatric subjects (0.3% vs. 0.4%, $p = 0.8$). These results demonstrate that effective BG control can be achieved over a wide range of insulin needs and subject ages with an adaptive bionic pancreas. These results showed that the changes that were made to the adaptation features of the algorithm clearly improved mean BG in children and reduced hypoglycemia in adults. This improved algorithm is the one that we will be using in the trial described by this protocol.

In the third trial we also tested the accuracy and reliability of two new CGM devices, the G4 Platinum (DexCom) and the Enlite (Medtronic), in addition to the FreeStyle Navigator, over the full duration of each experiment. Venous BG measurements (GlucoScout, International Biomedical) obtained every 15 minutes ($n = 4294$ reference values) were paired in time with corresponding CGM glucose measurements. The accuracy and precision of the G4 Platinum outperformed the Navigator, with aggregate mean absolute relative differences (MARDs) of all paired points of 10.8% ± 9.9% and 12.5% ± 12.4%, respectively. Both were significantly different from the Enlite with a MARD of 18.2% ± 16.0%. Data reporting percentages, a measure of reliability, were 99.7% for the G4 Platinum, 99.5% for the Navigator, and 96.9 % for the Enlite. The performance of the G4 Platinum represents substantial improvements in accuracy compared to the previous generation DexCom (Seven Plus), while the performance of the Enlite represents only a modest improvement in accuracy compared to the previous generation Medtronic device (Guardian). In our previous comparative trial with $n = 2360$ reference values (29) these sensors had aggregate MARDs for all paired points of 16.5 ± 17.8% and 20.3% ± 18.0% respectively vs. 11.8 ± 11.1% for the Navigator. The data reporting percentage of the G4 Platinum also represents a marked improvement from 75.9% for the Seven Plus. These data reveal substantial improvements in performance of CGM devices now available in the US market (see Appendix C.) We conclude that either the Navigator or the DexCom G4 Platinum have sufficient accuracy to drive closed-loop BG control. We have therefore built a mobile bionic pancreas using the DexCom G4 Platinum CGM as the input device.

I. d. Rationale and Potential Benefits

The logical endpoint in the evolution of exogenous insulin therapy is to treat type 1 diabetes with an automated, integrated closed-loop glucose-control system. All three enabling technologies (i.e. sensor, controller, and pump) required to realize this goal have developed to a stage at which they can be successfully integrated. Not since the discovery and purification of insulin by Banting and Best in 1921 (4,5) have we been in a better position to improve the lives of people with diabetes. The one technical hurdle remaining is to integrate these technologies into a safe and effective automated closed-loop BG control system.

Our experiments to date in human subjects with type 1 diabetes have demonstrated the practicality of an automated, closed-loop control system for robust glucose regulation using venous BG as the input to the controller as well as continuous glucose monitoring devices.

We hypothesize that the bionic pancreas BG control system we have developed will provide automatic BG regulation, eliminate hypoglycemic episodes, and spare patients with diabetes the relentless tasks of carbohydrate counting, frequent BG monitoring, and manual drug administration, which are painstaking, aggravating, and demand continuous diligence and vigilance. The ultimate purpose of such a system would be to dramatically reduce the deleterious and debilitating complications of type 1

diabetes by achieving superior BG control.

Despite technical limitations of the pump and CGM components, we have shown that a bi-hormonal bionic endocrine pancreas is capable of achieving good BG control with minimal hypoglycemia during two continuous days in the face of high-carbohydrate meals and exercise. Control was particularly good at night, achieving mean BG values in the normal range with no clinically significant hypoglycemia. The studies to date pave the way for longer-term, more definitive studies of a wearable version of this system incorporating more robust pump technology in settings similar to an outpatient setting, yet with close supervision for safety.

In our first trial of this type, which began in February, 2013, adult research volunteers stay in a hotel at night and have freedom of movement in the downtown Boston area during the day. They have minimal restrictions on their activities, food intake, exercise, and schedule over a closed-loop control period of five continuous days to fully test the capabilities of the bionic pancreas device. Despite the great degree of freedom that research volunteers have during the study period, they also have very close supervision by nurses who stay with them at all times and monitor them around the clock for safety. This study, called the Beacon Hill Study, has been approved by the FDA and the MGH Institutional Review Board (IRB) and will conclude in June, 2013.

The current study is designed to test the capabilities of the bionic pancreas system in youth in a realistic, challenging environment with close supervision for safety. We have chosen the diabetes camp environment for this study because it will present the bionic pancreas with challenges to blood glucose control that are as great or greater than would be faced in the daily life of children with diabetes, yet affords the opportunity for close supervision and monitoring of multiple children participating in the study simultaneously. This study is planned for June through August of 2013 at the Joslin Diabetes Camp (boys) and the Clara Barton Diabetes Camp (girls).

Recently, a study using a closed-loop system to do nighttime-only closed-loop control was published (30). This trial compared closed-loop control to usual care for one night each in a cross-over design in 56 volunteers. This study found less hypoglycemia and a trend towards lower BG in the closed-loop group, although the latter trend did not reach statistical significance. Our study is considerably more ambitions; 32 volunteers will each participate in five days of closed-loop and five days of usual care in a crossover design for 160 nights and days of closed-loop control. Notably, daytime control is considerably more challenging as glucose disturbances caused by meals and exercise must be managed by the bionic pancreas system.

We are currently performing a study in adults similar to the study we are proposing here. The Beacon Hill Study enrolls adults for five days of closed-loop control with a bionic pancreas and five days of usual care. During the closed-loop period the volunteers stay in a hotel near MGH at night and are free to roam a three square mile area of Boston during the day. A nurse stays with them for safety during the day and we do remote monitoring from an adjoining hotel room at night. At the time of submission, two volunteers have completed the study and the bionic pancreas system has performed well, both in terms of reliability and in terms of blood glucose control. By the time we begin the Camp Study in July, 2013 at least 20 volunteers will have completed the Beacon Hill Study.

The results of the adult (Beacon Hill) and pediatrics (Summer Camp) studies will lead the way to testing our bionic endocrine pancreas in an outpatient setting with less supervision and monitoring in future studies.

II. Hypothesis and Specific Aims

We hypothesize that our wearable closed-loop blood glucose (BG) control system can provide BG control in volunteers with type 1 diabetes using the estimated BG signal from a continuous glucose monitor (CGM) as the input signal to the controller in an outpatient environment, one that will minimally constrain the behavior of volunteers while still allowing close observation for risk mitigation, high density data collection, and human factors analysis. The specific aims of this study are:

Aim 1. To test the safety and efficacy of the bi-hormonal closed-loop bionic pancreas that is mobile, wearable, and adaptive in regulating BG in youth 12-20 years of age in a diabetes camp environment.
The bionic pancreas will be compared to usual care in a crossover design in which each volunteer will serve as his or her own control. Each volunteer will be under closed-loop glucose control for five days and usual camp level of diabetes care for five days in random order with a one day washout period in between. The study will be carried out at the Clara Barton Diabetes Camp and the Joslin Diabetes Camp. Both camps are in North Oxford, MA and both are managed under the Barton Center for Diabetes Education with an integrated health care team and Medical Directors. Volunteers will participate in the usual camp activities during the day, will eat the usual camp meals, and will stay in camp cabins at night. They will be fully integrated into the non-study population and will have blood glucose monitoring as usual during both closed-loop and usual care periods except that 3:00 AM BG check that is sometimes done in normal camp care will be replaced by a 3:45 AM check done routinely in study volunteers. In addition, capillary BG checks for study volunteers will be tested using a highly accurate, laboratory equivalent meter (HemoCue). Blinded continuous glucose monitoring will be done during the usual care period. During the entire experiment, the CGM data of all volunteers will be continuously monitored by study staff around the clock using telemetry. The primary outcome measures will be the difference between closed-loop and usual care in mean blood glucose and the fraction of BG measurements < 70 mg/dl. Secondary outcomes will include the same measures as defined by CGM, and CGM accuracy, as well as hypoglycemia requiring intervention with carbohydrate or rescue glucagon.

Aim 2. To document the interaction of the volunteers with the closed-loop device for human factors analysis, with the goals of optimizing the user interface for the device.
Any problems with device functioning will be carefully documented with the efforts required for resolution. An electronic log will be created of all user interactions with the closed-loop device. Study staff will also document comments made by the volunteers about the device over the course of the study. The study staff's role will be observational, except for interventions required to maintain the safety of the volunteer (for instance, to treat hypoglycemia) and to maintain data integrity. There will be a brief structured interview for participants at the beginning of the study and at the end of the study to gather data on attitudes towards closed-loop BG control before and after an extended period of closed-loop control. To further investigate the behavioral aspects and experience of participating in bionic pancreas research trials a post study interview will be conducted by phone with a randomly selected subset of subjects. Subjects will be invited by email and/or phone to participate and will sign and addendum consent prior to participation. A study physician or nurse practitioner will conduct an hour-long interview via telephone with the subject. In order to help guide these interviews and analyze the responses, up to 3 biobehavioral specialists will also be on the telephone call with the subject. The subjects will be de-identified from the standpoint of the collaborators as the study physician or nurse practitioner will initiate the call and add the behavioral specialists to the call once the initial greetings have been completed. Subjects will be made aware of the collaborator involvement during the consent process. This information will be used to assess user satisfaction with the device, and to document any

specific complaints or suggestions for improvement, as well as guiding survey development for future studies.

III. Subject Selection

III. a. Inclusion Criteria

- Age 12-20 years with type 1 diabetes for at least one year.
- Diabetes managed using an insulin infusion pump and rapid- or very-rapid-acting insulins including insulin aspart (NovoLog), insulin lispro (Humalog), and insulin glulisine (Apidra) for at least three months prior to enrollment.
- Otherwise healthy (mild chronic disease such as asthma will be allowed if well controlled that do not require medications that result in exclusion).

No volunteers will be excluded on the basis of gender or race. The requirement that volunteers manage their diabetes using subcutaneous insulin infusion pump therapy is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

III. b. Exclusion Criteria

- Unable to provide informed consent, informed assent or parental consent
- Unable to comply with study procedures.
- Current participation in another diabetes-related clinical trial other than one that is primarily observational in nature.
- Total daily dose (TDD) of insulin that is > 2 units/kg.
- Pregnancy (positive urine HCG), plan to become pregnant in the immediate future, or sexually active without use of contraception
- Hypoglycemia unawareness (self-reported or legal guardian report of consistent lack of hypoglycemia symptoms when BG is < 50 mg/dl)
- End stage renal disease on dialysis (hemodialysis or peritoneal dialysis).
- Personal history of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma
- History of prolonged QT or arrhythmia
- History of congenital heart disease or current known cardiac disease
- Acute illness (other than non-vomiting viral illness) or exacerbation of chronic illness other than T1D at the time of the study.
- Seizure disorder or history of hypoglycemic seizures or coma in the last five years
- 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 second generation anti-psychotic medications, which are known to affect glucose regulation.
- Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference.
- Use non-insulin, injectable (e.g. exenatide, pramlintide) or oral (e.g. thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, acarbose) anti-diabetic medications.
- History of adverse reaction to glucagon (including allergy) besides nausea and vomiting.
- Unwilling or unable to completely avoid acetaminophen during the usual care and closed-loop BG control portions of the study.

- History of eating disorder 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
- Any factors that, in the opinion of the principal investigator, would interfere with the safe completion of the study procedures.

III. c. Source of Subjects

Volunteers who fit the selection criteria will be considered as candidates for this study. Advertisements will be posted at the MGH Pediatric Diabetes Center and through the Barton email distribution list. Previous camp participants will be contacted through the Barton Camp Recruitment process. Previous closed-loop volunteers may also participate if eligible. We will post basic information about the trial along with contact information on our website www.bioinicpancreas.org and on the website of Children with Diabetes (a support and advocacy group), the Family Diabetes Network, and the Joslin Diabetes Center and University of Massachusetts Medical School websites. The study will also be posted on www.clinicaltrials.gov. A letter will be sent to campers enrolled in the proposed weeks of camp study conduct and to previous campers and those interested in camp participation. Information on the trial may be posted on the camp website. We may also contact individuals who have previously inquired about participation in our studies and have asked us to keep their contact information on file.

IV. Subject Enrollment

For the purposes of the IRB and consent 12-17 years of age is referred to as pediatric and 18 and older is adult, but for the purposes of the FDA 21 years of age and older is considered an adult. For that reason experiments will be described by specific age ranges rather than as “pediatric” or “adult”.

IV. a. Number of Subjects

It is expected that we will have 32 volunteers, 16 females and 16 males, complete full-length closed-loop experiments (5 days of closed-loop BG control). We will attempt to recruit participants in roughly equal numbers in the following age cohorts: 12-13 years, 14-16 years, and 17-20 years. We expect that the experiments can be accomplished over a period of 4-6 months. Up to 64 volunteers with type 1 diabetes will be enrolled, 32 females and 32 males. 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). Studies will be conducted sequentially at the two proposed sites.

We will also ask non-participants meeting who are attending camp at the same time and who meet key criteria for study inclusion (age 12-20, use of insulin pump) for permission to review their camp records and to document pre-meal, pre-snack, bedtime, and midnight glucose values, as well as glucose interventions for hypoglycemia, and to get the result of their last A1c test prior to attending camp.

IV. b. Enrollment Procedures

Interested prospective participants will be briefed by a study staff member by phone regarding the study procedure and the inclusion and exclusion criteria. Potential volunteers will be sent a packet containing two copies of the informed consent document by mail along with screening laboratory forms (to be used only after consent is obtained). They may also be sent an electronic copy of the packet via email.

Non-participants will be asked for consent at either camp intake or on the last day of camp. They will be given a one page information sheet and provide verbal consent.

IV. c. Consent Procedures

Once potential subjects have had time to review the consent document, they will either meet in person or have a telephone conference with a study physician or nurse practitioner who will explain the study, answer any questions, and administer informed consent. For subjects 12-13 years of age the consent of a parent or legal guardian will be documented on the consent form, and the assent of the potential subject on the youth assent form. For subjects 14-17 years of age, the consent of the parent or legal guardian and the assent of the potential subject will both be documented on the consent form. Subjects 18 years of age and older will have consent documented on the consent form. In the event that a subject turns 18 during the course of the study, written consent will be obtained from the subject before proceeding with further study procedures.

If a nurse practitioner is administering the consent, a physician will be available as back-up for additional support if needed and subjects will be offered the chance to speak with a study physician if they wish. In the event that a subject is a patient of one of the study physicians or nurse practitioners, another study physician or nurse practitioner will answer questions and administer consent.

Due to the great deal of interaction between the subject and camp study personnel, all subjects enrolled in the study must be able to speak and understand English sufficiently. In the event that a minor who is interested in our study and sufficiently speaks English but their parents do not speak English, parents may give permission to enroll their child through use of a “short form” following the guidelines set forth by the PHRC.

When consent is obtained by phone, subjects and/or subject guardians will sign and date both forms and return to our office at MGH. Telephone consent will be documented on a case report form. Once we receive the signed consent forms, we will sign both and send the subject one copy and keep one copy for our files.

The study physician or nurse practitioner will also answer any questions that the subject 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 may choose to discontinue their participation at any time. Subjects and subject guardians will be informed that obtaining screening labs does not necessitate or guarantee participation in the study.

Non-participants will receive a one page information sheet. They will have the opportunity to ask a study staff member any questions they may have. Verbal consent will be obtained. If they consent they will be asked to sign a release of medical information form requesting only the latest hemoglobin A1c result and provide the fax number and/or address of their physician.

V. Study Procedures

Note that these study procedures apply only to study participants. The involvement of consenting non-participants will be limited to a retrospective review of their chart. They will have no direct contact with study staff, will interact with study devices or drugs, and there will be no modification or real-time monitoring of their camp care.

V. a. Screening data

- Age
- Sex
- Race and ethnicity
- Date of last menstrual period in female volunteers post-menarche
- 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
- Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
- Average total daily dose of insulin in the last 30, 60, and 90 days as available (from pump history)
- 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)
- History of insulin types used (beef insulin, pork insulin, regular human insulin, NPH insulin, ultralente insulin, insulin aspart, insulin lispro, insulin glulisine, insulin detemir, insulin glargine)
- Height and weight by report via phone screening
- Hemoglobin A1c (if a value in the last 3 months is not available, one will be obtained)

V. b. Drugs

The bi-hormonal study involves subcutaneous administration of insulin lispro (Humalog, Lilly) and glucagon (Lilly). Both are commercially available by prescription and are indicated for patients with type 1 diabetes.

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 less than 1000 µg. The recommended dose of glucagon for a patient suffering from severe hypoglycemia is 1000 µg as a single injection. Mean glucagon levels in our previous closed-loop studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of volunteers is expected to be modest.

V. c. Devices

Infusion sets:
Volunteers will wear two FDA approved commercially available infusion sets in the skin of the abdomen, one for insulin infusion and one for glucagon infusion. If an infusion set falls off or is clinically suspected of failing, it will be replaced with a new one. The insulin and glucagon infusion sets will be changed every 24 hours.

Continuous glucose monitors:
One transcutaneous glucose sensor for the DexCom G4 Platinum will be inserted in the abdominal subcutaneous tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the G4 receiver. If the G4 sensor fails for any reason during the experiment it will be replaced promptly.

Bionic Pancreas Control Unit:
The control unit consists of a stock iPhone 4S and a DexCom G4 Platinum receiver connected with a custom hardware interface and placed back-to-back in a custom enclosure. The G4 receiver converts the raw wireless signal from the transmitter into an estimated BG signal that is sent via a hardwired connection to the iPhone.

The iPhone runs iOS 6 in "Guided Access" mode, where the only app accessible to the subject is the Beta Bionics app, which runs the control algorithm. Access to other functions on the iPhone (namely, the home screen and the Settings app) is password protected and will be accessible to study staff personnel, but not to the subject. The control algorithm app has a graphical user interface (GUI) that displays the current CGM glucose, a graphical history of the 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 meal as larger than typical, typical in size, smaller than typical, or just a bite. 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 of meal.

The GUI can also be used to manage open-loop control of meal boluses and correction boluses during periods when the 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, which can be temporarily scaled up or down or suspended by the user. The automatically selected basal rate will be either based on the volunteer'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 iPhone communicates wirelessly via the Bluetooth Low Energy (BTLE) protocol with two Tandem t:slim insulin pumps to deliver insulin and glucagon.

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.

HemoCue Blood Glucose Meter:
The HemoCue is an FDA approved blood glucose meter with lab-equivalent accuracy. Blood glucose measurements will be obtained via fingerstick with the HemoCue meter per camp schedule during the usual care visit and at least seven times per day during the closed-loop visit. Standard care at camp is for BG to be checked at least six to seven times per day so this will follow a similar regimen with (occasionally) only one to two extra readings per day. HemoCue measurements will also be used to calibrate CGM devices during the usual care and closed-loop study visits.

V. d. Experimental Procedures and Data Collection

V. d. i. Screening Visit:

- All volunteers will have a screening visit to confirm eligibility.
- The volunteer will be interviewed and the case report form will be completed by a study nurse or study physician to establish whether the volunteer is eligible to continue with the screening.
- If a laboratory hemoglobin A1c drawn within 3 months of the time of screening is not available, one will be obtained.
- A study physician or nurse practitioner will review the case report form and laboratory result to determine volunteer eligibility.
- The screening visit may be performed over the phone
- The order of the usual care monitoring and closed-loop visits will be randomized in blocks of two volunteers.

V. d. ii. Summary of Normal Camp Policies and Procedures

During the usual care monitoring portion of the study, all of the usual camp procedures will be followed. **The full medical policy manual is provided as Appendix D, but a summary is provided here for context.**

Opening Day:

- Campers check in
- Review of insulin regimen by resident camp physician who writes insulin orders
- Basal rates typically decreased by approximately 20%
- Carbohydrate ratios and correction factors usually unchanged

Daily Routine:

- Breakfast ~7:30 AM on weekdays, 8:00 AM on weekends**
- Activity*
- Activity*
- Lunch 12:00PM**
- Activity*
- Activity*
- Dinner 5:45 PM**
- Activity*
- Snack 8:30 PM**
- 12:00 AM BG check (routine)

- 3:00 AM BG check if 12:00 AM check required intervention

*Activity periods are divided by intensity into More Active and Less Active categories. Campers typically have two More Active and two Less Active periods daily.

**BG checks are done 10–30 minutes before meals/snacks with insulin bolus 10–15 minutes before meals.

BG Testing:
BG values will also be performed before each meal (breakfast, lunch, dinner), before, bedtime snack, and at midnight.

Nutrition:
The menu is developed prior to camp and assessed for balance and compliance with the USDA's nutritional requirement suggestions. Alternative menu options are provided for restricted diets and food allergies. During each session, the dietitian intern will continue to evaluate the meal choice for nutritional breakdown and impact on blood sugar readings and activity levels. In addition, the dietitian works closely with the kitchen staff to assure healthy food options and preparation as well as provide an accurate carbohydrate count for insulin dosing. The dietitian intern is responsible for connecting with families regarding dietary restrictions and food allergies. Meals are served family style.

Medical supervision:
The resident camp physician and health care team will review the camper chart and develop guidelines and a plan of care. The camp healthcare provider is responsible for health care needs and supervision of insulin administration. Tasks may be delegated as per Massachusetts Department of Public Health and the Nurse Practice Act. A resident camp physician is on site and is available by cell phone or satellite phone in cases of emergency or camper illness.

BG target range:
During the day BG target is 80-120and at night BG target is 120-150 mg/dL.

Blood sugar monitoring:
BG is checked prior to each meal, snacks and at 12:00 AM. There may be additional BG checks between midnight and 6 AM as determined by the resident camp physician.

Ketone monitoring:
Blood or urine ketones are checked when BG readings are > 250 or with complaints of illness. Blood ketone results are preferred when a camper is on Depokote, and cases of suspected diabetes ketoacidosis.

Pump failures:
Contact the resident camp physician or on-call physician for orders regarding change in diabetes management. Inform the camper's parents if the pump is defective and needs to be replaced.

Hyperglycemia management, BG is ≥250 mg/dl:
- Check ketones (urine or blood)
- Negative ketones (trace urine ketones, < 0.6 mmol/l blood ketones)
    - Give a correction to the ordered target (typically 120–150) and increase fluids

    - May continue activity
    - Recheck in 1 hour If the blood sugar is coming down, recheck in another hour until BG < 250 mg/dl.
    - If the blood sugar is going up, give the correction by injection and change the pump site
- Positive ketones (small urine ketones or ≥0.6 mmol/l blood)
    - Change the pump site and increase fluids.
    - Give insulin correction by injection to ordered target (typically 120–150 mg/dl).
    - Obtain hourly blood glucose readings.
    - Discontinue activity until ketones have cleared
    - Notify the physician of blood sugar reading >300 mg/dl and anytime there are positive ketones.

Hypoglycemia preparedness:
Hypoglycemic reaction kits are located in each gathering location and are also carried by each member of the health care team. Reaction kits include: alcohol pads, single-use lancet device, glucometer, strips, cotton ball, reaction slips, pen, glucose tabs, juice or glucose gel, complex carb appropriate for nut allergies and celiac disease. Glucagon kits are available at the infirmary.
Mild hypoglycemia (mild signs and symptoms or BG 60–80 mg/dl, able to self treat):

- Give15 gm of rapid-acting carbohydrates (glucose tabs, juice, milk, gel, etc.)
- Wait 15–20 minutes and recheck BG
- If BG is >70 mg/dl, give15 grams of complex carbohydrate (typically snack crackers with peanut butter or cheese). Omit the 15 grams of complex carbohydrate if a meal or snack is scheduled within one hour.
- If BG is <70 mg/dl, restart treatment algorithm

Moderate hypoglycemia (having difficulty treating self or BG<60 mg/dl):

- Treat with 15 gm glucose (gel, juice, glucose tabs) or low dose glucagon
- Low dose glucagon dosing:
    - 10 units for ages 10 and under
    - 15 units for ages 11–15
    - 20 units for ages > 15
- Consider setting a temporary basal rate of 0% for 60 minutes
- Wait 15–20 minutes and recheck BG
- If BG is > 70 mg/dl, give 15 gm of complex carbohydrate
- If BG is < 70 mg/dl, restart treatment algorithm (may repeat low dose glucagon once)

Severely impaired or unresponsive (does not follow commands or seizure activity):

- Attempt instant glucose in the cheek while waiting for health care team to arrive.
- Suspend the pump or disconnect from the pump (do not remove the site)
- Administer glucagon 0.5 mg (for age 10 and under) and 1 mg (over the age of 10)
- Wait 15–20 and recheck the BG
- If the BG is>70 mg/dl after glucagon treatment and patient is alert enough to swallow, give water or sugar containing liquid before complex carbohydrates to assess vomiting
- Recheck BG in 15 minutes
- Continue to monitor blood glucose readings at least once per hour until individual is no longer vomiting and BG levels are stable.
- If the BG is not rising, there is a need to repeat glucagon, or the camper continues having a

seizure, the physician on site may consider calling 911 for assistance.
- Notify the parent/guardian (if in the middle of the night, wait until the morning)

Hypoglycemia Prevention:
- Snacking for physical activity:
  - 30–40 grams for hiking
  - 15–20 grams for adventure activities like kayaking.
- For impending hypoglycemia:
  - Treat with 15-20 gm of fast-acting carbs or low-dose glucagon, suspend activity for 15 minutes.
  - Recheck BG. If blood glucose is trending up, eat a small snack with protein or a meal. If not, repeat fast-acting carbs or may repeat low dose glucagon once.
- For especially intense physical activity:
  - Aim for a blood glucose target of 150–180 prior to activity
  - Pump: Set a reduced temporary basal of 50–75%for one hour before and up to 4 hours after the activity
  - If BG > 200 mg/dl, do not adjust insulin dose but monitor blood glucose throughout the activity. Consult with the physician prior to correcting the blood sugar.
  - If blood glucose is ≥ 300, correct the blood sugar to 200.
  - If ketones are present, do not exercise until they clear.

Meal and daytime snack insulin doses:
- Insulin dosing per resident camp physician orders
  - BG (mg/dl) Treatment
  - > 80 mg/dl Bolus/injection 15–20 minutes prior to the meal or snack
  - < 80 mg/dl Treat low BG as usual and bolus for the meal at the table

Bedtime snack insulin management:
- Insulin dosing per resident camp physician orders
  - BG (mg/dl) Treatment (based on 30 g carbohydrate snack)
  - < 70 Double snack (no coverage)
  - 70–99 Free snack (no coverage)
  - 100–149 One-half usual coverage for snack
  - 150–199 Cover the snack, do not correct BG
  - ≥ 200 Cover the snack, correct BG to 150 mg/dl

V. d. iii. Study-specific Procedures

Closed-loop and Usual Care Visit Day 0 – DexCom G4 Platinum Sensor Placement:
- Volunteers will check in to the camp the day before the start (Saturday) at 11:00AM.
- Up to 8 volunteers may perform a closed-loop experiment at the same time and be integrated with the other campers' accommodations. During bedtime hours study staff will have the ability to access all cabins so that they can respond to any issues or emergencies that may arise.
- Volunteers will bring any routinely used medications. The camp will be responsible for dispensing medications other than insulin and glucagon during the closed-loop portion of the experiment. During usual care, all medications will be dispensed by the camp.

- Any medical advice needed by the volunteers during their participation that is not directly related to BG control during the experiment should be obtained by them in the usual manner at camp.
- Subjects may take any over-the-counter medications that are recommended by the camp physician during the trial except acetaminophen, which will not be allowed due to potential interference with CGM sensing.
- If a volunteer develop an illness during the experiment camp guidelines will be used for sick day management. If vomiting occurs, a study physician or nurse practitioner will be notified and will evaluate the volunteer in person.
- Female volunteers post-menarche will provide a urine sample for urine pregnancy testing. If the test is positive the volunteer (and legal guardian if less than 18 years of age) will be informed of the result by the study staff and they will be excluded from participating.
- Height, weight, blood pressure and temperature will be measured. A brief history and physical will be performed by a study physician or nurse practitioner.
- The DexCom G4 sensor will be placed by 1:00 PM and linked to the CGM receiver in the bionic pancreas control unit. For volunteers in the control arm the bionic pancreas control unit will have a modified interface that does not report CGM glucose, but does include an interface to allow entry of BG values.
- Initial calibration (at 2 hours after placement, at approximately 3:00 PM) will be performed by the study staff using the HemoCue meter.
- An additional calibration will be performed before dinner.
- Volunteers have their BG managed according to usual camp protocols until the following day.

CGM Monitoring of Usual Care Days 1–6 (5 days):

- An additional calibration will be performed by the study staff before breakfast and before study start at 3:00 PM using the HemoCue meter.
- A member of the study staff will be monitoring all volunteers in the usual care arm via telemetry around the clock. The staff monitoring telemetry will be able to communicate with camp healthcare providers by radio or cell phone and there will be a study "runner" on call to deal with any issues that may arise with functioning of study device or if telemetry staff is unable to contact the cabin camp healthcare provider..
- The G4 CGM system will be blinded to the volunteers and the high and low glucose alarms will be turned off. This will ensure that volunteers will not use this data to modify their BG control strategy. The screen of the bionic pancreas control unit will be locked except for access to enter BG values and all audible alarms will be silenced. The bionic pancreas worn by volunteers in the usual care arm will be streaming data to the SweetSpot cloud service for remote real-time monitoring by study staff, but it will not be controlling insulin or glucagon infusion.
- All BG values taken as a part of usual care will be entered into the bionic pancreas interface.
- The experimental period will begin at 3:00 PM on the first day of the camp session (Sunday).
- Over the next five days (3:00 PM Sunday to 3:00 PM Friday) volunteers will have their BG managed according to the camp's health care manual. All BG measurements will be performed by study staff or camp healthcare providers with the HemoCue device. Study staff will calibrate the G4 before breakfast and before supper with the HemoCue BG meter.
- During the experiment the bionic pancreas device will be worn by the volunteer or kept nearby (such as when sleeping) at all times to ensure good radio-frequency signal reception. The device may be removed for short periods of time (no more than 30 minutes) for showering and swimming.
- If during the course of an experiment, a DexCom G4 sensor fails (reports sensor failure, ceases

to transmit data, reports multiple calibration failures, or reports questionable data) a new sensor will be inserted and calibrated.
- Volunteers who are counselors will have to remain on the camp grounds during their days off.
- There will be a camp health care provider assigned to each camp cabin throughout the usual care period.
- Camp nurses will be asked to document all hypoglycemia and carbohydrate interventions for hypoglycemia.
- Camp nurses and counselors will be asked to maintain a schedule of active and less active sessions for each camper.
- As a difference from the camp usual care protocol, BG levels will be measured at midnight and 3:45 AM (regardless of the value at 12:00 AM) using the HemoCue point of care BG meter. There may be additional BG checks between 11 pm and 7 am as determined by a nocturnal hypoglycemia alert system (see closed-loop section below). Extra BG checks may be performed during the day depending on how many episodes of hypoglycemia occur (which trigger more frequent measurements), or on order of the resident camp physician.
- The only other difference from usual camp protocol is that hypoglycemia intervention rules will follow the same protocol as in the closed-loop BG control group (described below).
- At 3:00 PM on day 6 (Friday) the usual care portion of the experiment will end. The DexCom CGM will be removed.
- The volunteer's insulin pump will be downloaded for information on insulin dosing and carbohydrate intake during the usual care period.

Closed-loop Blood Glucose Control Days 1–6 (5 days):
- A member of the study staff will be monitoring all volunteers in the closed-loop arm via telemetry around the clock. The staff monitoring telemetry will be able to communicate with camp healthcare providers by radio or cell phone and there will be a study "runner" on call to deal with any issues that may arise with functioning of study device or if telemetry staff is unable to contact the camp healthcare provider.
- Subjects will continue their normal basal insulin infusion through their own pump until 3:00 PM on the first day of camp (Sunday).
- The reservoir of one of the Tandem infusion pumps will be filled with 3 ml of insulin lispro (Humalog, U-100) according to the manufacturer's instructions and the reservoir of the second Tandem infusion pump will be filled with 2 ml of glucagon prepared from a Lilly kit (Lilly glucagon, 1 mg/1 ml) according to the manufacturer's instructions. These infusion pumps and associated tubing and infusion sets will be labeled with the drug they contain. The insulin reservoir in the pump will be replaced every 48 hours. The glucagon reservoir will be replaced every 24 hours with one that contains freshly reconstituted glucagon prepared from a new Lilly kit (Lilly glucagon, 1 mg/1 ml) according to the manufacturer's instructions. We have received an Investigational New Drug (IND) exemption from the FDA for use of glucagon in this application for up to 27 hours.
- Two infusion sets that are FDA approved for subcutaneous insulin infusion will be inserted in the abdominal area and infusion sites will be labeled. The infusion sets will be connected to the Tandem t:slim infusion pumps, one site for insulin and one for glucagon. The standard priming sequence will be performed according to manufacturer's instructions.
- The control algorithm will be initialized only with the volunteer's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the bionic pancreas (DexCom G4, iPhone running the control algorithm, Tandem t:slim infusion pumps) are in good communication with each other.

- Just before 3:00 PM the volunteer's own insulin infusion pump will be stopped and disconnected, its infusion set will be removed, and closed-loop control will begin. Once closed-loop control is started volunteers will be monitored by study staff in addition to camp staff.
- There will be two RNs and one NP or MD provider on site performing monitoring of study subjects at all times during the daytime. There will be at least one RN and one NP or MD provider monitoring study subjects overnight while campers are in their cabins. These study staff will be in addition to the camp providers, which consist of two camp physicians, one charge nurse, and one nurse or nursing school graduate (RN/NG) per cabin of campers.
- There is always one camp RN/NG with each group of campers wherever they are. Campers may be grouped with their cabin mates or may be grouped with similar aged campers based on their choices for activities. During activities the camp RN/NGs set up a testing/hypoglycemia treatment station for that activity and monitor all of the campers doing that particular activity. In some cases when an activity has more than one cabin worth of campers, two RN/NGs may be assigned to the group. Each group of campers also has at least one counselor with them at all times, which allows the camp RN/NGs to focus entirely on medical care.
- Study RNs and MD/NP providers will provide additional monitoring for study subjects above and beyond what is provided by the camp staff.
- During activity periods the subjects may be in up to five locations based on camp activities. During those times the study RNs and MD/NPs will circulate between the locations where study subjects are located, focusing their time more on subjects who, based on telemetry, may be more likely to become hypoglycemic or hyperglycemic. They will be in constant contact with the telemetry monitoring staff to facilitate this. If there are no indications of risk for any particular subject they will circulate between activities, focusing more time on activities that are more vigorous.
- There are some times when all of the campers congregate together, and for these times the staff RNs and MD/NPs will provide monitoring with at least one RN, MD, or NP per four subjects.
- There is no area of the camp that is commonly visited by campers that is more than ~ 300 yards from any other area, so it will be easy for study staff to circulate and to get from one area to another if needed. Under the unusual circumstances when campers go further than this (i.e. for a hike) a study staff member will accompany that group carrying all needed supplies (which will also be duplicated by the camp RN/NG who will also accompany such groups. The remaining members of the study team will remain at the main camp area, maintaining the same ratio of study staff to subjects.
- Before disconnecting from the device for shower:

BG	Treatment
< 100 mg/dl	15g rapid acting carbohydrate

- Over the next five days (3:00 PM Sunday to 3:00 PM Friday) the bionic pancreas will control insulin and glucagon dosing and the volunteers will otherwise be treated according to camp guidelines except for specifically noted exceptions in the protocol.
- During closed-loop control the glucose measurements from the CGM will be transmitted to the bionic pancreas. The control algorithm will respond by commanding SC doses of insulin and/or glucagon as appropriate through the Tandem t:slim pumps.
- During the experiment the bionic pancreas device will be worn by the volunteer or kept nearby (such as when sleeping) at all times to ensure good radio-frequency signal reception. The device may be removed for short periods of time (no more than 30 minutes) for showering and swimming.
- If during the course of an experiment, a DexCom G4 sensor fails (reports sensor failure, ceases to transmit data, reports multiple calibration failures, or reports questionable data), the bionic

pancreas will automatically switch to giving basal insulin based on historical basal insulin needs at that time of the day. In addition, any BG measurements entered into the bionic pancreas will be used to dose insulin and glucagon as if they were CGM values and the system will continue to accept meal announcements. . A new sensor will be inserted and closed-loop control will automatically resume once the new sensor is initially calibrated.

- Meals will be announced to the control algorithm 15-20 minutes prior to the meal at the same time as meal boluses are delivered for other campers. Low BG will be treated as usual, except that no action will be taken for BG > 70 mg/dl.
- We will ask parents/guardians to provide information regarding what is a typical small bite, smaller than usual, usual, and larger than usual meal for their child. We will then produce a subject specific range for each of these and note it in their chart. Study staff of camp RN/NGs will assist the subjects in announcing their meals based on the known carbohydrate content and these pre-determined ranges during the closed-loop period of the study.
- BG levels will be measured at midnight and 3:45 AM (regardless of the value at 12:00 AM) using the HemoCue point of care BG meter. Additional measurements may be performed between 11 pm and 7 am as determined by the nocturnal hypoglycemia alert system. These measurements will be done in both closed-loop and usual care arms of the study.
- The nocturnal hypoglycemia alert system will be active from 11 pm to 7:00 AM. It will prompt for nighttime BG checks for the purpose of averting or catching significant nocturnal hypoglycemia. At every 5-minute step in our bionic pancreas, the alert system will update its online projection of when a significant hypoglycemic episode is likely to occur, based on (i) the current CGM data (current level and the average slope over last 30 minutes) as well as (ii) the latest BG check that was entered into the bionic pancreas and how it had related to the CGM level at the time. All prompted BG checks will be taken into account by the alert system to update its hypoglycemia projections. The goal of the nocturnal hypoglycemia alert system is to trigger BG checks when the BG is predicted to be < 60 mg/dl without prompting too many (redundant) BG checks where there is no hypoglycemia or impending hypoglycemia. The alert system was validated using the nighttime G4 CGM data and 15-minute BG data that we have gathered in our latest feasibility Clinical Research Center (CRC) study in a cohort of 24 pediatrics and adults under closed-loop for 48 nights. In addition to mandatory checks at 12:00 AM and 3:45 AM, checks were ordered by the alert system on an additional 29 occasions over 48 nights. The system indicated a need to do a check within 15 minutes of all ten episodes of significant hypoglycemia (BG < 50 mg/dl) that occurred in this dataset. The system indicated the need for 19 additional checks, including 14 occasions where BG was < 70 mg/dl. The system produced only five completely false alerts (one every 12 nights, on average) when no hypoglycemia (BG < 70 mg/dl) occurred. The nadir BG values within 15 minutes of these checks were 75, 76, 78, 90, and 95 mg/dl.
- The volunteer will be free to participate in all camp activities
- Regardless of location, camp healthcare providers will be able to reach volunteers on short notice. Camp healthcare providers will have basic training on the closed-loop system and the key elements of the protocol. They will keep a charged cell phone with them at all times. If they have a question they will be able to immediately contact study personnel monitoring remotely. If the question or issue cannot be resolved over the phone, a study staff "runner" will be sent to the location. If there is a medical problem that cannot be resolved according to study protocol or camp medical procedures, they will call 911 immediately and provide their location.
- The camp healthcare provider will carry carbohydrates for hypoglycemia treatment and glucagon rescue kits for hypoglycemic emergencies. The central monitoring site will have spare insulin lispro in a cold pack, spare pump supplies, spare DexCom G4 sensors and transmitters,

and spare bionic pancreas control units. If there is a problem with the closed-loop device, study staff will be called and will troubleshoot the system or replace devices as needed.

- Camp healthcare provider's or counselors for each cabin will assist campers as required to announce their meals to the bionic pancreas by indicating approximate meal size on one of the input screens on the device interface. The indicated meal size will be based on the report of typical meal sizes from the volunteer and their parents, study-specific information obtained during the check-in process, and the number of carbohydrates chosen by the volunteer for that meal. The bionic pancreas will then provide some of the insulin for the meal. The algorithm chooses the meal-priming bolus size using an adaptive algorithm that attempts to provide 75% of the insulin for meals of a similar size eaten at the same time of day in the past. The initial parameters are conservative and weight based and adapt over time.
- Camp healthcare providers and counselors will carry any snack items needed for hypoglycemia. Study staff following patients will also have emergency supplies available including oral carbohydrates and glucagon kits.
- If there is an interruption in the DexCom G4 CGM output the bionic pancreas will automatically switch to giving basal insulin based on historical basal insulin needs at that time of the day. If the failure occurs early in the experiment before 24 hours of historical data has been accumulated by the device, the basal rate will be primarily based on the volunteer's weight. In addition, any BG measurements entered into the bionic pancreas will be used to dose insulin and glucagon as if they were CGM values and the system will continue to accept meal announcements.
- If there is an interruption in the DexCom G4 CGM output, study staff will assist the volunteer in recovering CGM data streaming. This may involve forced calibrations or replacement of the sensor and calibration. Once it is back online, closed-loop BG control will resume automatically.
- If there is a complete failure of bionic pancreas operation, BG control will default to usual care camp protocol and subjects will use their own insulin pump (which will be stored by the study staff) until the bionic pancreas can be brought back online.
- The DexCom CGM will be calibrated each morning before breakfast and each evening before dinner using the HemoCue meter. IF it is a good time to calibrate. This will be determined by a decision support algorithm. A good time to calibrate means a rate of change in CGM glucose < |1| mg/dl/min, no glucagon boluses in the last 15 minutes, and no carbohydrate intake in the last 30 minutes. These conditions are intended to reduce the likelihood of performing a calibration when there are rapid changes in BG and when there are changes in BG that are not yet reflected in CGM glucose due to physiologic lag.
- Additional calibrations may be performed if the following criteria are met:
  - If the CGM reported value does not meet the ISO standard (< 15 mg/dl difference for BG values < 75 mg/dl, < 20% absolute difference for BG values > 75 mg/dL) at the time of the BG measurement AND it is a good time to calibrate according to the decision support tool (the CGM derivative is < 1 mg/dl/min and there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes) a calibration will be performed.
  - If it is NOT a good time to calibrate, the difference between CGM glucose and BG may be due to the physiologic lag (roughly 15 min) between BG and interstitial fluid glucose, and this cannot be corrected by calibration. In this instance, a decision about performing an additional Hemocue BG check at the next good time to calibrate will be made by adjusting the ISO range to take into account the CGM trend. For example, if the CGM glucose is falling with a derivative of –2 mg/dl/min and the BG is 100 mg/dl, the CGM glucose can be up to 130 mg/dl (100 mg/dl + 15 min*2 mg/dl/min) without indicating the need to do

another BG check at the next good time to calibrate. If an additional BG check is indicated despite these correction factors, then at the next good time to calibrate a BG check will be performed and a calibration will be performed IF and ONLY IF the CGM is still not compliant with the ISO standard at the time of that additional BG check. This will avoid forcing extra calibrations when a large disparity between the CGM value and BG was due to the physiologic lag between BG and interstitial fluid glucose.

- At 3:00 PM on day 6 (Friday) the closed-loop portion of the experiment will end. Infusion sets and CGM sensor will be removed. Subjects will insert one of their own infusion sets and start their own basal insulin rate. Blood glucose control will then resume under usual care camp protocols.

Transition Between Study Arms:

- After the first arm of the study is completed on Friday at 3:00 PM, volunteers will go back to usual care camp protocols until Saturday afternoon, when a new DexCom G4 CGM sensor will be placed.
- Volunteers who were randomized to the closed-loop arm will switch to the usual care arm in the second week, and vice versa.

V. e. Response to Hypoglycemia

- All subjective symptoms of hypoglycemia will be investigated with a capillary BG using a HemoCue meter.
- Volunteers in both of the study arms (closed-loop and usual care) will take carbohydrates to treat hypoglycemia or symptoms consistent with hypoglycemia according to a protocol modified from the usual camp protocol as follows:
- Mild hypoglycemia (mild signs and symptoms or BG 60–80 mg/dl, able to self treat):
  - Wait 15–20 minutes and recheck BG
  - If BG is still < 70 give 15 gm of rapid-acting carbohydrates (glucose tabs, juice, milk, gel, etc.)
- The modified hypoglycemia protocol is intended to allow auto-treatment of mild hypoglycemia with glucagon by the control algorithm to occur without being preempted by carbohydrates given prior to the onset of hypoglycemia (for instance in the 70-80 mg/dl range) or when hypoglycemia is mild (BG 60-70 mg/dl). In order to maintain safety, as second BG check in 15-20 minutes is included so that hypoglycemia is treated if not averted by the closed-loop system.
- For experimental validity, the same modifications from camp policy need to be used for both the closed-loop and open-loop arms of the study. Note that treatment of BG < 60 mg/dl will be according to the normal camp protocol in both arms (immediate treatment with rapid-acting carbohydrates) AND subjects may take carbohydrates at any time for symptoms when BG is < 80 mg/dl
- Camp healthcare providers and camp counselors will carry rapid acting and complex carbohydrate interventions with them at all times. All carbohydrate treatments for hypoglycemia will be documented by study staff (amount and time).
- In any case in which two rapid-acting carbohydrate interventions must be administered by camp protocol or if glucagon is administered manually by injection, a study staff member will check the operation of the bionic pancreas system. Consideration will be given to replacing the glucagon infusion set and/or recalibrating the CGM.

V. f. Response to Hyperglycemia

- Any time a ketone check is mandated by camp protocol the closed-loop system will be checked for any malfunction and any such problems will be corrected. The insulin infusion set will be replaced if mandated by camp protocol or if there is any doubt as to its proper functioning.
- 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 started.
- While the new system is being replaced and calibrated the volunteer will use their own pump in open loop mode according to usual care camp protocols.
- If the blood ketone result is $\geq$ 0.6mmol/dL a study physician or nurse practitioner will be notified and will evaluate the volunteer in person.

V. g. Response to Nausea/Vomiting and Other Medical Needs

- Minimal nausea was noted in clinical trial of the bi-hormonal closed-loop system to date. In most cases, nausea that occurred did not correspond in time to dosing of glucagon, which is intermittent. However, nausea is a potential side effect of glucagon.
- If vomiting occurs in the setting of glucagon administration (e.g. within 15 minutes of the last dose of glucagon) a study physician or nurse practitioner will be notified and will evaluate the volunteer in person.
- If the volunteer experiences any non-emergent medical concerns outside the scope of diabetes care, he or she will see the camp physician. If the volunteer experiences urgent or emergent medical concerns outside the scope of diabetes care and camp physicians, the camp will escort the volunteer to a local emergency room or call 911 according to camp protocol. If a volunteer in the closed-loop arm of the study is transported away from the camp site for any reason, they will be transitioned to open-loop usual care and their participation in the study will be suspended until they return.

V. h. Monitoring of Closed Loop Device Performance

- Co-investigators (and bionic pancreas inventors and developers) Edward Damiano, Firas El-Khatib and/or an engineer trained by them will be readily available by phone for consultation at all times during the course of each experiment and will be able to reach the camp within 1 hour to troubleshoot if necessary.
- They will have the capability of viewing the controller (iPhone) display and diagnostic information 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. i. Supervision by Study Staff

A study physician or nurse practitioner will be available at the camp at all times during the course of each experiment. Trained study staff will also be continuously monitoring the function of each bionic pancreas via remote telemetry 24 hours a day throughout the experiment from a central location in the camp. The clinicians will also have the capability of remotely viewing the controller display on their iPhone or iPad and evaluating diagnostic information during the experiment to facilitate clear communication with nurses.

V. j. Modifications to the Control Algorithm

Certain parameters of the control algorithm may be adjusted between a proposed "dry run" with a small number of subjects prior to the main study and the start of the main study, as approved in the Investigational Device Exception, but no parameters may be adjusted once the main study has started.

VI. Biostatistical Analysis

VI. a. Data Collected

Prior to start of experiment:

- Age
- Sex
- Race and ethnicity
- Date of last menstrual period in female volunteers post-menarche
- Urine HCG for female volunteers post-menarche
- 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
- Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
- Average total daily dose of insulin in the last 30 days as available (from pump history)
- Duration of insulin pump use
- 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)
- History of insulin types used (beef insulin, pork insulin, regular human insulin, NPH insulin, ultralente insulin, insulin aspart, insulin lispro, insulin glulisine, insulin detemir, insulin glargine)
- Height and weight
- Blood pressure
- Hemoglobin A1c

During the monitoring of usual care period:

- CGMG (CGM glucose) every five minutes from the DexCom G4 Platinum CGM
- HemoCue BG measurements before meals, snacks, bedtime, 12:00 AM and 3:45 AM
- Any additional HemoCue BG values
- Estimated carbohydrate intake (from camp healthcare provider documentation)
- Exercise and activity level (from camp schedule)
- Number of hypoglycemic events and nadir BG for each (from camp healthcare provider documentation)
- Number of carbohydrate interventions for hypoglycemia (from camp healthcare provider documentation)
- Total daily dose of insulin (from insulin pump download)

During the closed-loop study period:

- CGMG every five minutes from the DexCom G4 Platinum CGM
- HemoCue BG measurements before meals, snacks, bedtime, 12:00 AM and 3:45 AM
- Any additional HemoCue BG values
- Estimated carbohydrate intake (from camp healthcare provider documentation)
- Exercise and activity level (from camp schedule)
- Number of hypoglycemic events and nadir BG for each (from camp healthcare provider documentation)
- Number of carbohydrate interventions for hypoglycemia (from camp healthcare provider documentation)
- Insulin and glucagon doses administered by the control system
- Timing of meal announcements and size of meals announced
- Number of meal announcements
- Time between meal announcement and start of meal
- Meal and snack number, and timing
- Bionic pancreas downtime – number, timing, and duration of periods offline, reasons for being offline (CGM sensor loss, system crash, communication problem between CGM and bionic pancreas, communication problem between bionic pancreas and pumps, pump malfunction, tubing occlusion, infusion set failure/pulled out)
- Insulin bolus dosing in open-loop mode during CGM downtime
- Basal rate adjustments, including suspensions, during bionic pancreas downtime

For consenting non-participants:

- BG measurements before meals, snacks, bedtime, and 12:00 AM
- Any additional BG values
- Estimated carbohydrate intake (from camp healthcare provider documentation)
- Exercise and activity level (from camp schedule)
- Number of hypoglycemic events and nadir BG for each (from camp healthcare provider documentation)
- Number of carbohydrate interventions for hypoglycemia (from camp healthcare provider documentation)

VI. b. Study Endpoints

Co-primary endpoint analysis:

- Difference in average BG between closed-loop and open-loop periods as determined from all scheduled HemoCue measurements. This mean will be evenly weighted across the daytime and nighttime hours.
- Difference between closed-loop and open-loop in the percentage of the above subset of BG values less than 70 mg/dl.

Secondary endpoint analyses - BG:

- All of following metrics will be generated from the HemoCue data during the closed-loop period and the usual care period, and the difference between the two periods will be reported unless otherwise specified:
- Average BG as determined from all HemoCue measurements taken during the day/nighttime including all extra measurements taken before meals, taken during exercise, and taken for hypoglycemia monitoring.

- Percentage of the above subset of BG values less than 70 mg/dl.
- Average BG as determined from the pre-meal, before bed, 12:00 AM, and 3:45 AM HemoCue measurements (6measurements per day)
- Percentage of the above subset of BG values less than 70 mg/dl.
- Percentage of subjects with mean BG < 154 mg/dl using all BG values
- Difference in the percentage of subjects with mean BG < 154 mg/dl using before meal and before bedtime BG values only
- Percentage of study days with mean BG < 154 mg/dl
- Number of hypoglycemic events as determined from all HemoCue measurements
- Nadir BG for each hypoglycemic event as determined from HemoCue measurements
- Fraction of scheduled BG measurements within each of the following glucose ranges as determined from all HemoCue measurements :
- < 70 mg/dl
- 70-120 mg/dl
- 70-180 mg/dl
- >180 mg/dl
- >250 mg/dl
- Risk of hypoglycemia and hyperglycemia >180 mg/dl and >250 mg/dl during hours with vs. without bionic pancreas downtime
- Difference of outcome measures on day 1 vs. remaining days (days 2-5) and on day 1-2 vs. on remaining days (days 3-5)
- Difference in average BG as determined from the pre-meal, before bed, and 12:00 AM measurements between the non-participants and the open-loop and closed-loop arms.
- Percentage of the above subset of BG values less than 70 mg/dl between the non-participants and the open-loop and closed-loop arms.
- Difference in the percentage of subjects with mean BG < 154 mg/dl using before meal and before bedtime BG values only between the non-participants and the open-loop and closed-loop arms.
- Number of hypoglycemic events as determined from all BG measurements
- Nadir BG for each hypoglycemic event as determined from BG measurements
- Fraction of scheduled BG measurements within each of the following glucose ranges as determined from all BG measurements :
- < 70 mg/dl
- 70-120 mg/dl
- 70-180 mg/dl
- >180 mg/dl
- >250 mg/dl

Secondary endpoint analyses – CGM:

- All of following metrics will be generated from the DexCom G4 Platinum CGM data during the closed-loop period and the usual care period, and the difference between the two periods will be reported unless otherwise specified. Each of these measures will be calculated for the entire period and separately for the full day and for the nighttime (11:00 PM to 7:00 AM).
- Mean CGMG
- Number of CGMG events < 70 mg/dl (episodes separated by < 15 minutes will be considered a single episode) and nadir for each
- Fraction of time spent within each of the following glucose ranges:

    - < 70 mg/dl
    - 70-120 mg/dl
    - 70-180 mg/dl
    - >180 mg/dl
    - >250 mg/dl
- Area over the curve and below 70 mg/dl (measure of total hypoglycemia exposure)
- Area over the curve and below 50 mg/dl (measure of significant hypoglycemia exposure)
- Percentage of subjects with mean CGMG < 154 mg/dl
- Percentage of study days with mean CGMG < 154 mg/dl
- Mean CGMG in the four hour period following meals
- Mean CGMG during exercise (more active periods, periods of activity greater than walking intensity based on accelerometer data)
- Number of incidents of hypoglycemia and nadir CGMG during exercise
- Correlation between exercise intensity (based on accelerometer data) and likelihood of a hypoglycemic event by CGMG
- Risk of hypoglycemia and hyperglycemia >180 mg/dl and >250 mg/dl during hours with vs. without bionic pancreas downtime (closed-loop period only)
- Mean absolute relative deviation (MARD) of CGM vs. scheduled HemoCue BG measurements
- Standard deviation of CGM values
- Standard deviation of CGM values at night (11:00 PM to 7:00 AM)
- MARD vs. all HemoCue BG measurements Additional accuracy measures using all of the HemoCue measurements as the standard. Statistics will include:
- Median, quartiles, and mean absolute relative difference (MARD) and mean absolute difference (MAD) between CGM and BG reported separately in hypoglycemic (< 70 mg/dl), normoglycemic (70-120 mg/dl), postprandial target (70-180 mg/dl), hyperglycemic (> 180 mg/dl and > 250 mg/dl) ranges.
- Pearson and Spearman correlation coefficient between CGM and BG values reported separately in each range (hypoglycemic, normoglycemic, hyperglycemic).
- Intercept and slope of best-fit line for CGM to BG correlation plots
- Percent of CGM values meeting International Organization for Standardization (ISO) criteria (< 15 mg/dl difference for BG values < 70 mg/dl, < 20% absolute difference for BG values > 70) in each range.
- Clarke Error Grid Analysis (EGA) for all CGM and BG pairs in hypoglycemic, normoglycemic, post-prandial target, and hyperglycemic ranges. The data will be reported as fraction of values in zones A (clinically accurate), B (benign), zone C (overcorrect), zone D (failure to detect), and zone E (erroneous).
- Continuous Clarke Error Grid Analysis (EGA) for all CGM and BG pairs, including point- and rate-EGA (P-EGA and R-EGA) for each volunteer in hypoglycemic, normoglycemic, post-prandial target, and hyperglycemic ranges. The data will be reported as fraction of values in zones A (clinically accurate), B (benign), zone C (overcorrect), zone D (failure to detect), and zone E (erroneous).
- Reliability index calculated as percent of possible values actually recorded by CGM.
- MARD during periods with and without exercise (by 15 minute periods).
- Difference of outcome measures on day 1 vs. remaining days (days 2-5) and on day 1-2 vs. on remaining days (days 3-5)

Secondary endpoint analyses – Non-glycemic:

- All of following metrics will be generated from the closed-loop and usual care periods and the differences will be reported unless otherwise specified:
- Number of carbohydrate interventions for hypoglycemia (day and night)
- Total number of grams of carbohydrate taken for hypoglycemia (day and night)
- Insulin total daily dose
- Mean daily basal insulin dose
- Mean daily bolus insulin dose
- Number of carbohydrate interventions for hypoglycemia during the daytime (7:00 AM – 11:00 PM)
- Total number of grams of carbohydrate taken for hypoglycemia during the daytime ((7:00 AM – 11:00 PM)
- Number of carbohydrate interventions for hypoglycemia overnight (11:00 PM – 7:00 AM)
- Total number of grams of carbohydrate taken for hypoglycemia overnight (11:00 AM – 7:00 AM)
- Mean meal carbohydrate content
- The following metrics will be generated from the closed-loop period:
- Insulin lispro dosing (u/kg/24 hours)
- Glucagon dosing (mcg/kg/24 hours)
- Fraction of time bionic pancreas in open-loop mode due to loss of CGM signal
- Fraction of time bionic pancreas completely off-line
- Fraction of time bionic pancreas off-line or not functioning properly for each of the following reasons: system crash, communication problem between CGM and bionic pancreas, communication problem between bionic pancreas and pumps, pump malfunction, tubing occlusion, infusion set failure/pulled out
- Difference in mean insulin dose per hour during periods of normal operation vs. periods of bionic pancreas downtime
- Fraction of bionic pancreas downtime during which automatic basal rate suspended or reduced
- Difference in mean insulin dosing during the four hour period after a meal during periods of normal operation vs. periods of bionic pancreas downtime (open-loop dosing)
- Difference of outcome measures on day 1 vs. remaining days (days 2-5) and on day 1-2 vs. on remaining days (days 3-5)
- All of following metrics will be generated from the closed-loop, usual care periods, and from the non-participants and the differences will be reported unless otherwise specified:
- Number of carbohydrate interventions for hypoglycemia (day and night)
- Total number of grams of carbohydrate taken for hypoglycemia (day and night)
- Insulin total daily dose
- Mean daily basal insulin dose
- Mean daily bolus insulin dose
- Number of carbohydrate interventions for hypoglycemia during the daytime (7:00 AM – 11:00 PM)
- Total number of grams of carbohydrate taken for hypoglycemia during the daytime ((7:00 AM – 11:00 PM)
- Number of carbohydrate interventions for hypoglycemia overnight (11:00 PM – 7:00 AM)
- Total number of grams of carbohydrate taken for hypoglycemia overnight (11:00 AM – 7:00 AM)

We will calculate means, median, percentages, standard deviations, standard errors, inter-quartile

ranges, and 95% confidence intervals in descriptive analyses. We will use paired t-test for comparison of means. We will use multivariate regression models with repeated measurements to compare means and percentages while adjusting for patient demographics characteristics (age, gender).

VI. c. Power Analysis

The number of volunteers proposed was chosen to allow capture of some of the variation between individuals in absorption of SC insulin and glucagon, sensitivity to insulin and glucagon, activity level, food choices, and CGM accuracy. We do not have the data required to perform a formal power analysis.

VI. d. Criteria for Success of the Study

The main criteria for success will be whether there is sufficient evidence of efficacy to warrant further study of the closed loop device in the diabetes camp and home settings. We will consider the study to be a success if the closed-loop system is able to achieve an aggregate mean BG and CGMG of less than or equal to a BG < 169 (equivalent to an A1C of < 7.5%) for 12–20 year olds over the study period without any severe hypoglycemia, less than 5% of the time spent less than 70 mg/dl according to the CGM dataset and less than 5% of the time less than 70 mg/dl according to the HemoCue BG dataset. We will likewise consider the study a success if the BG and CGMG measured glycemic control is superior during the closed-loop period vs. the usual care period.

VII. Risks and Discomforts

Volunteers may experience mild discomfort associated with the insertion of the infusion sets and DexCom CGM sensor into the SC tissue. Any discomfort is expected to be similar to that associated with injection of insulin. Once the infusion sets and sensors are in place, there should be no significant discomfort. The risk for developing inflammation in the SC tissue at the insertion sites is expected to be extremely low. There were no instances of inflammation or infection in the first three phases of experiments including over 100 volunteers. In addition all volunteers eligible for the study wear insured infusion sets routinely.

There is a potential risk of nausea or vomiting in volunteers due to the administration of exogenous glucagon. The experiments, however, involve small and infrequent SC glucagon doses. The recommended dose of glucagon for treatment of a pediatric patient with diabetes with hypoglycemia is 500-1000 mcg, given as a single subcutaneous injection. In practice, a smaller dose mcg is sometimes used initially to reduce the risk of nausea and vomiting. Per camp protocol, age groups under 10 years of age receive 500 mcg of glucagon and >10 years of age receive 1000 mcg glucagon for severe unresponsive hypoglycemia. The largest single dose to be administered in our study is 80 mcg. Nausea was rare in the first three phases of our closed-loop studies. In most of the cases where nausea was reported, the episodes of nausea did not correlate with periods of glucagon dosing, which is intermittent. The risks for nausea or vomiting in our study are therefore expected to be very small.

There is a potential risk of hypoglycemia, since exogenous insulin will be administered. Given (i) the small insulin doses that will be administered, (ii) the availability of glucagon doses to counter potentially excessive insulin dosing and prevent impending hypoglycemia, (iii) frequent BG monitoring, (iv) 24-hour real-time telemetric monitoring, and (v) frequent monitoring by camp healthcare providers, the risk of a hypoglycemic episodes leading to significant harm to volunteers is expected to be substantially lower than their risk during their usual therapy.

The only risk associated with chart review for the non-participants is taking the time to consent and provide contact information for their doctors.

VIII. Potential Benefits

Subjects enrolled in the study will benefit from intensive monitoring by study staff including 24 hour telemetric volunteering during both the closed-loop and usual care arms, which is likely to reduce the risk of harm from a severe hypoglycemic event.

The data derived from this study will allow us to improve the robustness and effectiveness of our closed-loop control system, and treatment is expected to systematically improve for subsequent participants and eventually for children with type 1 diabetes in general

The volunteers will be financially compensated for participating in the study.

Non-participants (chart review only) will not benefit from consenting to the study.

IX. Data and Safety Monitoring

IX. a. Monitoring of Source Data

The principal investigator (Steven Russell), a study clinical research fellow (physician), or a study nurse practitioner will review the eligibility of each volunteer based on the case report from the screening visit.

During the experiment, HemoCue and CGM data will be collected in various ways. 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 monitoring station where it will also be stored electronically to provide redundancy in data storage and mitigate the risk of data loss. HemoCue BG data will be entered into the bionic pancreas immediately after determination and then wirelessly streamed with the rest of the data to the monitoring station. 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.

The Study will be conducted by the staff of the MGH Diabetes Research Center, the engineering research team at Boston University, and the staff of Camp Barton and Camp Joslin. The PI and engineering team will be involved in education of the staff prior to the start of the protocol and will communicate with study staff at least twice a week to review Study progress, discuss any issues in study conduct, and review procedures. 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, the staff of the camps, and the Medical Directors of the camp 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 volunteer files is performed by a member of the Center at least biannually. The audit will be conducted by a Center 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 volunteer files, including a

review of consents, case report forms, and other data from study visits.

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

The study data may be shared with collaborators outside of Partners, 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 volunteers.

A de-identified dataset as described above will be stored for possible future analysis in the laboratory of the Boston University co-investigator Ed Damiano. Subjects may not withdraw their data, as it will be stored in non-personally identifiable form.

IX. b. Safety Monitoring

Once participants are enrolled in the study, a study physician, nurse practitioner or nurse will perform the insertion of the infusion sets and CGM sensor, ensuring that proper procedures are followed. Each of the BG measurements made will be available to the participant and staff for implementation of orders regarding the management of high and low BG values.

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 convened in the event that any subject has to be removed from the study due to an adverse event. 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.

It should be noted that there were no serious adverse events in the first three phases of our closed loop studies including 100 volunteers. There were instances of biochemical hypoglycemia which were treated according to protocol with oral carbohydrates. In one experiment in the first phase of the study in the hospital setting in 2009, hypoglycemia was treated with intravenous dextrose according to protocol despite only mild symptoms. Since then, there have been refinements to the algorithm and there has been no need for intravenous dextrose or high dose glucagon. No volunteers reported more than mild symptoms associated with the biochemical hypoglycemia, and only oral carbohydrates have been used for treatment in all other cases.

IX. c. Adverse Event Reporting Guidelines

The Principal Investigator and Co-investigators will review any adverse events after each experiment. Adverse events will be reported promptly to the Partner's IRB and to the BU IRB according to their respective adverse event reporting guidelines. Co-investigator Ed Damiano is the sponsor of a pending

Investigational Device Exception (IDE) for the closed loop device to be used in this trial. Reports of adverse events will be made to the FDA in compliance with the terms of IDE.

X. Subject Compensation

Financial compensation will be provided to all volunteers who complete the Screening Visit (which is typically completed either at MGH or remotely). Subjects will be paid $50 for completing the Screening Visit. Study participants will be compensated $1,000 for completing the camp portion of the study. The total compensation for a volunteer who completed the screening visit and the camp portion of the study would be $1,050. Volunteers who are unable to complete the study or chose to stop participation will receive prorated compensation at a rate of $3.50 per completed hour (12 days X 24 hours per day X $3.50 per hour = $1,008). Volunteers who must stop the study due to circumstances beyond their control will receive a minimum of $500.

Non-participants (chart review only) will not be compensated for their participation.

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