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Effect of Hybrid Closed-Loop Insulin Delivery on Glucose Counterregulation in Long Standing Type 1 Diabetes: A Proof of Concept, Mechanistic, Single-Arm Clinical Trial

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Investigational Product: Medtronic MiniMed 670G System and Tandem t:slimX2 Basal-IQ and Control-IQ

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List of Abbreviations

AE: Adverse event

BMI: Body mass index

CHPS: Center for Human Phenomic Science

CRF: Case report form

CSII: Continuous subcutaneous insulin infusion

DCCT: Diabetes Control and Complications Trial

DSMB: Data and safety monitoring board

DSMP: Data and safety monitoring plan

ECG: Electrocardiogram

FDA: Food and Drug Administration

HAAF: Hypoglycemia-associated autonomic failure

IRB: Institutional review board

LGS: Low glucose suspend

PHI: Protected health information

PI: Principal investigator

SAE: Serious adverse event

SAP: Sensor augmented pump

T1D: Type 1 diabetes

Study Summary

Title	Effect of Hybrid Closed-Loop Insulin Delivery on Glucose Counterregulation in Long Standing Type 1 Diabetes: a proof of concept, mechanistic, single-arm clinical trial
Short Title	Hybrid Closed-Loop for Hypoglycemia
IRB Number	827557
Protocol Number	NERP16-015 (Medtronic Diabetes)
Phase	Mechanistic
Methodology	Open label, single-arm trial of the effect of hybrid closed-loop insulin delivery on glucose counterregulatory mechanisms assessed by the stepped- hyperinsulinemic hypoglycemic clamp in patients with long standing type 1 diabetes complicated by hypoglycemia unawareness.
Study Duration	4.5 years
Study Center(s)	Single-center (Penn)
Objectives	Impaired glucose counterregulation and loss of hypoglycemia symptom recognition (hypoglycemia unawareness) develops in long standing type 1 diabetes, in part due to repeated exposure to hypoglycemia as a consequence of therapeutic hyperinsulinemia, and increases the risk for severe hypoglycemia, an important complication in itself and a significant barrier to the attainment of adequate glycemic control. This study aims to determine whether hypoglycemia avoidance achieved through implementation of hybrid closed-loop insulin delivery can improve glucose counterregulation in type 1 diabetic patients with hypoglycemia unawareness. *We hypothesize that the endogenous glucose production response to insulin-induced hypoglycemia will be greater in subjects after 6 months when compared to before implementation of hybrid closed-loop insulin delivery.* Glucose counterregulatory hormone, symptom, and endogenous glucose production responses will be measured using the stepped-hyperinsulinemic hypoglycemic clamp before, after 6 months' intervention, and after 18 months to assess the durability of any benefit from avoidance of hypoglycemia with continued use of the hybrid closed-loop system.
Number of Subjects	We will screen up to 30 participants in order to enroll 15-18 subjects with type 1 diabetes and hypoglycemia unawareness to receive hybrid closed loop insulin delivery.

Investigational Product (drug, biologic, device, etc.)	Medtronic MiniMed 670G system or Tandem t:slimX2 with Basal-IQ and Control-IQ technology using the Dexcom G6 sensor. Eligible subjects with type 1 diabetes will initiate hybrid closed-loop insulin delivery based on interstitial glucose monitoring via the MiniMed 670G system or the Tandem t:slimX2 insulin pump with the Dexcom G6 sensor according to Medtronic's and Tandem's labeling. These systems combine subject-delivered pre-meal boluses with automatic interprandial insulin delivery that include automated functions for both predictive and threshold suspension of insulin delivery intended to minimize exposure to glucose levels < 70 mg/dl.
Duration of administration (if applicable)	18 months
Reference therapy	There is no standard reference therapy against which the investigational product is being compared. The purpose of this small, proof-of-concept, mechanistic study is to determine whether hybrid closed-loop insulin delivery can achieve sufficient hypoglycemia avoidance in patients with long standing type 1 diabetes experiencing hypoglycemia and symptom unawareness despite receiving intensive insulin therapy standard-of-care to improve glucose counterregulation against insulin-induced hypoglycemia. The data generated will be available to power future randomized clinical trials to determine the comparative efficacy of emerging artificial pancreas and β-cell replacement approaches to achieve target glycemic control with amelioration of problematic hypoglycemia in type 1 diabetes.
Statistical Methodology	The difference in glucose counterregulatory responses obtained during the hypoglycemic clamp will be compared within subject from before to 6 months after implementation of hybrid closed-loop insulin delivery using paired t-tests or Wilcoxon matched-pairs tests as appropriate, and significance will be considered at $P \leq 0.05$ (two-tailed) for the primary outcome measure of the rate of endogenous glucose production. For the additional measures, multiple comparisons are being made without adjustments for multiplicity, and so any findings will be hypothesis generating. The additional responses at 18 months will be analyzed by repeated measures mixed model for longitudinal measurements over time.
Safety Evaluations	Safety evaluations will include direct questioning for the occurrence of severe hypoglycemia, defined as an event with symptoms or signs compatible with hypoglycemia in which the subject was unable to treat him/herself and which was associated with either a blood glucose level < 54 mg/dl [3.0 mmol/L] or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.
Data and Safety Monitoring Plan	The PI will be primarily responsible for monitoring the data quality and the ongoing safety of subjects. A study monitor independent from the study team will be assigned to oversee the implementation of the data and safety monitoring plan (DSMP). This plan will include the establishment of a data and safety monitoring board (DSMB). The mission of the DSMB will be to ensure that the risk associated with participation in research is being minimized to the extent practical.

BACKGROUND AND STUDY RATIONALE

This document is a clinical research protocol and the described study will be conducted in compliance with the protocol, Good Clinical Practice standards, associated federal regulations, and all applicable University research requirements. All episodes of noncompliance will be documented.

Introduction

1.1 Background and Relevant Literature

Hypoglycemia is a major barrier to the achievement of adequate glycemic control for most patients with insulin-dependent diabetes, both those with type 1 diabetes and advanced type 2 diabetes (Cryer, 2008). Inadequate glycemic control can lead to the development of diabetic retinopathy, nephropathy, and neuropathy, the leading causes of adult blindness, kidney failure, and non-traumatic amputation in the United States. The American Diabetes Association treatment guidelines recommend that adults with type 1 diabetes target HbA_{1c} levels < 7.0% unless there is a reason, such as significant hypoglycemia or hypoglycemia unawareness, to set a higher target (2015). However, even with HbA_{1c} < 7.0% the residual risk for cardiovascular and all-cause mortality in patients with type 1 diabetes remains more than twice that in nondiabetics (Lind et al., 2014), with the lowest mortality rates seen with HbA_{1c} ≤ 6.5% (Stadler et al., 2014). Unfortunately, despite tremendous advances in the technology available for insulin delivery and glucose monitoring, only 30% of adults with type 1 diabetes in the United States receiving care at specialty diabetes clinics are achieving a HbA_{1c} level < 7.0% (Miller et al., 2015). Despite this low proportion of patients reaching target average glycemic control, 8% reported experiencing a severe hypoglycemic event resulting in seizure or loss-of-consciousness in the prior 3 months, including 6% of those with a HbA_{1c} level < 7.0%, 8% of those with a HbA_{1c} between 7.0 – 9.0%, and 12% of those with a HbA_{1c} > 9.0% (Miller et al., 2015). Thus, current recommendations to set a higher HbA_{1c} target for patients with significant hypoglycemia or hypoglycemia unawareness (2015) are unlikely to impact the burden of severe hypoglycemia in type 1 diabetes, and may not be acceptable to patients striving to avoid or mitigate the micro- and macrovascular complications of this disease.

Severe episodes of hypoglycemia are life-threatening, fear of such episodes distressing, and the cumulative effects of recurrent hypoglycemia impair neurocognitive function. Diabetes-related death is the most frequent cause of mortality among patients under 30 years-of-age (Skrivarhaug et al., 2006; Feltbower et al., 2008), and while severe hypoglycemia is documented in only ~ 12% of diabetes-related deaths, this is likely an under representation due to the presence of twice as many unexplained diabetes-related deaths. Not uncommonly, young people with type 1 diabetes are found “dead-in-bed” (Tanenberg et al., 2010; Tattersall and Gill, 1991), an unfortunate consequence of likely severe hypoglycemia inducing brain death (Auer, 2004) or a fatal cardiac arrhythmia (Tu et al., 2010). In fact, patients reporting an episode of severe hypoglycemia experience a 3.4-fold increase in mortality over the subsequent 5 years (Mccoy et al., 2012). The risk of experiencing a severe hypoglycemic episode increases with long standing disease due to the progressive development of compromised physiologic defense mechanisms against a falling blood glucose concentration in the setting of therapeutic hyperinsulinemia. By 15 years of disease duration most patients have developed near total loss of functioning β-cells (C-peptide negative) (Tsai et al., 2006) resulting in loss of inhibition of endogenous insulin secretion as well as activation of glucagon secretion in response to declining blood glucose (Cooperberg and Cryer, 2010), which together normally increase endogenous (primarily hepatic) glucose production to circumvent the development of hypoglycemia. In the absence of these islet cell responses to hypoglycemia, epinephrine secretion and autonomic symptom generation become critical to increase endogenous glucose production and alert the individual to ingest food (**Figure 1**) (Cryer et al., 2003). Unfortunately, these sympathoadrenal responses are impaired by recurrent episodes of hypoglycemia leading to a syndrome of hypoglycemia unawareness, also known as hypoglycemia-associated autonomic failure (HAAF) (Cryer, 2013). Hypoglycemia unawareness is associated with a 20-fold increased risk for experiencing life-threatening hypoglycemia (Pedersen-Bjergaard et al., 2004). Clearly, new strategies are required to restore physiologic defense mechanisms against the development of severe hypoglycemia.

Technologic strategies with real-time continuous glucose monitoring (CGM) hold promise for the

amelioration of hypoglycemia in patients with type 1 diabetes, and particularly when incorporated into to an automated closed-loop glucose sensing and insulin delivery system, also known as the artificial pancreas. With the establishment of continuous subcutaneous insulin infusion (CSII) or pump therapy (Pickup, 2012), and CGM via a subcutaneous glucose sensor (Tamborlane et al., 2008) as viable technologies there has been increasing academic and industrial effort to develop a closed-loop artificial pancreas system. However, mechanical problems with insulin delivery (Heinemann and Krinelke, 2012), the delay and variability of insulin absorption from the subcutaneous space (Heinemann, 2002; Heinemann et al., 2009), and variability of insulin action (Hinshaw et al., 2013) coupled to the delay and potential inaccuracy of interstitial glucose measurements (Basu et al., 2013; Basu et al., 2015) represent key challenges to closed-loop control of blood glucose, particularly in the context of perturbations in glucose homeostasis introduced by meals, exercise, and illness. In order to advance component development prior to realization of an artificial pancreas system, a roadmap was accepted to include sequential steps beginning with automated mitigation of hypoglycemia progressing through control-to-range and control-to-target algorithms prior to adopting fully closed-loop control (Kowalski, 2009). Unfortunately, patients with long standing type 1 diabetes and defective glucose counterregulation with hypoglycemia unawareness, while most in need of new therapeutic strategies, have the most at stake in adoption of closed-loop control that can lead to severe hypoglycemia if the sensor overestimates the blood glucose and physiologic recognition of the development of low blood glucose is absent. Thus, understanding the effects of hybrid closed-loop insulin delivery on physiologic defense mechanisms against the development of low blood glucose is critical before fully closed-loop control can be attempted in this population.

Support for CGM in adults with type 1 diabetes is based on modest reductions in HbA_{1c} (~0.5%) from a baseline ≥ 7.0% with no increase in hypoglycemia for patients ≥ 25 years of age who used their glucose sensor during at least 6/7 days per week (Tamborlane et al., 2008). This and most studies of CGM excluded patients experiencing problematic hypoglycemia or hypoglycemia unawareness, whereas in clinical practice CGM is most often implemented in hopes of reducing hypoglycemia. In a retrospective clinic-based analysis, implementation of CGM for one year in patients with problematic hypoglycemia at baseline was associated with a reduction, but not elimination, of severe hypoglycemic events, but did not improve hypoglycemia awareness (Choudhary et al., 2013). Nocturnal hypoglycemia contributes to the development of HAAF (Cryer, 2004), is a frequent setting for experiencing severe hypoglycemia, and is an important contributor to mortality in type 1 diabetes (Tanenberg et al., 2010; Tattersall and Gill, 1991). Prediction and detection of nocturnal hypoglycemia is not fully addressed by CGM that depends on appropriate use and response to devise alerts (vibration) and alarms. Implementation of a strategy for hypoglycemia avoidance with the goal of recovery from HAAF will require mitigation of nocturnal hypoglycemia. Reduction of nocturnal hypoglycemia may be particularly amenable to automated suspension of insulin delivery with a sensor-augmented pump (SAP) (Bergenstal et al., 2013; Ly et al., 2013). Also known as low glucose suspend (LGS), the automated suspension of insulin delivery by a pump informed of the sensor glucose level marked the first step toward a closed-loop system dependent on information exchange between the CGM and insulin pump. Importantly, SAP with LGS has been shown to reduce nocturnal hypoglycemia by 38% compared to CGM alone without increasing HbA_{1c} (Bergenstal et al., 2013). Another trial that included patients with reduced awareness of hypoglycemia showed similar results plus a reduction in severe hypoglycemic events with use of LGS, but this study included rather young patients with short duration disease (Ly et al., 2013). Whether this strategy may similarly benefit patients with long standing type 1 diabetes complicated by hypoglycemia unawareness and lead to clinically meaningful improvement of glucose counterregulation is unknown, but will likely require even greater reduction in hypoglycemia exposure. In the present study (**Figure 1**), we will determine the effect of hybrid closed-loop insulin delivery on endogenous glucose production during insulin-induced hypoglycemia in type 1 diabetic patients with hypoglycemia unawareness using next generation systems from Medtronic or Tandem that automates interprandial insulin delivery including suspension for predictive hypoglycemia as well as when the glucose crosses a set low threshold, and so promises even greater hypoglycemia avoidance that may be required to reverse HAAF and improve glucose counterregulation and hypoglycemia symptom recognition. Demonstration of improved physiologic defense against hypoglycemia is critical to understanding whether protection from hypoglycemia may persist when the glucose sensor is not functioning properly.

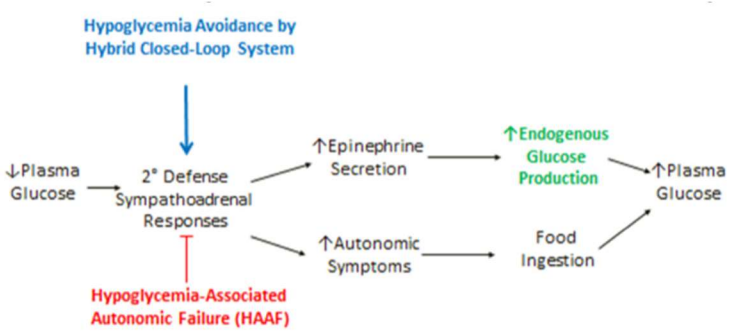

Figure 1. This study will determine the effect of hypoglycemia avoidance by hybrid closed-loop insulin delivery on the endogenous glucose production response to insulin-induced hypoglycemia. Glucose counterregulation will be assessed before and after 6 and 18 months' implementation of a hybrid closed-loop system in patients with long standing type 1 diabetes and hypoglycemia unawareness.

1.2 Name and Description of the Investigational Product

In the present study, we will assess the effect of hypoglycemia avoidance by hybrid closed-loop insulin delivery on endogenous glucose production during insulin-induced hypoglycemia in type 1 diabetic patients with hypoglycemia unawareness to determine its potential for restoring defective glucose counterregulation and protecting patients from experiencing future severe hypoglycemia episodes. The first of these advanced systems for automated insulin delivery, including predictive and threshold suspension for protection against hypoglycemia, is the latest one from Medtronic, the MiniMed 670G, which was approved for use in the US by the FDA in 2016. Medtronic's predecessor systems, the MiniMed 530G and MiniMed 630G, are FDA-approved and commercially available in the United States. All of these systems have a LGS feature based on automated suspension of insulin delivery when the sensor glucose crosses below a defined threshold. What is unique to the MiniMed 670G system is the automated interprandial insulin delivery (when in "auto" mode) as well as automated suspension of insulin delivery when the sensor glucose is *predicted* to cross below a defined threshold (when in "auto" or "manual" mode). This predictive function is more likely to prevent the ultimate development of low blood glucose, and so should be more effective in mediating hypoglycemia avoidance required for the reversal of HAAF and correction of defective glucose counterregulation and hypoglycemia symptom recognition. Thus, we will implement hybrid closed-loop insulin delivery using the MiniMed 670G system in the present study. The second of these advanced systems for automated insulin delivery, including predictive and threshold suspension for protection against hypoglycemia is the Tandem t:slimX2 insulin pump integrated with the Dexcom G6 continuous glucose monitoring (CGM) system. As stand-alone devices the Dexcom G6 and t:slimX2 pump are both FDA-approved and have been commercially available in the United States. However; on Dec 13, 2019, the FDA announced the approval of the Control-IQ Hybrid Closed Loop System from Tandem Diabetes Care. The approval of the Control-IQ system as a "controller" represents the first-ever approval of an interoperable algorithm for use in an automated insulin dosing system.

The Medtronic MiniMed 670G system includes the Guardian Sensor 3, Medtronic's newest and most advanced CGM sensor and the first and only sensor approved by the FDA for use in hybrid closed-loop insulin delivery, which is driven by SmartGuard technology that varies basal insulin delivery based on personalized needs, and that includes a predictive low glucose management algorithm, referred to as suspend before low, that suspends insulin delivery when the sensor glucose is predicted to fall within 20 mg/dl of a preset low glucose limit within 30 minutes, and automatically restarts basal insulin delivery on recovery from hypoglycemia. This strategy builds on the previous threshold suspend function that would suspend insulin delivery once the sensor glucose is below the preset low glucose limit. While alerts (vibration) and alarms may be set for activation of the predictive suspension, they remain mandatory should threshold suspension be reached. The user can manually restart basal insulin delivery at any time, and basal insulin delivery is automatically resumed after 2 hours of suspension regardless of the sensor glucose.

1.2.1 Clinical Data to Date

A study involving 124 subjects with type 1 diabetes (mean ± SD age 38 ± 14 years, 66% female, mean

disease duration 22 years) evaluated the MiniMed 670G system over a 3-month study period (Bergenstal et al., 2016). The system was in closed-loop mode for a median (IQR) 87% (75 – 92%) of the study period during which HbA1c decreased from 7.4 ± 0.9 to 6.9 ± 0.6% and time spent < 70 mg/dl decreased from 5.9 ± 4.1 to 3.3 ± 2.0% with an even greater reduction from 6.4 ± 5.3 to 3.1 ± 2.2% seen overnight. There were no episodes of severe hypoglycemia or ketoacidosis observed. Sensor and reference glucose values were in good agreement as indicated by an overall mean absolute relative difference of 10.3 ± 9.0%. There were 28 devise-related adverse events reported that were resolved at home, including 17 episodes of severe hyperglycemia (glucose > 300 mg/dl), 11 attributed to the infusion set as is expected with insulin pump delivery, 5 attributed to the algorithm controller, and only 1 attributed to the sensor. This overwhelmingly positive safety profile led to licensure by the FDA in late 2016.

Another study further tested the safety of the MiniMed 670G system in 8 subjects with type 1 diabetes (mean [range] age 18 [14-36] years, 63% female, mean disease duration 8 years) challenged with aerobic exercise and a purposefully over-calibrated glucose sensor and observed over 4 days that should both increase the risk of hypoglycemia (de Bock et al., 2017). Reassuringly, the system driven insulin delivery limits were effective in preventing exercise-induced and nocturnal hypoglycemia even in the presence of the over-calibrated glucose sensor over-reading the plasma glucose by 14%. The only hypoglycemia observed followed subject delivered meal or correction insulin boluses, with none being severe. Whether such protection against hypoglycemia is afforded to patients with long standing disease and defective glucose counterregulation will be assessed in the present study.

We have previously evaluated the effect of real time CGM on glucose counterregulation in 11 subjects with long standing type 1 diabetes complicated by hypoglycemia unawareness under IRB protocol #813094, funded by the previous cycle of the NIH grant sponsoring the current study. Results indicated that real time CGM can improve the endogenous glucose production response to insulin-induced hypoglycemia, but the effect was not evident until 18 months post-intervention (**Figure 2**) (Rickels et al., 2018). Autonomic symptoms became distinguishable under hypoglycemic vs. euglycemic clamp conditions at 6 and 18-month post-intervention; however, the change in autonomic symptom response to insulin-induced hypoglycemia was not significantly different over time.

The results of the first large-scale, 6-month randomized (2:1) clinical trial of closed-loop vs. sensor-augmented pump involved 168 participants ages 14-71 years, and demonstrated an 11 percentage point increase of time spent in the glucose range 70 – 180 mg/dl with closed-loop, as well as a 0.88 percentage point decrease of time spent with hypoglycemia (< 70 mg/dl) and 0.33 percentage point reduction in HbA1c (Brown et al., 2019). The trial compared the new Control-IQ hybrid closed loop vs. the same t:slimX2 pump and CGM without the control-IQ algorithm. Time in closed loop / Control-IQ (like the 670G “automode”) was 92%.

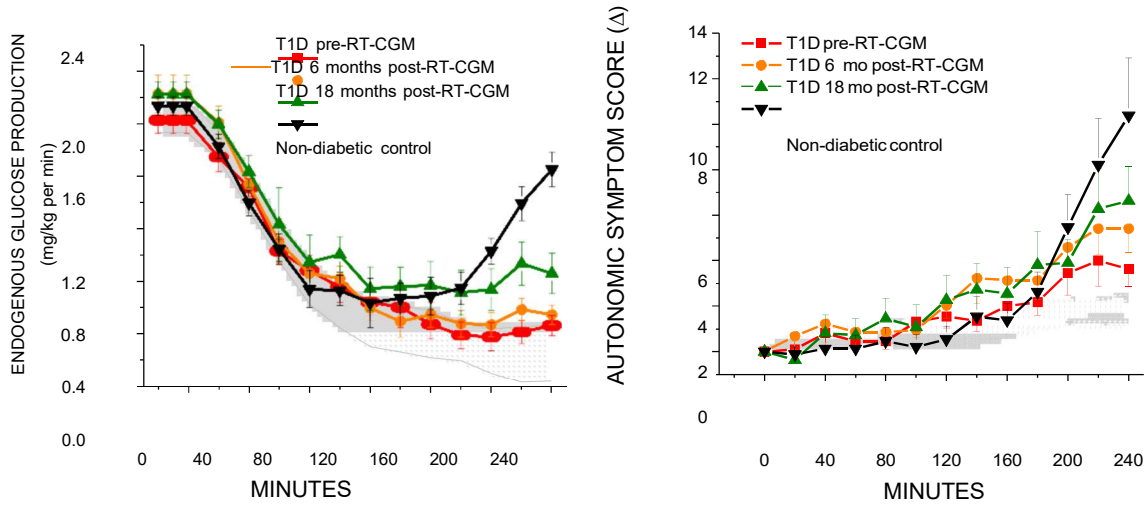

Figure 2. Results of glucose counterregulation testing from type 1 diabetic patients with hypoglycemia unawareness (n = 11) before and after 6 and 18 months' implementation of real time CGM, and from non-diabetic controls (n = 12). There was an improvement in the endogenous glucose production response to insulin-induced hypoglycemia by 18 months post-intervention ($P < 0.05$). The gray shaded region gives the 95% CI for results obtained during hyperinsulinemic euglycemic conditions. Autonomic symptoms, while not significantly improved, were not statistically different during hypoglycemia compared to euglycemia before, and were greater under hypoglycemic vs. euglycemic conditions post-intervention ($P <$ 0.05 at both 6 and 18 months).

This effect on glucose counterregulation was associated with reductions in both the Clarke score of hypoglycemia unawareness and the HYPO score of hypoglycemia severity (**Figure 3**), indicating clinical improvement in hypoglycemia awareness and less problematic hypoglycemia, with a reduction in the severe hypoglycemia event rate from 2.2 ± 0.7 per subject-year at baseline to 0.9 ± 0.5 per subject-year at 18 months ($P < 0.01$), and importantly no deterioration of glycemic control (HbA_{1c} 7.2 ± 0.2 % at baseline and 7.0 ± 0.2 % at 18 months).

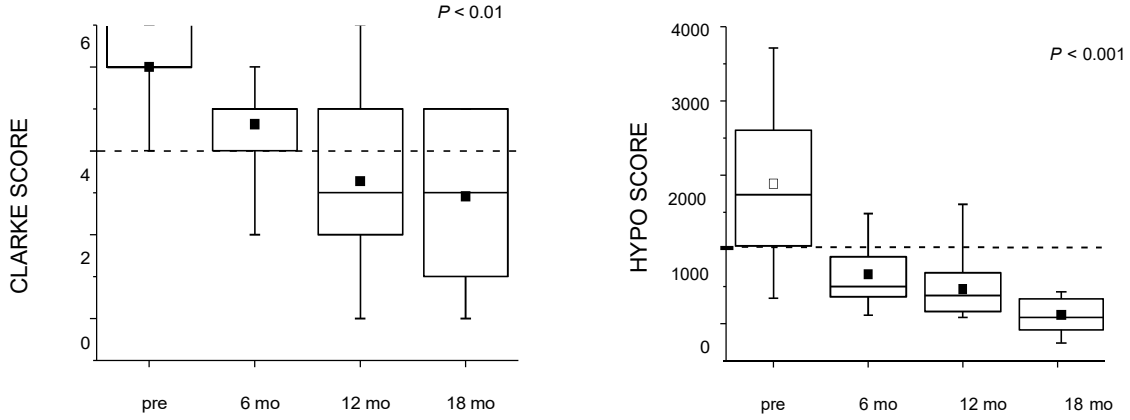

Figure 3. Measures of hypoglycemia unawareness and severity in response to implementation of real time CGM in type 1 diabetic patients with hypoglycemia unawareness (*n* = 11). The dashed line for the Clarke score indicates the cut-off for impaired awareness of hypoglycemia, and the dashed line for the HYPO score gives the 90th percentile cut off for 100 patients with type 1 diabetes (Ryan et al., 2004).

Interestingly, CGM measures of glycemic control indicated only a trend for improvement in glucose variability as measured by the glucose S.D. (*P* = 0.07), with no significant reduction in time spent hypoglycemic (< 60 mg/dl) despite the improvements in hypoglycemia awareness, hypoglycemia events, and glucose counterregulation (endogenous glucose production). Importantly, nocturnal hypoglycemia (< 60 mg/dl) remained present at ~ 5% of time between midnight and 6 a.m. throughout the 18-month study. The present study will more specifically target avoidance of nocturnal hypoglycemia by implementation of hybrid closed-loop insulin delivery that should significantly reduce time spent in the hypoglycemia range in order to affect even greater recovery in endogenous glucose production and autonomic symptom generation.

2 Study Objectives

This study aims to determine whether hypoglycemia avoidance achieved through implementation of hybrid closed-loop insulin delivery can improve glucose counterregulation in type 1 diabetic patients with hypoglycemia unawareness. *We hypothesize that the endogenous glucose production response to insulin-induced hypoglycemia will be greater in subjects after 6 months when compared to before intensive implementation of hybrid closed-loop insulin delivery.* Glucose counterregulatory hormone, symptom, and endogenous glucose production responses will be measured using the stepped-hyperinsulinemic hypoglycemic clamp before, after 6 months' intervention, and after 18 months to assess the durability of any benefit from avoidance of hypoglycemia with continued use of the hybrid closed-loop system.

3 Investigational Plan

3.1 General Design

Open label, single-arm clinical trial of the effect of hybrid closed-loop insulin delivery using the MiniMed 670G system (Medtronic Diabetes, Northridge, CA) or the t:slim Basal-IQ and Control-IQ technology (Tandem Diabetes, San Diego, CA) on glucose counterregulatory mechanisms in patients with long standing type 1 diabetes complicated by hypoglycemia unawareness. Comparisons will be made within subject with the primary outcome measure being endogenous glucose production in response to insulin-induced hypoglycemia after 6 months' intervention. Secondary outcome measures will include endogenous glucose production in response to hypoglycemia after 18 months' intervention, and glucose counterregulatory hormone and symptom responses to hypoglycemia after 6 and 18 months.

The purpose of this small, proof-of-concept, mechanistic study is to determine whether hybrid closed-loop

insulin delivery can achieve sufficient hypoglycemia avoidance in patients with long standing type 1 diabetes experiencing hypoglycemia and symptom unawareness despite receiving intensive insulin therapy standard-of-care to improve glucose counterregulation against insulin-induced hypoglycemia. As it remains critically important to understand the potential physiologic benefits of hypoglycemia avoidance by means of a hybrid closed-loop system in this population, studying each well characterized subject as his/her own control by a within subject design should serve the study purpose, and has been the standard approach to assessing the effects of various approaches to hypoglycemia avoidance in patients with unawareness (Fanelli et al., 1993; Cranston et al., 1994; Fanelli et al., 1994; Dagogojack et al., 1994; Liu et al., 1996; Rickels et al., 2016). The data generated will be available to power future randomized clinical trials to determine the comparative efficacy of emerging artificial pancreas and β-cell replacement approaches to achieve target glycemic control with amelioration of problematic hypoglycemia in type 1 diabetes.

3.1.1 Recruitment, Informed Consent and Screening Phase

Subjects will be recruited from the diabetes practices of the University of Pennsylvania Health System. Additional candidates for participation may be referred by their personal physicians, may respond to the website for the Penn Institute for Diabetes, Obesity & Metabolism, or may respond to the study posting on ClinicalTrials.gov or an IRB-approved secure on-line system iConnect. All inquiries will be subjected to a structured telephone interview conducted by a research coordinator to determine potential eligibility; in some cases, candidates' medical records may be reviewed by the PI after a signed release of medical records is received. If review of the phone interview and any medical records indicates that the potential participant is not eligible, s/he will be notified by the research coordinator and explained why this is so; if review indicates potentially unsuitable diabetes care, the potential participant may be referred to Penn's Rodebaugh Diabetes Center for further assessment and management; if review indicates that the potential participant may be eligible, s/he will be contacted by the research coordinator to schedule the screening visit and the informed consent form will be mailed to subjects for review.

At the screening visit, the study details and procedures will be discussed with a research coordinator and at least one of the PI or the research nurse practitioner. The potential participant is given adequate time to ask questions and review the informed consent document. Once satisfied that all questions have been answered, the potential participant will either decline to participate or sign the informed consent document. This may occur at a subsequent visit if the potential participant desires, in order to think further about what participation means and/or to consult with family, friends and/or a personal physician. The consent form is signed in the presence of a witness (research coordinator +/- family member). All participants must read, sign, and date a consent form before entering the study, undergoing physical examination or undergoing any testing. The informed consent form will be revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the studies.

Subjects will include adult (ages 25 - 70 years) patients with established (C-peptide negative) type 1 diabetes of equal to or more than 5 years duration complicated by hypoglycemia unawareness (Clarke score 4 or more (Clarke et al., 1995)), experiencing severely problematic hypoglycemia and/or marked glycemic lability (Ryan et al., 2004; Senior et al., 2015), despite the use of basal-bolus insulin analog delivery by multi-dose injection or pump therapy together with frequent blood glucose monitoring (more than 3 times daily) and/or CGM under the direction of an endocrinologist. Because modest hypoglycemia in the range 50 – 58 mg/dl (Heller and Cryer, 1991) and particularly overnight (Cryer, 2004) impairs subsequent counterregulatory responses to hypoglycemia, subjects will require at least 5% of time with a sensor glucose < 60 mg/dl including at least one episode occurring overnight in 7 days. Subjects will be excluded for severe obesity (BMI ≥ 38 kg/m^2), insulin resistance (daily insulin requirement ≥ 1.0 units/kg·d), poor glycemic control (HbA_{1c} ≥ 10%), uncontrolled hypertension, active cardiovascular disease, abnormal kidney, liver, or thyroid function, anemia, seizure disorder not related to prior severe hypoglycemia, pregnancy, and nursing. Eligibility will be confirmed through the performance of a history and physical examination by the PI or the research nurse practitioner, EKG, urine pregnancy test (if applicable), serum chemistries, TSH, cell counts, HbA_{1c} and C-peptide, completion of glycemic lability and hypoglycemia awareness and hypoglycemia severity questionnaires, placement of a 7 day blinded

CGM (iPro 2, Medtronic Diabetes, Northridge, CA) unless CGM is available for downloading, and 7 day accelerometry (WGT3X-BT, Actigraph LLC, or Actiwatch2) to define the nocturnal period. Only after all eligibility criteria (inclusion and exclusion) are met, will a potential subject be enrolled. Repeated clinical testing throughout the study (please see **Table 1**) will ensure the continued safety and minimization of risk for the enrolled participants.

3.1.2 Study Intervention Phase

Eligible subjects will complete a baseline assessment of glucose counterregulation by stepped-hyperinsulinemic hypoglycemic clamp prior to starting intervention with the hybrid closed-loop system (MiniMed 670G system, Medtronic Diabetes, Northridge, CA) or the t:slim Basal-IQ and Control-IQ technology (Tandem Diabetes, San Diego, CA). Unless a system becomes available to the subject via their insurance carrier, one will be provided for them or we will cover the upgrade fee as dictated by their insurance. In addition, subjects using the Medtronic system will also receive a study glucometer (Contour Next Link 2.4, Bayer, Indianapolis, IN) that communicates with the MiniMed 670G insulin pump for bolus dosing calculation and glucose sensor calibration. Subjects who cannot maintain > 80% (or 6/7 day) compliance with the sensor component as assessed at each study visit may be dropped since less compliance has not been associated with any benefit of CGM to glycemic control (Tamborlane et al., 2008), and limits the potential for benefit from LGS on hypoglycemia avoidance. Accuracy of the sensor will be assessed at each visit through devise download and interpretation (Mastrototaro et al., 2008). Study visits will occur weekly for the first month, then monthly until month 6, and then every 3 months until month 18. Month 1, 2, 4 & 5 visits may be performed via telephone if the device has been uploaded to the Care Link Medtronic platform or to the t-connect Tandem platform. This schedule will allow for determination of possible benefit from hybrid closed- loop insulin delivery on glucose counterregulation after 6 months of intensive provider support, and then for assessment of the durability or potential further gains in beneficial effects after another 12 months of more typical provider interaction occurring every 3 months. Weekly visits may be performed via telephone with uploading devise data to Care Link or t-connect for review and interpretation. Uploaded or downloaded insulin delivery, blood and sensor glucose monitoring, insulin dose settings and CGM calibration accuracy, alert settings, time spent in auto and manual modes, and LGS threshold and activity will be assessed at each visit, targeting > 80% CGM and LGS compliance, adjusting basal and bolus insulin dosing in order to minimize glycemic excursions while maximizing hypoglycemia (< 60 mg/dl) avoidance, with adjustment of alarms set to alert the subject to rapidly increasing or decreasing glucose and predict the occurrence of elevated or low blood glucose (Tamborlane, 2008). During manual mode, target glucose ranges will be 90 – 140 mg/dl before meals, < 180 mg/dl after meals, and 120 – 160 mg/dl at bedtime, with correction dosing to no lower than 100 mg/dl during the day, and 120 mg/dl overnight. Alarm settings may be individualized to target these ranges, but the hypoglycemia alarm for LGS will not be set lower than 70 mg/dl (Cryer, 2009). During auto mode, the automated interprandial basal insulin delivery will adjust according to the closed-loop algorithm to target a sensor glucose of 120 mg/dl, which may be temporality increased to 150 mg/dl if needed to further minimize exposure to hypoglycemia during exercise or overnight. Prior to each 3 monthly visit, subjects will wear an actigraph monitor (WGT3X-BT, Actigraph LLC or Actiwatch2) for three weeks in order to define the nocturnal period. Every 6 months' measures of hypoglycemia awareness (Clarke score) and severity (HYPO score), and the glycemic lability index (LI) will be calculated from questionnaires, event diaries, and device downloads, respectively (Senior et al., 2015). At 6 months and at 18 months, subjects will again undergo assessment of glucose counterregulation by stepped-hyperinsulinemic hypoglycemic clamp testing.

Table 1. Schedule of Events

	Screening	*Baseline*	*Month 1*[7]	*Month 2*[7]	*Month 3*	*Month 4*[7]	*Month 5*[7]	*Month 6*	*Month 9*	*Month 12*	*Month 15*	*Month 18*
Consent	X											
H&P[8]	X	X			X			X	X	X	X	X
EKG[1]	X											
HCG[2]	X	X						X				X
BMP[3]	X							X				X
LFTs[4]	X							X				X
TSH[5]	X											
CBC[3]	X							X				X
HbA1c[3]	X				X			X		X		X
C-peptide[6]	X											
Download	X	X	X	X	X	X	X	X	X	X	X	X
Actigraphy	X				X			X	X	X	X	X
CSM & PSQUI	X											
ISI & ESS	X				X			X	X	X	X	X
Clarke Score	X							X		X		X
HYPO Score	X							X		X		X
HypoA-Q	X							X		X		X
Lability Index	X							X		X		X

[1]EKG, electrocardiogram within 6 months.
[2]HCG, human chorionic gonadotropin by serum or urine.
[3]BMP, basic metabolic panel, CBC, complete blood count, and HbA1c within 3 months.
[4]LFTs, liver function tests within 6 months.
[5]TSH, thyroid stimulating hormone within 12 months.
[6]Any documented C-peptide < 0.3 ng/ml.
[7]Month 1, 2 4 or 5 may be done via phone if participant is comfortable uploading pump to Carelink website
[8]H & P not required monthly

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary outcome measure will be endogenous glucose production in response to insulin-induced hypoglycemia after 6 months of hybrid closed-loop insulin delivery.

3.2.2 Secondary Study Endpoints

Secondary outcome measures will include endogenous glucose production in response to insulin-induced hypoglycemia after 18 months' intervention with the hybrid closed-loop system, and glucose counterregulatory hormone and symptom responses to hypoglycemia after 6 and 18 months.

3.2.3 Primary Safety Endpoints

The primary safety measure will be incidence of severe hypoglycemia, defined as an event with symptoms or signs compatible with hypoglycemia in which the subject was unable to treat him/herself and which was associated with either a blood glucose < 54 mg/dl or prompt recovery after oral carbohydrate, IV glucose, or glucagon administration.

4 Study Population and Duration of Participation

The evaluation of the effect of hybrid closed-loop insulin delivery on endogenous glucose production during insulin-induced hypoglycemia will involve subjects with long standing type 1 diabetes complicated by hypoglycemia unawareness. The inclusion/exclusion criteria are:

4.1 Inclusion Criteria

Subjects who meet *all* of the following criteria are eligible for enrollment:

- Male and female subjects age 25 to 70 years.
- Subjects who are able to provide written informed consent and to comply with the procedures of the study protocol.

- Clinical history compatible with type 1 diabetes with disease onset < 40 years of age and insulin dependent for ≥ 5 years.
- Absent C-peptide (< 0.3 ng/ml).
- Involvement in intensive diabetes management defined as the use of basal-bolus insulin analog delivery by multi-dose injection (MDI) or continuous subcutaneous insulin infusion (CSII) together with self-monitoring of blood glucose values more than 3 times daily and /or continuous glucose monitoring (CGM) under the direction of an endocrinologist, diabetologist, or diabetes nurse practitioner with at least 3 clinical evaluations during the previous 12 months.
- Hypoglycemia unawareness manifested by a Clarke score of 4 or more AND at least 1 of the following: HYPO score greater than or equal to the 90th percentile (1047); OR marked glycemic lability defined by a glycemic lability index (LI) score greater than or equal to the 90th percentile (433 mmol/l^2/h·wk^{-1}); OR a composite of a HYPO score greater than or equal to the 75th percentile (423)
  and a LI greater than or equal to the 75th percentile (329) (Senior et al., 2015).
- Documented > 5% time spent in the hypoglycemic range (glucose < 60 mg/dl) by 7 day real-time or blinded CGM; at least one episode of hypoglycemic during the 7 days must occur overnight.

4.2 Exclusion Criteria

Subjects who meet *any* of these criteria are *not* eligible for enrollment:

- BMI ≥ 38 kg/m^2.
- Insulin requirement of ≥ 1.0 units/kg·day.
- HbA_{1c} ≥ 10%.
- Untreated proliferative diabetic retinopathy.
- Uncontrolled hypertension: systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.
- Active cardiovascular disease
- Abnormal kidney function: eGFR < 60 ml/min/1.73 m^2.
- Abnormal liver function: persistent elevation of liver function tests > 1.5 times the upper limit of normal.
- Untreated hypothyroidism, Addison's disease, or Celiac disease.
- Anemia: baseline hemoglobin concentration < 11 g/dl in women and < 12 g/dl in men.
- Presence of a seizure disorder not related to prior severe hypoglycemia.
- Use of glucocorticoids greater than 5 mg of prednisone daily, or an equivalent physiologic dose of hydrocortisone.
- For female participants of child-bearing potential: Positive pregnancy test, presently breast-feeding, or unwillingness to use effective contraceptive measures for the duration of study participation. Oral contraceptives, intra-uterine devices, Norplant®, Depo-Provera®, and barrier devices with spermicide are acceptable contraceptive methods; condoms used alone are not acceptable.
- Treatment with any anti-diabetic medication other than insulin within 4 weeks of enrollment.
- Use of any investigational agents within 4 weeks of enrollment.
- Any medical condition that, in the opinion of the PI, will interfere with the safe completion of the study.

4.3 Subject Recruitment

Subjects will be recruited from the diabetes practices of the University of Pennsylvania Health System. Potentially eligible patients will be referred by their diabetes providers, may respond to IRB approved recruitment flyers placed in the diabetes practices, or may be identified by EPIC chart review conducted by the research team, in which case permission to contact a patient will be obtained from the diabetes provider. Subjects who have either participated in a prior research study of the PI, or may be screened but are either not interested in or not eligible for another research study of the PI, may also be approached for consideration of participation in this study. Additional candidates for participation may be referred by their personal physicians, may respond to the study listing on the website for the Penn Institute for

Diabetes, Obesity & Metabolism, or may respond to the study posting on ClinicalTrials.gov or an IRB-approved secure on-line system iConnect.

If physicians at our Diabetes Center attend a Diabetes conference, a slide with contact information for research participation will be included. We will also include a phrase in the Diabetes Center's newsletter.

We also plan on using the full Trial X iConnect platform in order to take advantage of everything they have to offer including but not limited to their social media campaigns such as the "ClinicalResearch@Penn" Facebook page. This Facebook page posted by the Office of Clinical Research via a Redcap application will link to various websites such as the Diabetes Center, CT.gov, iConnect and Clinical Trials at Penn page. By utilizing iConnect we will be able to track our recruitment advertisement, and enhance recruitment using the platform features such as flyer build, recruitment tracker, volunteer registry and mobile app creation. Through iConnect we can manage volume by creating pre-screeners in the system and we can also promote our diabetes clinical research initiatives using their "cure talks" platform, a social initiative that organizes bi-weekly online talk shows.

Subjects recommended by physicians or indicating interest in research participation to their physicians will be contacted using the myPennMedicine portal, @pennmedicine email and/ or via telephone. In addition, we will be contacting departed Endocrine physicians whom have completed their fellowship at UPenn and practice within a commutable distance.

We may also use the UPenn Clinical Trials Unit (CTU) to assist with recruitment. Their methods for attracting potential subjects may also include local IRB-approved flyers, email blasts, Craig's List posts, Septa ads, social media ads including Facebook, community outreach, radio, internet and newspaper advertisements targeting the Delaware Valley region. All ads used will have IRB approval before use. Subjects may also be recruited from PennSeek, Pennomics, iConnect research portal, and Bio-Bank queries. They plan to use Facebook ads, specifically Facebook - Boosted Posts, Unpublished Posts, and Instagram. Penn Medicine Marketing has referred the CTU team to use the ad agency named Evariant. This is the vendor which they use to place all of their ads, and Evariant already has access to the Penn Medicine Facebook page.

4.4 Duration of Study Participation

Study subjects' participation will involve at least 1 month for the screening phase that includes the collection of 4 weeks of glucose monitoring and diary data, and once baseline testing is scheduled, the anticipated 18-month intervention phase. Thus, subjects can anticipate involvement in the study for an approximately 20-month time period.

4.5 Total Number of Subjects

This is a single-site study being conducted at Penn that will involve the enrollment of up to 30 subjects to ensure a minimum of 15 and maximum of 18 subjects complete the primary outcome assessment at 6 months, all of whom will be anticipated to complete the 18 months of intervention and secondary outcome assessments.

4.6 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Intervention (Study drug, device, biologic, vaccine, food etc.)

5.1 Description

The Medtronic MiniMed 670G system is comprised of a MiniMed 670G insulin pump containing closed- loop algorithm software, insulin reservoirs, and infusion sets required for standard continuous subcutaneous insulin infusion (CSII) therapy, and new Guardian Sensor 3 and Guardian Link 3 transmitters for communication of the subcutaneously placed interstitial glucose sensor to the insulin pump for display, and triggering of alerts (vibration), alarms, and according to a predictive low glucose management

algorithm, referred to as suspend before low, automated suspension of insulin delivery when the sensor glucose is predicted to fall within 20 mg/dl of a preset low glucose limit within 30 minutes, and when in auto mode, automated interprandial basal insulin delivery.
Following automated suspension of insulin delivery, the system automatically restarts basal insulin delivery on recovery from hypoglycemia. This strategy builds on the previous threshold suspend function that would suspend insulin delivery once the sensor glucose is below the preset low glucose limit. While alerts (vibration) and alarms may be set for activation of the predictive suspension, they remain mandatory should threshold suspension be reached. The user can manually restart basal insulin delivery at any time, and basal insulin delivery is automatically resumed after 2 hours of suspension regardless of the sensor glucose. This protects against subsequent hyperglycemia should the sensor glucose be erroneously low, and the user unresponsive to the alerts and alarms (e.g. due to sleep) that would otherwise prompt the user to obtain a confirmatory blood glucose level. The MiniMed 670G insulin pump also communicates with the Contour Next Link 2.4 glucometer (Bayer, Indianapolis, IN) that will be provided to subjects for bolus dosing calculation and glucose sensor calibration.

The Control-IQ uses the TypeZero/Dexcom hybrid closed loop algorithm which is based on standard insulin pump settings. The t:slimX2 insulin pump is comprised of the t:slimX2 pump, the t:slim 3mL cartridge and a compatible infusion set. The Dexcom G6 continuous glucose monitor is comprised of the Dexcom transmitter, the Dexcom sensor and a receiver. The Control-IQ system aims to keep users between 70-180mg/dl as much as possible using a combination of strategies. The Basal-IQ is equivalent to “predict before low” mode and the Control-IQ is equivalent to “auto” mode in the closed loop system.

Tandem and Dexcom G6 information, user guides and support can be found at:
https://www.dexcom.com/guides and https://www.tandemdiabetes.com/support/documents

Medtronic 670G information, user guides and support can be found at:
https://www.medtronicdiabetes.com/products/minimed-670g-insulin-pump-system

5.1 Intervention Regimen

At the baseline visit, the research nurse practitioner will train subjects in the use of the system the participant has selected, and set individualized insulin dosing and glucose monitoring alerts, with the low glucose limit not set less than 70 mg/dl. Target glucose ranges will be 90 – 140 mg/dl before meals, < 180 mg/dl after meals, and 120 – 160 mg/dl at bedtime, with correction dosing to no lower than 100 mg/dl during the day, and 120 mg/dl overnight. Basal and bolus insulin dosing will be adjusted at every visit, or as necessary in response to subject inquiry, in order to minimize glycemic excursions while maximizing hypoglycemia (< 60 mg/dl) avoidance, with adjustment of alarms set to alert the subject to rapidly increasing or decreasing glucose and predict the occurrence of elevated or low blood glucose (Tamborlane, 2008). Study visits will occur weekly for the first month, then monthly until month 6, and then every 3 months until month 18. Weekly visits, as well as any interim visits, may be performed via telephone with uploading devise data to Medtronic Care Link or Tandem t-Connect website for review and interpretation.

5.2 Receipt and Storage

Unless a MiniMed 670G system becomes available to the subject via their insurance carrier, one will be provided for them together with a Contour Next Link 2.4 study glucometer. The research team will receive the MiniMed 670G system and associated supplies directly from Medtronic Diabetes for a discounted research rate under an investigator-initiated research support agreement NERP16-015. Study devices and supplies will be maintained under double lock in the research staff office, and given to eligible subjects at the time of training during the baseline visit. Additional supplies will be provided to subjects at scheduled or interim visits as necessary to ensure optimal compliance with use of the system for the duration of the study. Subjects will be encouraged to receive associated supplies available through insurance, for example glucose test strips, via their carrier. If a participant prefers the t:slim Basal-IQ and Control-IQ system, study will cover the cost of the insulin pump upgrade as dictated by each individual’s insurance and the length of time the current pump has been used.

5.3 Administration and Accountability

The research coordinator will track the ordering and dispensing of all study related devices and supplies on a per subject basis using a standardized, dated form throughout the study period. Upon receipt of the study treatment supplies, an inventory will be performed and a supply receipt log filled out and signed by the person accepting the shipment. The research coordinator will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable devices or sensors in a given shipment will be documented in the study files and returned to the manufacturer.

5.4 Subject Compliance Monitoring

Compliance will be assessed at each visit through device download and interpretation of insulin dosing, sensor glucose, and blood glucose data (Mastrototaro et al., 2008). Visits month 1, month 2, month 4 and month 5 may take place via telephone if the participant is comfortable uploading their system to the Medtronic Carelink or the Tandem t-Connect website. The downloaded sensor and blood glucose monitoring data will be used both for assessing CGM calibration accuracy, as well as durations of CGM and LGS use, targeting > 80% CGM and LGS compliance, or 6/7 days, and time spent in manual and auto mode. Reasons for less compliance will be assessed, and if addressable, re-evaluated at the next scheduled visit. If compliance remains under target, or if the reason for sub-optimal compliance is not addressable, the subject will be considered non-compliant with the product regimen and withdrawn from participation in the study. In the case of subject withdrawal, the subject will be asked to return the study MiniMed 670G system and related supplies at a final study visit when they will be returned to their pre-study insulin delivery and glucose monitoring regimen.

5.5.1 Return or Destruction of Investigational Product

Upon completion of study participation, all subjects maybe asked to return the study MiniMed 670G system and related supplies at their final study visit when they will be returned to their pre-study insulin delivery and glucose monitoring regimen. If the MiniMed 670G system becomes available to any subject via their insurance carrier at any time during the study, they will be able to return the study MiniMed 670G system and continue in the study using their own MiniMed 670G system. Any usable devices or supplies remaining at the termination of the study will be donated to study participants for their ongoing use to offset out-of-pocket expenses.

6 Study Procedures

Stepped-Hyperinsulinemic Hypoglycemic Clamp

Glucose counterregulation will be assessed using the hypoglycemic clamp technique (Rickels et al., 2005). Subjects will be admitted to the Penn Center for Human Phenomic Science (CHPS) the evening prior to each study day after avoiding strenuous exercise for 3 days. Following 12-hours of overnight fasting, at *t* = -120 min a primed (5 mg/kg · fasting plasma glucose/90 for 5 min) continuous (0.05 mg/kg·min for 355 min) infusion of 6,6-$^{2}H_{2}$glucose (99% enriched; Cambridge Isotopes Laboratories, Andover, MA) will be administered to assess endogenous glucose production before and during the induction of hypoglycemia (Bernroider et al., 2005). After baseline blood samples at *t* = -20, -10, and -1 min, at t = 0 min a continuous infusion of insulin (1.0 mU/kg·min for 240 min) will be administered to produce hyperinsulinemia. Subsequently, a variable rate infusion of 20% glucose will be initiated to achieve hourly plasma glucose steps of 80, 65, 55, and 45 mg/dl. To reduce changes in plasma enrichment of 6,6-$^{2}H_{2}$-glucose during the clamp, the variable glucose infusion will be enriched to ~ 2.0 % with 6,6-$^{2}H_{2}$-glucose (Bernroider et al., 2005).

Blood samples will be taken every 5 min, centrifuged, and measured at bedside with an automated glucose analyzer (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH) to adjust the glucose infusion rate and achieve the desired plasma glucose concentration. Additional blood samples will be taken at t = 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, and 240 min for biochemical analysis and verification of the plasma glucose levels. The total amount of blood sampled will be 168 ml. A questionnaire will be administered every 20 min during the study in order to quantitate autonomic symptoms as the sum of scores ranging from 0 (none) to 5 (severe) for each of the following symptoms: anxiety, palpitations, sweating, tremor, hunger, and tingling (Towler et al., 1993).

Biochemical Analysis: Plasma glucose and lactate will be determined in duplicate by the oxidase method using an automated glucose/lactate analyzer (YSI 2900). Plasma free fatty acid levels will be measured in duplicate using enzymatic colorimetrics (Wako Chemicals, Richmond, VA). Plasma insulin, glucagon, and pancreatic polypeptide will be measured in duplicate by double-antibody radioimmunoassays (Millipore, Billerica, MA, or for pancreatic polypeptide, ALPCO Diagnostics, Windham, NH), and plasma epinephrine and norepinephrine will be measured by high-performance liquid chromatography (HPLC) with electrochemical detection, by the Penn Diabetes Research Center Radioimmunoassay and Biomarker Core. Enrichment of 6,6-2H2-glucose will be measured by gas chromatography-mass spectrometry analysis by the Penn Institute for Diabetes, Obesity & Metabolism Metabolic Tracer Resource. Samples for radioimmunoassay and HPLC from before and 6 months after intervention will be assayed simultaneously using the same assay kit.

Calculations: Basal rates of endogenous glucose production (EGP) will be calculated using the formula: basal EGP = IR ([enrichment$_{inf}$ /enrichment$_{plasma}$] – 1), where IR is the basal 6,6-$^{2}H_{2}$-glucose infusion rate in mg/kg per min, enrichment$_{inf}$ is the percent enrichment of the 6,6-$^{2}H_{2}$-glucose infusate, and enrichment$_{plasma}$ is the percent basal plasma 6,6-$^{2}H_{2}$-glucose enrichment. The rate of appearance (R_a) of glucose during the clamps will be calculated using Steele's non-steady state equation modified for the use of stable isotopes: $R_a = F-(V[((C_2+C_1)/2)]\ [(E_2-E_1)/(t_2-t_1)]/(E_2-E_1)/2)$ where C_2 and C_1 are the glucose concentrations at the times (t) 2 and 1 respectively; V is the effective volume of distribution of glucose (40 ml/kg), F is the tracer infusion rate, and E represents the isotopic enrichment at the respective time points. EGP during the clamps will be calculated from the difference between the rate of appearance of glucose in the plasma and the infusion rate of exogenous glucose. We will determine counterregulatory responses from the hypoglycemic clamp as the glucagon, pancreatic polypeptide, epinephrine, norepinephrine, incremental autonomic symptom, and endogenous glucose production values obtained during the last 60 min of hypoglycemia.

Sleep Questionnaires: 4 short sleep/activity-related questionnaires will assist in the analysis of sleep / wake data obtained from the participants. 2 of the questionnaires will be administered as a baseline and 2 at the various protocol time-points when the participants wear the Actigraph watch or Actiwatch 2. These questionnaires would be administered either via paper or electronically into Redcap.

6.1 Screening

Once informed consent is obtained as described above, subjects will undergo a history and physical examination and review of their glucometer download, insulin pump download (if applicable), CGM download (if applicable), EKG, fasting serum biochemistries (glucose, C-peptide, electrolytes, creatinine, and liver function tests), HbA_{1c}, TSH, complete blood count, HCG (females), and retinal status. Subjects will have a blinded 7 day CGM (iPro 2) placed (to be returned by mail) unless on CGM available for downloading, undergo 7 day accelerometry (Actigraph wGT3X-BT monitor or Actigraph2) to define the nocturnal period, and be given a glucose log for recording 4 times daily monitoring for a 4-week period in order to calculate a lability index. Subjects who may experience difficulty affording a sufficient supply of test strips for their glucometer, or whose glucometer is not suitable for downloading, will be provided a OneTouch device for use during the screening period. Subjects will complete hypoglycemia questionnaires required to calculate HYPO and Clarke scores.

6.2 Study Intervention Phase

6.2.1 Visit 1 (run-in visit)

Eligible subjects will return to download their glucometer, insulin pump (if applicable), and CGM (if applicable), and confirm that all eligibility criteria (inclusion and exclusion) are met, and if so, will then undergo standard Medtronic training on the MiniMed 670G system and Contour Next Link 2.4 study glucometer or standard Tandem t:slim training on the t:slimX2 pump and Dexcom G6 CGM. Subjects will use the MiniMed 670G system or the t:slimX2 Basal-IQ and Control-IQ system without the automated features for a 2 week period to ensure understanding of and compliance with the devices. Subjects will receive a follow-up phone call the next morning, and then at one-week to inquire about any difficulties with MiniMed 670G system or the t:slimX2 Basal-IQ and Control-IQ system until the

next visit.

6.2.2 Visit 2 (baseline visit)

Subjects will return after 2 weeks in the afternoon to download their MiniMed 670G system and Contour Next Link 2.4 study glucometer or their t:slimX2 pump with Basal-IQ and Control-IQ system, and confirm tolerability of, compliance with, and willingness to continue the system, and if so, will then be admitted to the CHPS where they will receive dinner and then fast overnight after 8 p.m. After 9 p.m. subcutaneous insulin therapy will be held and the blood glucose will be maintained in the normoglycemic range overnight by a low-dose i.v. insulin infusion according to CHPS protocol. At 7 a.m. a stepped-hyperinsulinemic hypoglycemic clamp will be performed as described above under **Study Procedures**. Once the clamp test is completed, subjects will receive lunch, and undergo further training on the MiniMed 670G system or t:slimX2 pump with Basal-IQ and Control-IQ system in order to enable the automated features. Once training is complete, and the automated system is operational in manual mode, the subject will be discharged. Subjects will receive a follow-up phone call the next morning, and then weekly phone calls to inquire about any difficulties with MiniMed 670G system or t:slimX2 pump with Basal-IQ and Control-IQ system until the next visit. At the first weekly phone call the system will be switched in to auto mode or Control-IQ. During the weekly phone calls, subjects will upload their insulin dosing, glucose sensor, and glucometer data to Care Link or t-Connect for review and interpretation with the research nurse practitioner.

6.2.3 Visits 3 – 7, Months 1 – 5

Subjects will return at month 3 for a history and targeted physical examination by the research nurse practitioner. At months 1,2, 4 and 5 if subjects are comfortable uploading their device to the Carelink platform, the visits may be done over the phone. At all 5 visits their MiniMed 670G system and Contour Next Link 2.4 study glucometer or the t:slimX2 pump with Basal-IQ and Control-IQ system will be downloaded and reviewed in order to assess compliance with their use of CGM and LGS, time spent in auto and manual modes, re-educate as necessary, interpret their glucose data, and adjust their insulin dosing. At the Month 3 Visit 5, subjects will wear the actigraph / Actiwatch2 monitor for the preceding three weeks, and an HbA1c will be checked. At each visit a decision will be made whether to continue weekly phone contact with data upload to Care Link or t-Connect. At the Month 5 Visit 7, subjects will receive a glucose log for recording 4 times daily blood glucose monitoring for a 4week period.

6.2.4 Visit 8, Month 6

Subjects will return for a history and targeted physical examination, to turn in their glucose log and actigraph /Actiwatch2monitor, and complete hypoglycemia questionnaires, download their MiniMed 670G system and Contour Next Link 2.4 study glucometer or or t:slimX2 pump with Basal-IQ and Control-IQ system as for regular monthly visits, return the actigraph / Actiwatch 2 monitor after three weeks of wear, and check fasting serum biochemistries (glucose, electrolytes, creatinine, and liver function tests), HbA1c, complete blood count, and HCG (females). Subjects will be admitted to the CHPS where they will receive dinner and then fast overnight after 8 p.m. After 9 p.m. subcutaneous insulin therapy will be held by suspending the MiniMed 670G system, and the blood glucose will be maintained in the normoglycemic range overnight by a low-dose i.v. insulin infusion according to CHPS protocol. At 7 a.m. a stepped-hyperinsulinemic hypoglycemic clamp will be performed as described above. Once the clamp test is completed, subjects will receive lunch, resume the MiniMed 670G system or the t:slimX2 pump with Basal-IQ and Control-IQ system, and be discharged.

6.2.5 Visit 9, Month 9

Subjects will return for a history and targeted physical examination, download their MiniMed 670G system and Contour Next Link 2.4 study glucometer or the t:slimX2 pump with Basal-IQ and Control-IQ system in order to assess compliance with their use of CGM and LGS, time spent in auto and manual modes, interpret their glucose data, and adjust their insulin dosing as may be appropriate, return the actigraph / Actiwatch2 monitor after 3 weeks of wear, and check an HbA1c.Visit 10, Month 12

6.2.6 Visit 10, Month 12

Subjects will return for a history and targeted physical examination, to turn in their glucose log and complete hypoglycemia questionnaires, download their MiniMed 670G system and Contour Next Link 2.4 study glucometer or the t:slimX2 pump with Basal-IQ and Control-IQ system in order to assess

compliance with their use of CGM and LGS, time spent in auto and manual modes, interpret their glucose data, and adjust their insulin dosing as may be appropriate, return the actigraph / Actiwatch2 monitor after three weeks of wear, and check an HbA_{1c}.

6.2.7 Visit 11, Month 15
Subjects will return for a history and targeted physical examination, download their MiniMed 670G system and Contour Next Link 2.4 study glucometer or the t:slimX2 pump with Basal-IQ and Control-IQ system in order to assess compliance with their use of CGM and LGS, time spent in auto and manual modes, interpret their glucose data, and adjust their insulin dosing as may be appropriate, return the actigraph / Actiwatch2 monitor after three weeks of wear, and check an HbA_{1c}.

6.2.8 Visit 12, Month 18
Subjects will return for a history and targeted physical examination, to turn in their glucose log and actigraph / Actiwatch 2 monitor, and complete hypoglycemia questionnaires, download their MiniMed 670G system and Contour Next Link 2.4 study glucometer or t:slimX2 pump with Basal-IQ and Control-IQ system as for regular monthly visits, return the actigraph/ Actiwatch 2 monitor after three weeks of wear, and check fasting serum biochemistries (glucose, electrolytes, creatinine, and liver function tests), HbA1c, complete blood count, and HCG (females). Subjects will be admitted to the CHPS where they will receive dinner and then fast overnight after 8 p.m. After 9 p.m. subcutaneous insulin therapy will be held by suspending the MiniMed 670G system or the t:slimX2 pump with Basal-IQ and Control-IQ system, and the blood glucose will be maintained in the normoglycemic range overnight by a low-dose i.v. insulin infusion according to CHPS protocol. At 7a.m. a stepped-hyperinsulinemic hypoglycemic clamp will be performed as described above. Once the clamp test is completed, subjects will receive lunch, resume their pre-study insulin delivery and glucose monitoring regimen unless they have obtained their own MiniMed 670G system that would resume, and be discharged.

6.3 Subject Withdrawal
Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the PI for lack of adherence to intervention or study procedures or visit schedules, AEs, or due to persistent insufficient compliance with CGM and LGS use that should be targeted to > 80% or 6/7 days. Reasons for less compliance will be assessed, and if addressable, re-evaluated at the next scheduled visit. If compliance remains under target, or if the reason for sub-optimal compliance is not addressable, the subject will be considered non-compliant with the product regimen and withdrawn from participation in the study. In the case of subject withdrawal, the subject will be asked to return the study MiniMed 670G system or t:slimX2 pump with Basal-IQ and Control-IQ system and related supplies at a final study visit when they will be returned to their pre-study insulin delivery and glucose monitoring regimen. The PI may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects who withdraw early will have one final visit to collect the investigational supplies and to follow up regarding adverse events.

6.3.1 Data Collection and Follow-up for Withdrawn Subjects
Subjects who withdraw consent to participate in the study will be seen for one final visit to collect the investigational supplies and to be returned to their pre-study insulin delivery and glucose monitoring regimen.

6.4 Early Termination Visits
Early termination visits will include a history and targeted physical examination to assess for adverse events, download of the MiniMed 670G system and Contour Next Link 2.4 study glucometer or t:slimX2 pump with Basal-IQ and Control-IQ system in order to interpret glucose data, and inform return to pre-study insulin delivery and glucose monitoring, and measurement of an HbA_{1c}.

7 Statistical Plan

7.1 Primary Endpoint

The primary outcome measure of this study will be the rate of endogenous glucose production in response to insulin-induced hypoglycemia after 6 months of intervention. This measure will be calculated from the final hour of the stepped-hyperinsulinemic hypoglycemic clamp test, and compared between the month 6 and baseline study visits using a paired t-test or the Wilcoxon matched-pairs tests as appropriate, with significance considered at $P \leq 0.05$ (two-tailed).

7.2 Secondary Endpoints

Secondary outcome measures will include the rate of endogenous glucose production in response to insulin-induced hypoglycemia after 18 months of intervention, and counterregulatory hormone and symptom responses to hypoglycemia after 6 and 18 months. For the additional measures, multiple comparisons are being made without adjustments for multiplicity, and so any findings will be hypothesis generating. The additional responses at 18 months will be analyzed by repeated measures mixed model for longitudinal measurements over time.

7.3 Sample Size and Power Determination

Based on our preliminary work in 11 subjects completing 18 months intervention with real time CGM alone, the mean ± S.D. endogenous glucose production response pre-intervention was 0.42 ± 0.28 mg/kg·min and increased marginally to 0.54 ± 0.24 mg/kg·min at 6 months and further to 0.84 ± 0.50 mg/kg·min at 18 months. To detect a 0.42 mg/kg·min difference from before to 6 months after intervention with the hybrid closed-loop system will require 15 subject completers to have > 80% power at $\alpha = 0.05$ (two-tailed) using a paired t-test. We plan on enrolling up to 18 subjects to ensure at least 15 subjects complete the 6 month assessment.

8 Safety and Adverse Events

8.2 Definitions

8.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

For FDA regulated studies the FDA defines an adverse event as the following:

Adverse event means any untoward medical occurrence associated with the use of a device in humans whether or not considered device related.

8.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period
The study period during which adverse events will be reported is the period from the initiation of study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the completion of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by the PI until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, an investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery will be documented as an adverse event if the condition meets the criteria for an adverse event.

- Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances: Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the PI.

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc).
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Recording of Adverse Events

At each contact with the subject, an investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, and will be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

8.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be characterized by the PI and classified as definitely related, probably related, possibly related, unlikely or unrelated.

8.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Investigators will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Additionally, all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual and below.

8.4.1 Follow-up report

If an AE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator will be responsible for ensuring that all SAE are followed until either resolved or stable.

8.4.2 Investigator Reporting: Notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the study's regulatory binder.

Reporting Deaths: more rapid reporting requirements
Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Penn IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Penn IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable events:
For clinical trials, the following events are also reportable to the Penn IRB:

- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.

- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality.
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.

Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.5 Medical Monitoring

8.5.1 Data and Safety Monitoring Plan

The PI will oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. In addition, medical monitoring will be conducted by a study monitor and data and safety monitoring board (DSMB) as described in the data and safety monitoring plan (DSMP).

8.5.2 Data Safety Monitoring Board

A data and safety monitoring board (DSMB) will be established. The mission of the DSMB is to ensure that risk associated with participation in research is being minimized to the extent practical. This mission will be accomplished by charging the DSMB to determine safe and effective conduct of the study and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. The DSMB will consist of 3 members independent from the trial and the study team and having no conflicts of interest with any company developing insulin pumps, glucose sensors or related technology, with at least one being a clinical investigator and at least one an endocrinologist experienced in the care of subjects with type 1 diabetes. A CV for each member will be obtained and updated annually. The CVs will be kept on file in the Sponsor section of the Regulatory Binder to document the qualifications of the DSMB members. One member will serve as chair for meetings of the DSMB.

The DSMB will meet either by teleconference, or if possible, in person, at least annually and more often if requested due to the appearance of unexpected and possibly related serious adverse events, or an unexpected number of serious adverse events regardless of their relatedness. Each member will receive a monitoring manual including the current protocol, most recent approved consent form, CRF, and DSMP. The annual DSMB meeting will be scheduled as soon as possible following submission of the annual report to the IRB, and that report containing all adverse events will be reviewed by the DSMB together with any available interim efficacy data. All unexpected and possibly related serious adverse events will be reported expeditiously to both the IRB and the DSMB chair; all other serious adverse events regardless of their relatedness will be reported expeditiously to the DSMB chair. Based on such reporting, the DSMB chair may convene a meeting of the board at any time.

The annual DSMB meeting will be scheduled as soon as possible following submission of the annual report to the IRB, and that report containing all adverse events will be reviewed by the DSMB together with any available interim efficacy data. All unexpected and possibly related serious adverse events will be reported expeditiously to both the IRB and the DSMB chair; all other serious adverse events regardless of their relatedness will be reported expeditiously to the DSMB chair. Based on such reporting, the DSMB chair may convene a meeting of the board at any time.

Each DSMB meeting will start as an open meeting including the PI and any co-investigators and study personnel, where the PI will present the safety and efficacy materials for review to the DSMB and be available to answer any and all questions from the Board. The meeting will then be conducted as a closed meeting of the DSMB members for any further discussion and voting as to whether the study should continue or be placed on hold with 2/3 votes being required for a recommendation. In addition to study safety and efficacy data, the DSMB will consider participant recruitment, accrual and retention, participant risk versus benefit, and any scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study. The research coordinator will keep minutes on the open meeting, and the Board chair will keep minutes on the closed meeting; the research coordinator will compile both sets of minutes and the recommendation into a report for approval by the DSMB prior to submission to the PI and the IRB.

9 Study Administration, Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study;
- Who will have access to that information and why;
- Who will use or disclose that information; and
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the PI, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Data Collection and Management

Participants' privacy and confidentiality will be respected throughout the study. Each participant is assigned a sequential identification number, and these numbers rather than names are used to collect, store, and report participant information. Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. The University of Pennsylvania will be the only site where the research will be performed. Screening visits will involve the documentation of medical history, vital signs, and objective physical examination findings, and collection of urine and blood specimens as occurs routinely during standard care for patients with type 1 diabetes. Medical history, laboratory, and other reports will be reviewed in the electronic medical record (EPIC®) or upon written consent of the potential study participant to obtain outside medical records. Specimens will consist of blood and urine samples, to be assayed for metabolic and hematological parameters, and to exclude pregnancy. Clinical laboratory test results may be made available to each subject's personal physicians upon their consent and written release of information. Additional data collected will include glucose diaries, hypoglycemia questionnaires, adverse event logs, insulin pump, glucometer, CGM, and actigraph / Actiwatch 2 monitor downloads, and symptom questionnaires and metabolic response data derived from the hyperinsulinemic hypoglycemic clamp experiments conducted before and at 6 and 18 months following implementation of hybrid closed-loop insulin delivery. Paper source documents and medical and research records, as well as the code linking subjects and ID numbers are maintained under lock and key at Penn until data analysis is

complete at which point they are archived appropriately. Clinical specimens are assayed promptly.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, it will be marked "N/D". If the item is not applicable to the individual case, it will be marked "N/A". All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialed and dated. For clarification of illegible or uncertain entries, clarification will be printed above the item, then initialed and dated. Data culled from source documents will be transferred directly to a password protected database containing only the subject identification number. Subject ID numbers are assigned sequentially to each participant and these numbers rather than names are used to collect, store, and report participant information. None of the 18 biometric identifiers are entered into the database, however, date of birth, and dates of visits and adverse events are maintained under lock and key in the source documents for monitoring and analysis purposes. Specimens that are archived or that may be sent out for future analyses are coded with subject ID numbers and do not contain any of the 18 biometric identifiers.

All research samples are identified by code only. Only authorized research personnel will have access to source documents and research records. Additionally, regulatory personnel from the University (Office of Regulatory Affairs and the Office of Human Research) will have access to these records as part of the quality assurance and legal responsibilities of the investigation. Unless required by the laws that permit copying of records, only the coded identity associated with documents or with other participant data may be copied (and all personally identifying information must be obscured). The study database will not contain any protected health information, and even so, the database at Penn is user ID and password protected. Each user is provided with a unique personal ID and password.

9.3 Records Retention

The PI will retain all essential study documents for at least 2 years after acceptance of the final manuscript for publication related to this protocol.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan in the **Attachments**. The PI will allocate adequate time for such monitoring activities. The PI will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. Investigational Drug Service pharmacy, Center for Human Phenomic Science, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The PI will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The PI will ensure the capability for inspections of applicable study-related facilities (e.g. Investigational Drug Service pharmacy, Center for Human Phenomic Science, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional

Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator/sponsor before commencement of this study.

11.1 Risks

The risks of hybrid closed-loop insulin delivery include local discomfort, skin irritation, bruising, bleeding, or rarely infection at the site of insulin infusion cannula or glucose sensor insertion. These risks are minimized through proper instruction in insertion technique, including sterile procedures, by our diabetes research nurse practitioner. While the use of a hybrid closed-loop system has been shown to reduce time spent in the hypoglycemic range, there is a risk of severe hypoglycemia if an inaccurate sensor glucose reading is used to make dosing adjustments to insulin delivery. This risk is minimized through intensive education that includes prohibiting insulin dose decisions on the basis of a sensor glucose recording, and safety measures that are built-in to the closed-loop algorithm during auto mode that monitors for extreme sensor discordance and will automatically exit the closed-loop function. There is also a risk of marked hyperglycemia should an insulin infusion set become occluded or when inaccurate sensor glucose triggers suspension of insulin delivery; rarely diabetic ketoacidosis could develop. This risk is minimized through intensive education that includes recognition of faulty insulin cannulas, rotating insertion sites every 2-3 days, and appropriate calibration of the glucose sensor at least 3 times daily. Also, the automated suspension of insulin delivery is programmed to last no more than 2 hours, less if delivery is resumed by the patient. Finally, acceleration of retinopathy with acute correction in glycemic control was seen in the Diabetes Control and Complications Trial (DCCT), although the subjects studied here will already be receiving intensive insulin therapy as implemented in the DCCT, and so this risk is probably not significant. Nonetheless, all subjects will be required to have stable retinopathy documented by their ophthalmologist or retinologist prior to participation as exclusion of patients with unstable retinopathy should minimize this risk.

Blood drawn for standard of care plus research labs including for the stepped-hyperinsulinemic hypoglycemic clamp test will not exceed 450 ml in any six-week period. Nonetheless, blood counts will be checked at the time of each clamp test to monitor for the development of anemia, and the exclusion of subjects with anemia at baseline should minimize this risk. Additional procedural risks include those pertaining to blood draws, maintenance of intravenous catheters, and the delivery of test substances (glucose and insulin) during the clamp procedures. Blood draws and intravenous line placement for clamp testing may cause the subject to experience some discomfort or bruising at the site of the needle/catheter entry. The risks of intravenous line placement for clamp testing include bleeding, displacement, and interstitial infusion of fluids; rarely local vein thrombosis, infection or thrombophlebitis may develop. The administration of insulin intravenously during the clamp procedures may lead to a greater degree of hypoglycemia than expected, but would be rapidly corrected with intravenous glucose. The stable isotope of glucose infused during the glycemic clamps is tested for identity, sterility, and absence of pyrogens by the Penn Investigational Drug Service, and so carries no additional risks. The conduct of these study procedures in the CHPS by experienced research nurses and nurse practitioners greatly minimizes the risks of needle/catheter placement and administration of test substances.

11.2 Benefits

The type 1 diabetic subjects participating in this study will benefit from close follow-up, and may also benefit from the guaranteed access to a hybrid closed-loop system and the intensive education and support required that is not presently fully reimbursed by insurance carriers. Indeed, if the proposed studies demonstrate an improvement in glucose counterregulation with use of hybrid closed-loop insulin delivery, then the selected subjects here with long standing disease complicated by hypoglycemia unawareness may benefit from a significant reduction in risk of experiencing severe episodes of hypoglycemia.

11.3 Risk Benefit Assessment

The alternative to participation is on-going standard management of type 1 diabetes with available insulin delivery and glucose monitoring technologies, which may include SAP with LGS utilizing a threshold

suspension of insulin delivery only, and not the predictive suspension and automated delivery available through the MiniMed 670G system or the t:slimX2 pump with Basal-IQ and Control-IQ system being used in this study. Given the inclusion criteria that selects subjects with type 1 diabetes experiencing hypoglycemia unawareness and problematic hypoglycemia and/or marked glycemic lability at increased risk for experiencing severe hypoglycemia despite compliance with standard management, the risks of participating in the study are outweighed by the potential benefit of reduced exposure to hypoglycemia and decreased risk of experiencing a severe hypoglycemia episode from participating in the study.

12 Study Finances

12.1 Funding Source

This study is financed through Public Health Services research grant 2R01-DK-091331 to the PI from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.

12.2 Conflict of Interest

No participating investigator has a conflict of interest with this study. All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

12.3 Subject Stipends or Payments

Subjects will receive $150 compensation for each CHPS inpatient visit for clamp testing and $50 compensation for each outpatient visit to either the Rodebaugh Diabetes Center or CHPS, as well as reimbursement for parking and travel related expenses in order to encourage study completion and compliance with all study visits. No compensation will be provided for injury that may be incurred as a result study participation. Subjects will receive a Greenphire Clincard which the study team will load after visit completion. Cash will be given at each visit for parking and travel related expenses.

13 Publication Plan

Publication and presentation of the data derived from this protocol will be the responsibility of the PI. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study investigator/sponsor.

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15 Attachments

- Data and Safety Monitoring Plan
- Informed Consent