Protocol Title: Restoring brain metabolism and function in older adult T1DM patients using an AP system.

Approval Date: 25 July 2022

Clinicaltrials.gov Registration #: NCT03353792

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL

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Principal Investigator: Raimund I. Herzog, MD

Version Date: 13 March 2019

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INSTRUCTIONS

This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:**

1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.
2. If a section or question does not apply to your research study, type "Not Applicable" underneath.
3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

a) **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
6 years

b) Does this study have a Clinical Trials Agreement (CTA)?
Yes☒ **No☐**

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a. If so, does it require compliance with ICH GCP (E6)?

Yes☒ **No☐**

c) Will this study have a billable service? **Yes ☐** **No☒**

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

d) Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **Yes ☒ No ☐**

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes ☒ No ☐**

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **Yes ☐ No ☒**

c. Will a novel approach using existing equipment be applied? **Yes ☐ No ☒**

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
The goal of this study is to confirm the safety and effectiveness of a predictive low glucose suspend (PLGS) system in older patients with type 1 diabetes mellitus (T1DM) in order to reverse brain metabolic adaptations and restore metabolic sensitivity, hypoglycemia awareness and appropriate hormonal counterregulatory responses (CRR). The ultimate purpose of our study is to demonstrate the clinical usefulness of a technology-driven approach in older adults with T1DM to achieve tight glycemic control without exposing these particularly vulnerable patients to the risks of profound hypoglycemia.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

a. Counterregulatory failure and hypoglycemia unawareness in intensively treated older adult type 1 diabetic patients.

While the complications of uncontrolled hyperglycemia in diabetic patients can be avoided via intensive insulin therapy [1, 2], recent studies indicate that long-term exposure to the frequent hypoglycemia encountered under this treatment alters brain structure and function [3] and increases the fear of hypoglycemia as a severe complication of T1DM treatment [4-6]. Constrained by these two extremes, measures allowing intensive glucose control that preserve normal brain function are still needed. In non-diabetic individuals, hypoglycemia initiates counterregulatory responses (CRR) that restore normal plasma glucose levels. These mechanisms occur on several levels: pancreatic insulin secretion is suppressed; glucagon and epinephrine are released, and conscious measures are taken to reverse this possibly life-threatening state [7]. In T1DM patients, several of these responses may be compromised. The loss of endogenous insulin secretion and the reliance on insulin injections render rapid shut-off in case of hypoglycemia impossible. This problem is often accompanied by the loss of hypoglycemia induced glucagon release [8] and patients become particularly vulnerable to impairments in catecholamine secretion. This scenario is commonly associated with intensive insulin therapy and worsened with increasingly frequent hypoglycemic episodes and old age [9-12]. It is thus a functional disorder linked to iatrogenic hypoglycemia, since scrupulous avoidance of hypoglycemia can restore normal

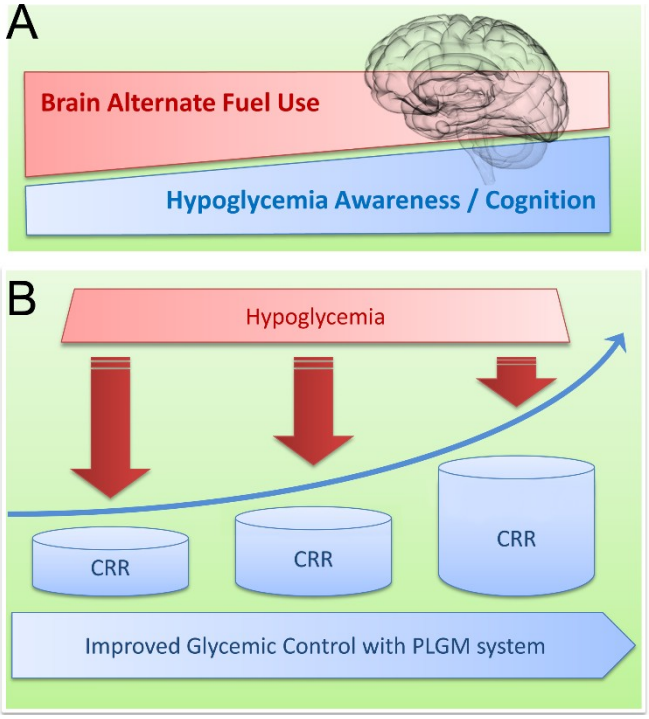

Figure 1: Overall Hypothesis: Improved glycemic control and strict avoidance of hypoglycemia via 8-week use of a close-loop/artificial pancreas system reverses brain metabolic adaptations in older adult T1DM patients (A). This reduces the uptake of alternate fuels into the brain and their contribution to brain energy metabolism. B) As a result, counterregulatory responses (CRR) with appropriate glucagon and epinephrine release are restored and patients regain hypoglycemia awareness. Reestablishment of brain energy homeostasis improves cognition, quality of life and overall health in older adults.

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CRR [13-15]. Finally, symptom awareness often becomes impaired ("hypoglycemia unawareness") in conjunction with the reduced sympathoadrenal response to hypoglycemia [16] (also referred to as hypoglycemia associated autonomic failure or HAAF) [17]. As a result, many T1DM patients are reluctant to commit to intensive insulin therapy because their immediate fear of hypoglycemia exceeds their fear of future long-term complications. Because insulin-induced hypoglycemia remains the major limiting factor to optimal glycemic management in T1DM [7] it is our goal to protect these patients from the negative consequences of recurrent hypoglycemia (RH). New insulin delivery technologies like PLGS pumps that halt basal insulin delivery for impending hypoglycemia have emerged as promising new clinical tools. However, while they have been shown to reduce RH in younger patients with T1DM, their benefit in elderly patients has not been evaluated and the potential mechanism of their benefit remains undefined (see Fig.1). A better grasp of the metabolic and regulatory mechanisms responsible for the effects of hypoglycemia, particularly in the brain, will permit tighter glycemic control of diabetic patients without increasing the risk of serious hypoglycemic injury.

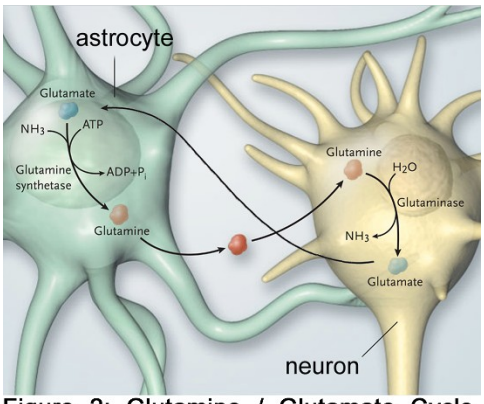

Figure 2: Glutamine / Glutamate Cycle. Synaptic neurotransmitter glutamate is taken up by astrocytes, in which glutamine synthetase converts glutamate to glutamine. Glutamine is then transferred back to glutamatergic neurons. Within the neuron glutaminase hydrolyzes glutamine to reform glutamate.

b. Hypoglycemia in the brain.

The negative impact of hypoglycemia on brain function and development early in life is well established [3, 5, 18]. We have recently shown how T1DM in young patients with varying degrees of glycemic control results in cognitive and brain structural changes [19-21]; however, very little is known about this structure-function relationship in older adults with T1DM. Profound hypoglycemia in T1DM affects higher brain structures of the fully developed brain, with the most vulnerable cells located in the hippocampus and the frontal cortex [22-24]. Interestingly these are the brain regions responsible for higher cognitive function and memory and are specifically those involved in the cognitive and memory deficits affected by hypoglycemia [25] and the phenomenon of hypoglycemia unawareness [6]. Underscoring the importance of normal glucose homeostasis in the brain of older individuals, regional mitochondrial dysfunction with reduced ATP production has recently been linked to several neurodegenerative and psychiatric disorders [26-28] and likely also explains the higher association between T1DM and depression [29, 30]. Consequently, attempts to restore glucose homeostasis and impaired brain energy are of great clinical interest [31-34]. Similar approaches may be beneficial in the treatment of complications associated with T1DM; however, recent efforts remain limited by our lack of knowledge of the changes induced by frequent shifts in brain glucose levels. To overcome this barrier, we have applied state-of-the-art technology such as magnetic resonance spectroscopy (MRS) and hypoglycemic clamps to define brain energy metabolism and its regulation in the context of diabetes and frequent hypoglycemia. Using carbon-13 labeling of glucose and alternate energy substrates in our rodent model as well as patients with T1DM we arrived at a more complete understanding of brain alternate fuel metabolism in the context of hypoglycemia [35, 36]. However, since these observations outlined below were mostly generated in younger patients, little is known about their applicability to older adults. Using further advances in MRS methodology, we will refine our understanding of brain energy metabolism in older T1DM patients experiencing frequent hypoglycemia.

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c. Quantifying brain energy substrate metabolism in the context of hypoglycemia.

Use of energy substrates labeled with the non-radioactive isotope carbon-13 (13C) and in vivo MRS allow real time measurement of their brain uptake and metabolic flux via the tricarboxylic acid (TCA) cycle into different amino acid and neurotransmitter pools. In what is referred to as metabolic compartmentalization and the glutamine-glutamate cycle, accumulation of the excitatory neurotransmitter glutamate in the synaptic cleft to toxic levels is prevented by its rapid uptake by astrocytes, where glutamine synthetase, present only in these cells, converts it to glutamine. Glutamine is then transported back to neurons, where glutaminase converts it to glutamate, replenishing the neuronal glutamate pool (see Fig.2) [37-39]. In vivo measurement of the appearance rates of 13C-label in the C4 carbon-positions of glutamate and glutamine, [4-13C]-Glu and [4-13C]-Gln, respectively, allows fitting of the data with a three-compartment blood-neuronal-astroglial metabolic model that our group developed to calculate relevant metabolic rates, including the relative substrate contributions to the astrocytic or neuronal TCA cycles [37, 38, 40-43]. With this model, we can determine brain metabolism under different physiological conditions and disease states. While broadly applicable to different brain regions in rodent models with significantly smaller brain volumes, in vivo MRS studies in humans were up to now technically limited to measurements of regions within the occipital cortex. This area is responsible for processing of visual information, however, and metabolic adaptations to hypoglycemia observed here may not be the same throughout the brain. Further studies are therefore needed to characterize metabolism in the regions associated with the cognitive deficits recently identified in older adult patients with longstanding T1DM and frequent hypoglycemia [44]. Use of MRS permits measurement of brain fuel uptake and metabolism in real time, which is particularly suited to characterize adaptations to hypoglycemia in T1DM patients. Technologic innovations presented in this proposal will allow us for the first time to conduct localized carbon-13 MRS measurements in the frontal cortex of older adults, the region associated with higher cognitive function.

d. Brain alternate fuel metabolism influences CRR and hypoglycemia awareness.

In addition to glucose the brain can also utilize alternative substrates such as the monocarboxylic acids acetate, lactate and ketones, to maintain its energy requirements, particularly under hypoglycemia [45-48]. Interestingly these substrates cross the blood brain barrier (BBB) via a class of shared monocarboxylic acid transporters (MCTs). Once in the brain, glucose and most alternate substrates enter both the astrocytic and neuronal TCA cycles (see Fig.3); however, acetate is predominantly incorporated into astrocytes due to the exclusive presence of glutaminase in these cells [40-43]. Application of these principles to the investigation of brain energy metabolism under hypoglycemia provides the basis for a better understanding of the characteristic changes distinguishing T1DM patients from healthy subjects [48, 49]. Our prior observation that infused acetate showed enhanced uptake and increased contribution to metabolism in the cortex of intensively treated T1DM patients (see Fig.4) [48] led us to perform similar experiments in our animal model that accurately reflects the salient features of the clinical symptoms encountered in T1DM patients, such as counterregulatory failure with low epinephrine and

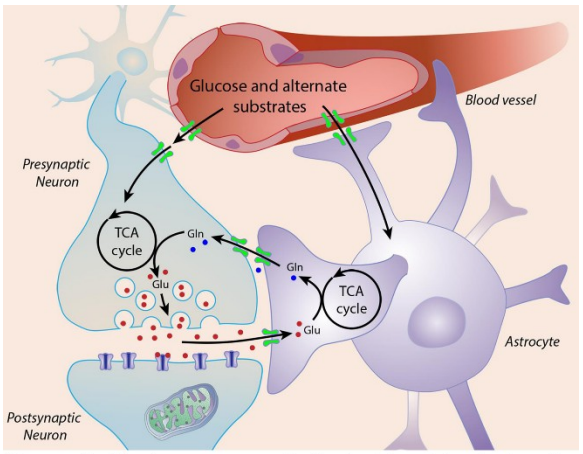

Figure 3: Brain energy substrate blood brain barrier (BBB) transport and metabolism. Energy substrates cross from the blood into the brain via different transporters at the BBB and contribute to different degrees to astrocytic and neuronal energy metabolism.

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glucagon release under hypoglycemia [50, 51] and cognitive impairment [52]. We found that the uptake of acetate and lactate, was significantly facilitated in non-diabetic animals exposed to hypoglycemia, demonstrating that exposure to hypoglycemia, and not the overall glycemic control, is both necessary and sufficient to induce these adaptations [35, 36]. These exciting findings were recently confirmed in human studies, demonstrating enhanced lactate uptake into the brain of T1DM patients with frequent hypoglycemia [53], and thus form the scientific premise for the work presented herein. Intriguingly, it had been shown earlier that higher lactate levels in the brain region responsible for maintenance of peripheral glucose homeostasis, the hypothalamus, impair hormonal counterregulation to hypoglycemia in an animal model [54]. This makes it likely that impaired CRR in patients is indeed caused by higher alternate fuel contributions in the hypothalamus, a region currently not yet fully accessible to MRS metabolic measurements [55]. Since we have also shown in our animal model that lactate maintains neuronal firing activity under hypoglycemia [35], it is very likely that, as was recently suggested, even small contributions of alternate energy substrates to brain metabolism can make glucose deficits (i.e. as under hypoglycemia) unnoticeable to patients, thus perpetuating hypoglycemia unawareness [56]. Since most studies thus far have been cross-sectional phenotypic characterizations, it is not clear whether this association is due to patient characteristics such as genetic predisposition and personal attributes or whether they stem from a reproducible sequence of adaptations like those seen in our rodent model. Our study, which proposes a prospective 8-10-week PLGS insulin pump intervention to strictly avoid hypoglycemia and combines simultaneous measurements of brain metabolism and CRR hormones, will be scientifically more rigorous and thus ideally suited to address this scientific question.

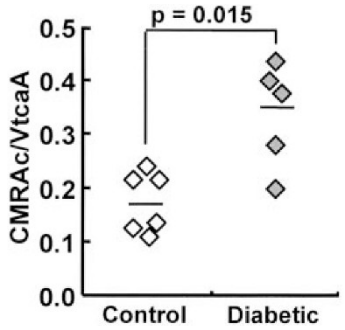

Figure 4: Increased brain acetate utilization in T1DM patients with hypoglycemia unawareness. Tightly controlled T1DM patients with hypoglycemia unawareness show higher brain acetate oxidation under hypoglycemia than healthy controls. (CMRAc - cerebral metabolic rate of acetate; VtcaA - astrocytic TCA cycle flux)

e. <u>Meticulous avoidance of hypoglycemia restores CRR and hypoglycemia awareness and may affect cognition.</u>

Few studies to date have specifically evaluated whether reduction of hypoglycemia reverses its negative effect on the brain. Most were very lengthy and resource intensive [57-60] and found that CRR and hypoglycemia awareness were reversible in both patients with short term (<7 years duration) T1DM [13]), and with longstanding disease [14]. While early improvements were shown to occur after as little as 2 days, most studies lasted from 2 weeks to up to 4 months. To date no study has been conducted to determine whether older T1DM patients with several decades of disease exposure, where long-term adaptations may be less reversible (i.e., 'fixed metabolic defects'), might similarly benefit from strict hypoglycemia avoidance. A recent case control study defining risk factors for severe hypoglycemia in older adults not only identified glucose variability and hypoglycemia unawareness as the most relevant predisposing contributors [44], but also showed that the group with more hypoglycemia and glycemic excursions performed worse on tests of executive function and psychomotor processing speed. A randomized trial investigating use of different technologies on restoration of hypoglycemia awareness [61] found that continuous glucose sensor use had the biggest impact on patients' ability to avoid hypoglycemia during the day, however, since most severe and life threatening hypoglycemic episodes occur during sleep, when patients cannot take immediate action, the urgent need for an automated system that can eliminate hypoglycemia becomes apparent. These observations raise the intriguing possibility that the same metabolic adaptations that result in

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hypoglycemia unawareness also contribute to impairment of cognitive performance and may as such be reversible by strict hypoglycemia avoidance. Our specific aims will specifically address this question.

f. Predictive low glucose suspend (PLGS) systems.
The current "state-of-the-art" treatment for T1DM in the US is sensor-augmented insulin pump therapy. Large-scale studies have demonstrated the benefit of these devices on HbA1c and a reduction in hypoglycemia [62-65]. Despite these improvements, human control of sensor-augmented pump therapy requires frequent, almost nearly continuous, surveillance of the system, and despite the use of audible alarms to warn of actual or impending hypoglycemia, sensors alone do not eliminate the risk of hypoglycemia. The true power of continuous glucose sensors can be better exploited in a "closed-loop" system in which sensor-detected glucose levels dynamically inform and adjust insulin delivery commands through the pump and even suspend basal insulin infusion in the setting of hypoglycemia. This so-called "low-glucose suspend" feature would by design limit hypoglycemia duration and/or magnitude. Due to the greater risk of severe hypoglycemia with seizures at night [66-69], and since most patients don't respond to alarms when asleep [70], such automatic "threshold suspend" pumps, now approved by the FDA and widely available for T1DM patients, have been very effective in reducing the magnitude and duration of hypoglycemia by up to 30% [71, 72]. However, while these results are encouraging, they were not specifically tested in more vulnerable older adults with T1DM. In addition, the degree to which PLGS technology can reverse brain metabolic adaptations to hypoglycemia has not been determined. This study will, for the first time, define the effect of PLGS systems on reducing the impact of hypoglycemia on brain metabolism and function in older T1DM patients.

g. Special considerations regarding older adults with T1DM.
The dramatic reduction of microvascular complications reported by the DCCT [1] and UKPDS [2] have long motivated pursuit of long-term tight glycemic control as the goal of successful diabetes management. Recent evidence demonstrating that frequent and severe hypoglycemia contributes to morbidity and mortality in older, more vulnerable patients [73-76], however, suggests that these treatment goals should be adjusted, particularly in older adults who have already reached several decades of disease exposure and are at especially high risk for realization of long term complications. Instead of liberalizing therapy with resultant higher average glucose, which as we have shown impairs cognition in patients with T1DM [21], the true goal remains maintenance of euglycemia while avoiding hypoglycemia at all cost. While many patients can properly calculate daily insulin doses [44] and manage insulin pumps with high degrees of treatment satisfaction, with increasing age, progressive impairment of vision and particularly declining cognition, everyday diabetes self-care becomes more and more difficult. It is for these reasons that this patient population may especially benefit from automated insulin pumps that eliminate hypoglycemia while requiring minimal user intervention. To conduct this study we have partnered with the Yale Program on Aging, a center of excellence focused on maintenance of health status in older adults, to test the novel hypothesis that implementation of a PLGS system can positively impact cognitive performance, psychomotor function and treatment satisfaction.

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits**

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specifying their individual times and lengths. Describe the setting in which the research will take place.

We hypothesize that meticulous avoidance of recurrent hypoglycemia for 8 weeks using FDA approved PLGS systems reverses brain metabolic adaptations and ameliorates their adverse consequences in older adults with longstanding T1DM. To address this hypothesis we designed a single-site, parallel group, randomized clinical trial. Following enrollement and CGM documentation of hypoglycemia during the 4-week run-in period, study participants are randomized to intervention and control groups. The intervention group consists of treatment with a PLGS-enabled insulin pump/CGM combination (Medtronic MiniMed 670G pump with Guardian sensor, or Tandem t:slim X2 pump with Dexcom sensor) in auto mode for Medtronic users and with Basal-IQ for Tandem users; subjects in the control group will use the same PLGS-enabled insulin pump/CGM combination but in manual mode for Medtronic users or without Basal-IQ for Tandem users (see Fig.5A). Patients will continue to use their own insulin as specified in their clinical plan, separate from the study

Auto Mode: The MiniMed 670G Insulin Pump is capable of continuous insulin delivery, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. When used with the CGM components (Guardian 3 sensor and transmitter), the pump system is capable of continuous or periodic monitoring of glucose levels in the interstitial fluid under the skin and detection of possible low or high blood glucose episodes. The pump also displays continuous glucose values, storing this data so that it can be retrospectively analyzed to track patterns and improve diabetes management. These features are similar to the commercially available Medtronic sensor-enabled system. The MiniMed 670G Insulin Pump also includes the closed loop algorithm and SmartGuard feature that may be enabled by the user. The SmartGuard feature enables insulin to suspend before a sensor glucose threshold is reached. The closed loop and SmartGuard feature will not be active at the same time. When closed loop is enabled on the MiniMed 670G insulin pump, the sensor glucose values received from the transmitter by the insulin pump will be used to automatically calculate the insulin dose. It will then deliver insulin to the patient, at five minute intervals, to achieve glycemic control. This is in addition to user-defined insulin boluses that patients will continue to require for meals. When Closed Loop is not enabled, the user may have the SmartGuard feature enabled. Here it will suspend basal rate delivery before the sensor glucose value has reached the programmed low threshold.

Manual Mode: If neither the Closed-Loop nor the SmartGuard features are enabled, the pump will deliver pre-programmed basal rates without modulation by the sensor. In this way, manual mode functions like any other insulin pump system. That is, there is no change in the level of technology when compared to the subject's existing insulin pump. The only exception to this is if the SmartGuard feature is enabled, which will be determined by experienced study clinicians.

Basal-IQ: The Basal-IQ feature helps reduce the frequency and duration of low-glucose events by predicting glucose levels 30 minutes ahead and suspending insulin if the patient is expected to drop below 80 mg/dL or if glucose is currently below 70 mg/dl and falling. The system resumes basal insulin delivery once glucose values start to rise.

All participants will undergo MRS measurement of brain [2-^{13}C]-acetate metabolism under controlled hypoglycemia (hyperinsulinemic hypoglycemic clamp) before and after the 8-week intervention (see Fig.5B). To determine the effect of strict hypoglycemia avoidance in the intervention group we will measure brain acetate metabolite enrichment time courses, which will be fitted with our metabolic

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model to determine whether acetate contribution to brain oxidative capacity is diminished. In addition, we will assess how counterregulatory epinephrine and glucagon responses under hypoglycemia are affected by the intervention. The day before each MRS session, cognitive performance and hypoglycemia awareness will be also assessed. Blood Volumes collected and Schedule of Events Tables are included at the end of this application (see Appendix 1-2).

a) Screening visit and Run-in Period (YNHH Hospital Research Unit):

At the screening visit, study subjects will complete the informed consent form for participation in voluntary clinical research. Demographic and clinical data collected will be reviewed by study personnel to confirm eligibility.

Once consented, all subjects will be further screened with a medical history and physical examination, blood work (electrolytes, hematocrit, creatinine, liver function tests and HbA1c) and a 12-lead electrocardiogram (EKG). In subjects who do not already take advantage of continuous glucose monitor (CGM) systems, a CGM (iPRO monitor, Medtronic) will be applied and keep in position for 7 days. After 7 days, glucose CGM data will be downloaded to determine degree and frequency of hypoglycemia during a brief visit. In subjects already using a CGM system, glucose data will be downloaded and analyzed by study staff to determine degree and frequency of hypoglycemia. The subject will perform a preliminary cognitive test (Montreal Cognitive Assessment) and a questionnaire to evaluate hypoglycemia unawareness, see Appendix 3).

If the subject is eligible for the study, the subsequent sessions to complete the study will be scheduled. The subject will be asked to record CGM data in the 4 weeks before the first study session (run-in period) to collect baseline data on glucose control. In the event that scheduling issues preclude the sequencing of scanning sessions as described below, certain modifications can be made to accommodate a subject. In particular, the duration of the intervention may vary from 8 to 10 weeks and the cognitive assessments may be scheduled up to 1 week before the corresponding MRS session.

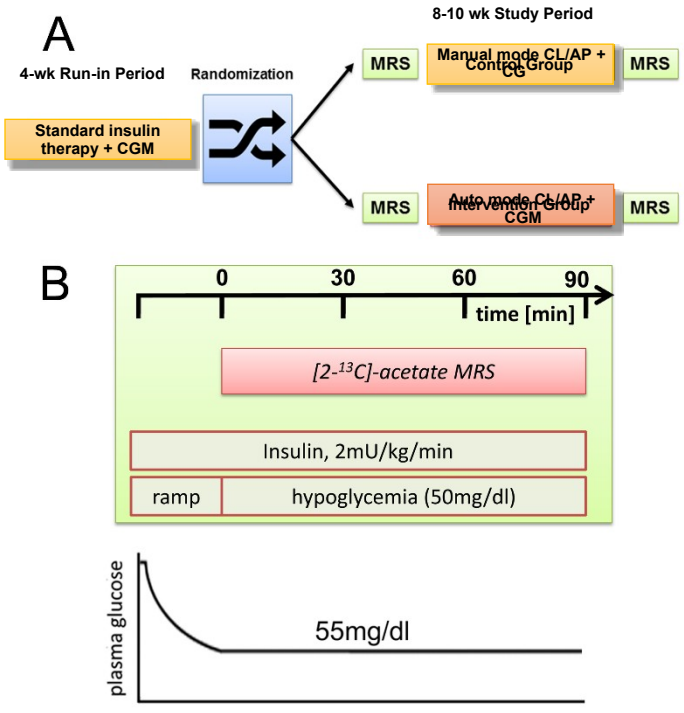

Figure 5: Overall Study Design. A) Following a 1 week of CGM screening for hypoglycemia, eligible T1DM patients will undergo 4 weeks of CGM for run-in and then will be randomized to 8-10-week therapy with PLGS insulin pump in either auto or manual mode. B) MRS study with timeline for hyperinsulinemic-hypoglycemic clamp and carbon-13 tracer infusion.

b) MRS studies and hyperinsulinemic hypoglycemic clamps (Magnetic Resonance Research Center)

Subjects will be asked to remain fasting from midnight prior to the study and to check their blood glucose at home before bed and on awakening to ensure that the glucose level is above 70mg/dl and below 200mg/dl. They will be

instructed to call Dr. Herzog with any readings outside of this range. Upon arrival to the MRRC (7:30AM), their blood glucose will be checked as a safeguard, and insulin received via the insulin pump will be held. An IV catheter will be inserted for infusion of insulin and glucose to maintain normal glucose levels. A urine pregnancy test will be completed on all female subjects of child bearing potential. Any female testing positive will be excluded from the study. A second IV catheter will be inserted for arterialized venous blood sampling and then patients will be placed in the scanner for MRS. MRS measurement will be performed under clamped insulin-induced hypoglycemia as described below. At the end of the clamp procedure, a symptom questionnaire will be administered, asking the subjects to rate the intensity of their symptoms on a scale from 0 to 7 (none to severe) [13] (Appendix 4). Neuroglycopenic (dizziness, tingling, blurred vision, difficulty in thinking, faintness) and autonomic symptoms (anxiety, palpitations, hunger, sweating, irritability, or tremor) are included in this assessment, which has been well validated over time. The visit will last no longer than 4 hours, including ~130 minutes of hypoglycemic clamp and MR spectroscopy.
After 8 weeks, both groups will undergo repeat MRS assessment of brain metabolism study according to the same procedures. They will then resume their previous out-patient care via insulin pump.

Hypoglycemic Clamp: To produce a controlled hypoglycemic state with a target glucose level of 55mg/dl, we will use the hyperinsulinemic-hypoglycemic clamp method that gently lowers plasma glucose levels according to the protocol that was developed at Yale and is broadly used for these types of studies [29, 27, 28]. All subjects will receive a continuous insulin infusion (2mU/kg/min) and a variable infusion of 20% dextrose (see Fig.6B), which is titrated based on plasma YSI glucose measurements sampled every 5 minutes from a second IV line placed in the opposite arm. During the clamp procedure the plasma glucose level will be gently lowered from the initial level of 95-100mg/dl to the target of 50 ± 3 mg/dL.
Throughout, blood is obtained for glucose, ketones, lactate, insulin, glucagon, cortisol, and catecholamines and will be assayed using established RIA, HPLC & ELISA methods in the YCCI Core Lab (see blood draw schedule below).

	start hypo clamp	**glucose ~55mg/dl** for ~10-15min	**glucose ~55mg/dl** for ~20-25min							
Timeline	-60 min	-10 min	**^{13}C-tracer Baseline** start infusion*	+5	+10	+15	+30	+60	+90	+120
Insulin	X		X			X	X	X		X
Ketones	X		X			X	X	X		X
Lactate	X		X			X	X	X	X	X
C^{13} enrichment			X	X	X	X	X	X	X	X
Counterreg. hormones	X	X	X				X	X		X
Glucose	----------glucose every 5 min during hypo clamp----------									

* blood draws timed to labeled acetate infusion
Counter-regulatory hormones = epinephrine, norepinephrine, glucagon, cortisol, growth hormone

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At the end of the study, insulin will be stopped and the 20% dextrose infusion increased to restore normoglycemia. Subjects will eat and IV cannulas will be removed. Once each subject is clinically recovered with stable blood glucose levels above 80 mg/dL, they can be discharged.

Magnetic Resonance Spectroscopy: During the MRS studies, subjects will lie supine in a 4T 94 cm bore magnet. After head positioning under the coil, anatomical images will be obtained for localization of a circa 30ml voxel within the frontal cortex. Following power calibrations, non-iterative shimming and achievement of stable hypoglycemia all study subjects will receive a bolus of [2-13C]acetate (Isotech, Williamsburg, OH) 6 mg/kg · min administered for 5 minutes followed by a continuous infusion of 3 mg/kg · min for a total of 120 minutes, according to our previously published protocol [11, 66]. Then localized 1H-[13C]-MRS measurements with a temporal resolution of 5 min/ spectrum will be performed and selective POCE data acquired to the steady state label concentrations and fractional enrichments of acetate, and the C4 positions of glutamate and glutamine.

c) Cognitive, symptom and quality of life assessment (YNHH Hospital Research Unit/MRRC/ Long Wharf Diabetes Research Suite (#503) at 1 Long Wharf Drive):

On a day close to each MRS study, subjects will arrive at the Long Wharf Diabetes Research Suite to perform a baseline assessment of cognitive performance. CGM data will be obtained. A battery of validated cognitive tests that were shown to be associated with severe hypoglycemia in older adults with T1DM will be completed, including Symbol Digit Modalities, Trail Making Test, Grooved Pegboard Test [77]. In addition, we will use validated questionnaires to determine the degree of hypoglycemia unawareness, quality of life and satisfaction of insulin therapy [78-80] (see Appendix 4).

d) Randomization and follow-up visits between MRS assessments (YNHH Hospital Research Unit/MRRC/Long Wharf Diabetes Research Suite (#503) at 1 Long Wharf Drive):

After completion of the first MRS session, subjects will randomized to either the intervention or control group. The intervention group consists of treatment with a PLGS-enabled insulin pump/CGM combination (Medtronic MiniMed 670G pump with Guardian sensor, or Tandem t:slim X2 pump with Dexcom sensor) in auto mode for Medtronic users and with Basal-IQ for Tandem users; subjects in the control group will use the same PLGS-enabled insulin pump/CGM combination but in manual mode for Medtronic users or without Basal-IQ for Tandem users. All subjects will undergo a PLGS system training session with a study nurse or nurse practitioner. Subjects will have weekly phone calls with study team members (physician and/or advanced practice nurse or registered nurse) to review blood glucose logs and insulin doses, potential adverse events, and other clinical or device-related issues. Subjects can also speak with a study physician, advanced practice nurse or registered nurse more frequently if there are any questions or concerns.

The two pump devices that will be used are: Medtronic MiniMed™ 670G system or Tandem t:slim X2 with Control IQ software. For subjects who use multiple daily injections as part of their standard insulin therapy or for subjects who do not use the MiniMed 670G pump or t:slim X2 pump, a loaner MiniMed 670G system will be provided. For subjects who use multiple daily injections as part of their standard insulin therapy, the training and support described above will be provided and may potentially be provided on a more frequent and/or intensive basis depending on the needs of the subject. A washout is not required given that regardless of method of administration (pump or injection), the insulin and dosages remain the same. Likewise, the risks remain similar. Furthermore, regardless

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of the method of administration that the subject uses in their usual standard of care, all subjects will be trained and supported as much as is necessary in order to ensure that they understand how to use the PLGS system, and any subject who, in the opinion of the clinical study staff, is deemed to not be able to safely use the system will not continue in the study.

Program on Aging field core staff will remain in close contact with study participants via phone to identify and eliminate any obstacles to successful study completion.

4. **Genetic Testing N/A ☒**
   - **A.** Describe
     i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
     ii. the plan for the collection of material or the conditions under which material will be received
     iii. the types of information about the donor/individual contributors that will be entered into a database
     iv. the methods to uphold confidentiality
   - **B.** What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
   - **C.** Is widespread sharing of materials planned?
   - **D.** When and under what conditions will materials be stripped of all identifiers?
   - **E.** Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
     i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?
   - **F.** Describe the provisions for protection of participant privacy
   - **G.** Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

We will enroll 30 patients aged 50-80yrs (at least 50% over the age of 65) with tightly controlled (Hb_{A1c} <8%), c-peptide-negative T1DM of >10 years duration. Male and female subjects of all races and ethnicities will be targeted for study. Additional criteria will be BMI <35 kg/m^2 and a history of frequent hypoglycemia with unawareness (defined as 2 or more episodes of severe hypoglycemia within one year (requiring assistance) and 2 or more glucose values < 54 mg/dL during a week of CGM (iPRO monitor, Medtronic) prior to enrollment. Hypoglycemia awareness will be assessed by detailed interviews and answering Ryan, Gold and Clarke questionnaires [78-80] that will be compared to hypoglycemic episodes recorded during blinded CGM. Exclusion criteria will be any significant medical comorbidities, significant alcohol intake and vegetarian diet since both are known to have an impact on counterregulation and brain metabolism [81, 82]. All inclusion and exclusion criteria are listed in the section below (Inclusion/exclusion criteria).

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6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? **Yes ☐ No ☒**

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion criteria:

- Provide signed and dated informed consent form
- Male or female
- Age 50-80 years (at least 50% over the age of 65)
- T1DM (>10 years duration)
- C-peptide undetectable
- HbA1c of < 8%
- History of frequent hypoglycemia with unawareness (defined as 2 or more episodes of severe hypoglycemia within one year requiring assistance) and 2 or more glucose values < 54 mg/dL during the week of Continuous Glucose Monitoring (CGM) (iPRO monitor, Medtronic) prior to enrollment
- BMI <35 kg/m2
- Good general health as evidenced by medical history and blood screening
- Willing to comply with all study procedures and be available for the duration of the study
- Willing to fast for a limited time period on the morning of a clamp study

Exclusion Criteria

- Significant diabetic complications (untreated proliferative retinopathy, creatinine ≥1.5 mg/dl, urinary albumin levels 300 mg/day, autonomic neuropathy, painful peripheral neuropathy)
- Significant alcohol intake and vegetarian diet since both are known to have an impact on counterregulation and brain metabolism
- Any contraindications for MRI scanning, including presence of metallic implants or claustrophobia.
- Heavy exercise on a regular basis (i.e. marathon runners)

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- Known allergic reactions to components of the study product(s)
- Treatment with another investigational drug or other intervention
- Active infection including hepatitis C, hepatitis B, HIV
- Any past or current history of alcohol or substance abuse
- Psychiatric or neurological disorders under active treatment
- Weighing less than 110 lbs
- Baseline hemoglobin < 10.5 g/dL in females, or < 12.5 g/dL in males.
- Blood donation within 30 days of the study
- History of coagulopathy or medical condition requiring long-term anticoagulant therapy (low-dose aspirin treatment is allowed)
- Co-existing cardiac, liver, and kidney disease
- Abnormal liver function tests
- Women who are pregnant (as assessed by pregnancy test that will be performed on female participants at reproductive age), planning to become pregnant, or lactating.
- Any medical condition or medication that, in the opinion of the investigators, will interfere with the safe completion of the study or study outcomes

8. How will **eligibility** be determined, and by whom?

   Eligibility will be determined based on information collected at the screening visit after consent is obtained. This will include findings from physical examination, medical history, EKG, and laboratory testing in accordance with the inclusion and exclusion criteria listed above.
   Eligibility to participate in the study will be determined by the licensed medical practitioners listed on this protocol (see personnel section).

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

   i. Intravenous catheters. The placement of intravenous catheters and/or the use of intravenous infusions can result in local hematoma formation or thrombophlebitis. Transient vasovagal symptoms including nausea, sweating, and lightheadedness may also occur during intravenous catheter placement.

   ii. Blood sampling. Same as above and frequent blood sampling may result in a drop in hematocrit levels.

   iii. Hyperinsulinemic hypoglycemic clamp technique. The hyperinsulinemic hypoglycemic clamp technique can result in hypoglycemia symptoms of varying severity. Subjects may experience autonomic symptoms including hunger, anxiety, tremor, palpitations, and/or diaphoresis. Others may experience fatigue, concentration difficulties, and/or mild confusion. The risk of plasma

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glucose levels falling below the target value of 50 ± 3 mg/dL is small but present; affected patients may experience exaggerated symptoms, as well as the development of dizziness, blurred vision, and/or confusion. All such symptoms would be rapidly reversible with an intravenous dextrose infusion.

iv. Infusion of labeled acetate. Carbon-13 is a stable isotope of a naturally occurring substance. There are no known side effects associated with the administration of 13C-acetate, which has been safely used by our group here at Yale for many years.

Predictive low glucose suspend system (PLGS). The subjects enrolled in this study are T1DM patients at high risk of recurrent hypoglycemia who can largely benefit by a reduction in frequency, duration, and severity of hypoglycemia potentially achieved by using a PLGS system [83-85]. The main risk of the use of the PLGS pump system is a worsening of glycemic control, which could be an increased frequency of hyperglycemia or hypoglycemia.

v. Magnetic resonance imaging/spectroscopy. The risks due to the magnet study are similar to clinical MRI. Radio frequency and magnetic fields to be used for 1H and 13C spectroscopy in this study present no known hazards to human subjects whose bodies do not contain any para-magnetic metals. Subjects will be questioned using the protocol developed by Diagnostic Imaging concerning heart pacemakers, metallic objects, IUDs, vascular clips, electrodes, cochlear implants, neurostimulators, shunts, heart valve implants, penile implants, vascular filters, rods & screws, post CABG pacer wires, colored contact lens, dental prostheses, limb prostheses, eye prostheses, shrapnel, metal in head, eye, or skin, and embolization coils. If they cannot be removed safely, the subject will be excluded from the study. Proton decoupling, which is used in 13 spectroscopy, presents the potential risk of tissue heating. However, the regional heat deposition will never exceed the FDA guideline of 4 watts/kg. In over 1,000 experiments to date using proton decoupling, we have not experienced any patient complaints about tissue heating.

vi. Questionnaires: Some subjects may feel discomfort or distress in responding to certain items on the questionnaires.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

The primary risks to the subject are impact by magnetic objects accidentally brought into the magnet room, anxiousness, irritation due to the IV blood sampling, and hypoglycemia after the glucose infusion. The investigators in this protocol pioneered human infusion studies of stable isotope labeled metabolic substrates in MR systems and have been routinely performing these studies since 1988. Studies of brain metabolism using stable isotope infusion in the MRC have been performed since 1990. To date there have been no patient injuries during these studies and only minor adverse incidences (anxiety, IV irritation).

To confront the specific risks listed above:

i. Intravenous catheters. Intravenous catheters will be placed under sterile conditions by experienced HRU staff members. All infused solutions will be prepared in sterile form by the YNHH pharmacy and will be tested for pyrogenicity and sterility prior to use. During dextrose infusions, 20%

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dextrose will be used to reduce the risk of thrombophlebitis normally associated with the use of excessively hypertonic glucose solutions.

(i) Blood sampling. No subject with a hematocrit less than 37% for males and less than 33% for females will be studied. Total blood loss (~515 cc) for each subject, spread over the screening visit and 2 study visits (8-10 weeks apart), will exceed the amount obtained during a typical blood donation by about 10%. People who are in good health are not usually affected by this kind of blood loss. To protect against adverse events, all patients with significant baseline anemia (see exclusion criteria) will be excluded from the study. All patients who have donated blood within 30 days of the study will be asked to wait 6 weeks before participating in the study. Study participants will undergo a hematocrit check prior to the second clamp visit. Should a value of less than 37% for males and less than 33% for females be measured, the second clamp will be postponed by at least 6 weeks, to ensure adequate recovery. Patients will be advised to refrain from blood donations for 8 weeks after study completion. All subjects will be given a telephone number to enable immediate communication with the PI or one of the co-investigators, to report any delayed adverse effects and to receive recommendations for treatment of any adverse effects.

ii. Hyperinsulinemic hypoglycemic clamp technique. All study procedures, including the hyperinsulinemic clamp, will be performed under the direct supervision of a qualified, licensed practitioner. To avoid excess hypoglycemia during the hyperinsulinemic clamp, plasma glucose will be checked every five minutes using a bedside glucose monitor. Based on these measurements, the plasma glucose will be adjusted via the 20% dextrose infusion.

iii. Infusion of unlabeled acetate. Stable isotope infusions will be prepared in sterile form by the YNHH pharmacy and will be tested for pyrogenicity and sterility prior to use. The MRRC has extensive experience with stable isotope infusions including BHB, glucose and lactate (HIC # 10605, Rothman PI; HIC#1208010648, Robert Sherwin PI)) and to date there have been no adverse events due to the infusion.

iv. PLGS system. The primary risk of PLGS therapy is worsening of glycemic control, either more frequent hyperglycemia or hypoglycemia. Both are frequent occurrences in people with type 1 diabetes, and by study design, the subjects enrolled will already have a history of frequent and/or severe hypoglycemia. Published studies of PLGS systems have not demonstrated an increased risk of hypo- or hyperglycemia using these devices. To minimize these risks:

iv.1 All subjects undergoing therapy with PLGS insulin therapy will have an in-depth training session with an experienced study nurse to adequately train the use of the system. Our study team has trained hundreds of subjects on the use of sensor-augmented pump therapy and over 30 subjects on the use of the specific system used in this application. Sensors will initially be placed by study nurses, and subjects will be trained on how to insert and remove them. Supplemental training materials will be available for use for subjects at home.

iv.2 All subjects will have weekly visits (in person or on the phone) with study nurses and physicians to review blood glucose logs and insulin doses, potential adverse events, and other clinical issues. Changes will be made to diabetes management as deemed necessary by study physicians/nurses.

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iv.3 All subjects will be able to reach study physicians/nurses at all times of day or night for urgent issues through the use of a dedicated cell phone carried by study physicians/nurses.

iv.4 All subjects using CGM will be instructed to insert sensors using clean technique to minimize infection and irritations. Subjects will be instructed to assess skin sites at the item of sensor removal for irritation or infection and will call the study team as needed for further evaluation.

v. Magnetic resonance imaging/spectroscopy. The primary risks to the subject from MRI are impact by magnetic objects accidentally brought into the magnet room, anxiousness, irritation due to the IV blood sampling, and hypoglycemia after the glucose infusion. The investigators in this protocol pioneered human infusion studies of stable isotope labeled metabolic substrates in MR systems and have been routinely performing these studies since 1988. Studies of brain metabolism using stable isotope infusion in the MRC have been performed since 1990. To date there have been no patient injuries during these studies and only minor adverse incidences (anxiety, IV irritation). To confront the specific risks listed above:

v.1 All potential study subjects will also be screened for MR safety using the standard MR safety protocol developed by Yale New Haven Hospital's Diagnostic Imaging department. Subjects with claustrophobia, a history of panic attacks or with other contraindications to MR scanning will be excluded from the study. The MR safety screening process will be performed both during the screening interview and on the day of an MR study.

v.2 Study subjects will be closely followed by an experienced clinical research team, including an experienced nurse with ACLS training who is with a patient at all times, a licensed MD, and an experienced MRS technologist. All personnel involved in the study will be trained in MR safety procedures. The MD and technologist who are outside of the room have direct visual contact with the subject and nurse through a window, a TV monitor, and audio contact through a speaker system. Subjects who become claustrophobic in the magnet will be removed immediately from the magnet room. Patients who experience distress in the magnet room for any reason including seizures, loss of consciousness, or pain will be removed from the magnet room in accordance with well-established procedures developed for the Magnetic Resonance Research Center. Should an emergency arise, the technologist will telephone the hospital emergency operator and have an ambulance with personnel trained in resuscitation sent to the MR Center. The other members will remove the patient via the detachable patient bed from the magnet room if immediate resuscitation is needed the physician present during the study will perform this procedure, using a fully equipped crash cart which will be in the console room during the study.

vi. Questionnaires: All subjects will be able to speak to a study physician or nurse at any time if responding to certain questions produces discomfort and/or distress. Subjects will be referred to appropriate counseling and support if deemed appropriate by study physician/nurse.

All subjects will be given a telephone number to enable immediate communication with the P.I. or one of the co-investigators, to report any delayed adverse effects and to receive recommendations for treatment of any adverse effects.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)

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a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
Moderate

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
N/A

c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
   i. Minimal risk
   ii. Greater than minimal

The risks associated with the current study are deemed moderate for the following reasons:
We do not view the risks associated with the combined use of insulin and dextrose as minimal. Given our experience with the combined co-administration of insulin and dextrose, we do not view the proposed studies as high risk. Although PLGS systems were not specifically tested in vulnerable older adults with T1DM, safety data collected in other populations are reassuring.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods.
Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and
attributed to the study procedures / design by the principal investigator Dr Herzog according to the following categories:
a.) Definite: Adverse event is clearly related to investigational procedures.
b.) Probable: Adverse event is likely related to investigational procedures.
c.) Possible: Adverse event may be related to investigational procedures.
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures.
e.) Unrelated: Adverse event is clearly not related to investigational procedures.

Plan for Grading Adverse Events:
The following scale will be used in grading the severity of adverse events noted during the study:
1. Mild adverse event
2. Moderate adverse event
3. Severe

Plan for Determining Seriousness of Adverse Events:
Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:
1. is life-threatening

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2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect OR
5. results in death
6. based upon appropriate medical judgment, may jeopardize the subject's health
and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the HIC or HSC is necessary.

Plan for reporting serious AND unanticipated AND related adverse events, anticipated adverse events occurring at a greater frequency than expected, and other unanticipated problems involving risks to subjects or others to the HIC or HSC.
The investigator will report the following types of adverse events to the HIC or HSC:
a) serious AND unanticipated AND possibly, probably or definitely related events;
b) anticipated adverse events occurring with a greater frequency than expected; and
c) other unanticipated problems involving risks to subjects or others.
These adverse events or unanticipated problems involving risks to subjects or others will be reported to the HIC or HSC within 48 hours of it becoming known to the investigator, using the appropriate forms found on the website.

Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Center for Clinical Investigation Research Subject Advocates (RSAs), Cancer Center's Quality Assurance, Compliance and Safety Committee (QUACS) Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):
- All Co-Investigators listed on the protocol.
- Yale Center for Clinical Investigation Research Subject Advocates (RSAs)

The principal investigator Dr Herzog will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for which the Yale PI serves as the lead investigator:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
   ii. What provisions are in place for management of interim results?
   iii. What will the multi-site process be for protocol modifications?
   N/A

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10 **Statistical Considerations:** Describe the statistical analyses that support the study design.
To test the hypothesis that "*Strict avoidance of hypoglycemia for 8 weeks reduces frontal cortex ^{13}C-acetate utilization by 25%"* a two-sided nonparametric Wilcoxon rank sum test will be used. SAS® statistical software, version 9.4, will be used to conduct data analyses.
Sample size estimation and power calculation have been conducted with PASS statistical software. [86, 87]. Sample size estimates are based on published human acetate data, as well as our previously published differences between control and RH animal studies [48, 56]. These differences correspond to a decrease of approximately 25% or more in brain acetate utilization in the group of T1DM patients undergoing the PLGS intervention. We estimate that sample sizes of 12 subjects per group will achieve 80% power to detect this 25% reduction with estimated group standard deviations of 0.18 and 0.10 in the respective control and intervention groups, using a two-sided Wilcoxon rank sum test and assuming a significance (alpha) level of 0.05. To adjust the sample size for possible missing values, three additional study participants will be enrolled per treatment group; we thereby estimate that a sample size of 15 per group will be adequate to test the proposed primary hypothesis.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. RADIOTRACERS

N/A

B. DRUGS/BIOLOGICS

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

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Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

1) The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☒**YES** ☐**NO**
2) The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☒**YES** ☐**NO**
3) The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☒**YES** ☐**NO**
4) The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☒**YES** ☐**NO**
5) The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☒**YES** ☐**NO**

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐ i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

☐ Blood grouping serum
☐ Reagent red blood cells
☐ Anti-human globulin

☐ ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐ iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

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Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.
According to our previously published protocol [11, 66], subjects will receive a bolus of [2-13C] acetate 6 mg/kg · min administered for 5 minutes followed by a continuous infusion of 3 mg/kg · min for a total of 120 minutes. The MRRC has extensive experience with stable isotope infusions including BHB, glucose and lactate (HIC # 10605, Rothman PI; HIC#1208010648 Herzog PI) and to date there have been no adverse events due to the infusion. Of note, carbon-13 is a natural isotope of carbon. It is non-radioactive and has no side effects.

3. **Source:** Identify the source of the drug or biologic to be used.
[2-13C] acetate, Isotec, Williamsburg, OH

a) Is the drug provided free of charge to subjects? ☒**YES** ☐**NO**
If yes, by whom?
The drug is used only for experimental purpose during the MRS sessions and will be charged on investigators' funds.

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
Stable isotope infusions will be prepared in sterile form by the YNHH pharmacy and will be tested for pyrogenicity and sterility prior to use according to standard procedures.

Check applicable Investigational Drug Service utilized:

☒ **YNHH IDS**	☐ **Yale Cancer Center**
☐ **CMHC Pharmacy**	☐ **West Haven VA**
☐ **PET Center**	☐ **None**
☐ **Other:**	

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

1. Use of Placebo: ☒Not applicable to this research project

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If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.

b) State the maximum total length of time a participant may receive placebo while on the study.

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.

d) Describe the procedures that are in place to safeguard participants receiving placebo.

Continuation of Drug Therapy After Study Closure ☒Not applicable to this project
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ **Yes** If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☐ **NO** If no, explain why this is acceptable.

C. DEVICES

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☒Yes No The two pump devices that will be used are: Medtronic MiniMed™ 670G system or Tandem t:slim X2 with Control IQ software

***If Yes, please be aware of the following requirements*:**

A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request**; AND

Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

GENERAL RISKS related to the MiniMed™ 670G insulin pump system may include:

- Hypoglycemia
- Hyperglycemia
- Diabetic Ketoacidosis
- Seizure
- Coma
- Death

GENERAL WARNINGS

- Do not use the pump when a flammable anesthetic mixture with air, oxygen, or nitrous oxide is present. These environmental conditions can damage your pump and result in serious injury.
- Always use the fingertip for blood samples used for calibrating the sensor while in Auto Mode. The fingertip was the only site studied for use with Auto Mode. Do not use blood samples from the palm to calibrate the sensor as this site was not studied for use with Auto Mode and the performance of the system is not known.
- Do not make treatment decisions, such as determining your insulin dose for meals, using the MiniMed™ 670G continuous glucose monitor (CGM) values, as they are not intended to be used to make such treatment decisions. The MiniMed™ 670G CGM does not replace a blood glucose meter. Always use the values from your blood glucose meter for treatment decisions. Blood glucose values may differ from sensor glucose values. Using the sensor glucose readings for treatment decisions could lead to high or low blood glucose.
- Never rely on the pump beeps or vibrations alone to navigate through the pump screens or menus. Always check your pump screen as you navigate. The pump beeps and vibrations are intended to notify you of a condition that may require attention. Relying on the pump beeps or vibrations alone to navigate can result in incorrect menu selection or settings.
- Do not use your pump if the screen appears broken or unreadable. In some instances, impact to the pump can damage the screen while the buttons continue to function. If the screen is broken or unreadable, do not press any buttons. Remove the pump and begin using your backup insulin plan per the direction of your healthcare professional. If the pump is accidentally programmed while the screen is broken or unreadable, this could result in high or low blood glucose levels. If your screen is damaged, contact the 24-Hour Technical Support to arrange for shipment of a replacement pump.
- Only use rapid acting U100 insulin (Humalog® and Novolog®) that has been prescribed by your healthcare professional for use with an infusion pump. Do not put any other drugs or medications inside your reservoir for use with this pump. Other drugs or medications are not intended for use with this pump. Use of other drugs or medications can cause serious injury.
- Always make sure the infusion set is disconnected from your body before you rewind your pump or fill the infusion set tubing. Never insert the reservoir into the pump while the tubing is connected to your body. Doing so could result in an accidental infusion of insulin.
- Do not insert the reservoir in the pump if you did not rewind your pump. Doing so could result in an accidental infusion of insulin.
- Do not use the MiniMed™ 670G insulin pump or additional system devices adjacent to other electrical equipment which may cause interference with the normal system operation. This includes mobile communication devices such as cell phones, GPS navigation systems, anti-theft systems, and any electrical equipment that has an output transmitter power greater than 1W. For more information about recommended separation distance guidelines between the insulin pump and common RF emitters, see Guidance and manufacturer's declaration, on page 335. The recommended separation distance between the insulin pump and common RF emitters is 12 inches. Other electrical equipment that may compromise normal system operation has been contraindicated.
- Do not unscrew or retighten the tubing connector on the reservoir while the infusion set is connected to your body. Doing so could result in an accidental infusion of insulin.

- Do not use standard Luer sets with the MiniMed™ 670G insulin pump. Luer sets are not compatible with the pump. MiniMed™ reservoirs and MiniMed™ infusion sets are specifically designed for use with the MiniMed™ 670G insulin pump.
- Do not change or modify your MiniMed™ reservoir or MiniMed™ infusion set unless expressly approved by Medtronic Diabetes. Modifying the devices can cause serious injury, interfere with your ability to operate the device, and void your warranty.
- Do not rely on preset pump alarms or reminders alone to prompt you to check your blood glucose. This can cause you to forget to check your blood glucose. Set additional reminders on other devices, such as your cell phone.
- Do not change or modify the internal RF transmitter or antenna unless expressly approved by Medtronic Diabetes. Doing so could interfere with your ability to operate the equipment.
- Do not attempt to use the MiniLink™™ transmitter (MMT-7703), the Guardian™ Link transmitter (MMT-7763), or the Guardian™ Connect transmitter (MMT-7821) with the MiniMed™ 670G insulin pump. These transmitters do not communicate with this insulin pump.
- If other devices that employ radio frequencies are in use, such as cell phones, cordless phones, and wireless networks, they may prevent communication between the transmitter and the insulin pump. This interference does not cause any incorrect data to be sent and does not cause any harm to your devices. Moving away from, or turning off, these other devices may enable communication. If you continue to experience RF interference, please contact the 24-Hour Technical Support.
- Special Precautions regarding Electromagnetic Compatibility (EMC): This body worn device is intended to be operated within a reasonable residential, domestic, public or work environment, where common levels of radiated “E” (V/m) or “H” fields (A/m) exist; such as cellular phones, Wi-Fi®, Bluetooth®, electric can openers, microwave and induction ovens. This device generates, uses, and can radiate radio frequency energy and, if not installed and used in accordance with the provided instructions, may cause harmful interference to radio communications.
- Portable and mobile RF communications equipment can affect Medical Electrical Equipment as well. If you encounter RF interference from a mobile or stationary RF transmitter, move away from the RF transmitter that is causing the interference.
- Do not rely on glucose sensor-enabled features when Airplane Mode is on because the pump does not receive sensor readings from the transmitter. Glucose sensor-enabled features include CGM, SmartGuard™, and Auto Mode. When using Airplane Mode, always rely on your blood glucose (BG) values when making therapy decisions to avoid hypoglycemia or hyperglycemia.
- This device can generate, use, and radiate radio frequency energy and, if not installed and used in accordance with the instructions, may cause harmful interference to radio communications. If the device does cause interference to radio or television reception, you are encouraged to try to correct the interference by one or more of the following measures:
- Decrease the distance between the transmitter and the insulin pump to 6 feet (1.8 meters) or less.
- Decrease the distance between the meter and the insulin pump to 6 feet (1.8 meters) or less. •
- Increase the separation between the transmitter and the device that is receiving/emitting interference.

Note: Harmful interference is defined by the FCC as follows. Any emission, radiation or induction that endangers the functioning of a radio navigation service or of other safety services or seriously degrades, obstructs or repeatedly interrupts a radio communications service operating in accordance with FCC rules.

- The safety of the MiniMed™ 670G system has not been studied in people with impaired kidney function. Please let your healthcare professional know if you have kidney disease so you and your healthcare professional can determine if the potential benefits of using the system outweigh the risks.
- The safety of the MiniMed™ 670G system has not been studied in pregnant women, people with type 2 diabetes, or in people using other antihyperglycemic therapies apart from insulin. Please let your healthcare

professional know if any of these conditions apply to you so you and your healthcare professional can determine if the potential benefits of using the system outweigh the risks.

- The safety of using Auto Mode, Suspend before low, and Suspend on low in people who have no pump experience is not known. Auto Mode, Suspend before low, and Suspend on low should not be used if insulin pump settings have not been previously established. Insulin pump settings include basal rates, insulin to carb ratio, or insulin sensitivity factors. Always discuss with your healthcare professional before using Auto Mode, Suspend before low, or Suspend on low. Reservoir and infusion sets For the most current warnings, see the user guide that came with your device.
- Only use rapid acting U100 insulin (Humalog® and Novolog®) that has been prescribed by your healthcare professional for use with an infusion pump. Do not put any other drugs or medications inside your reservoir for use with this pump. Other drugs or medications are not intended for use with this pump, and can result in serious injury.
- If insulin, or any liquid, gets inside the tubing connector, it can temporarily block the vents that allow the pump to properly prime the infusion set. This may result in the delivery of too little or too much insulin, which can cause hyperglycemia or hypoglycemia. If this occurs, start over with a new reservoir and infusion set.
- Do not reinsert the introducer needle into the infusion set. Reinsertion may cause tearing of the soft cannula, which may result in unpredictable medication flow.
- If infusing insulin, and your blood glucose level becomes unexplainably high, or an occlusion alarm occurs, check for clogs and/or leaks. • If in doubt, change the infusion set because the soft cannula may be dislodged, crimped and/or partially clogged. Should any of these problems arise, make a plan with your healthcare professional for rapidly replacing insulin. Test your blood glucose level to make sure the problem is corrected.
- Reuse of the infusion set may cause damage to the cannula/needle and lead to infection, site irritation, and/or inaccurate medication delivery.
- Dispose of transfer guard safely in sharps container.
- Never prime the set or attempt to free a clogged line while the set is inserted. You may accidentally inject too much medication.
- Do not put disinfectants, perfumes, or deodorants on the infusion set as these may affect the integrity of the set.
- Dispose of the infusion set and introducer needle safely, in a sharps container, after a single use. Do not clean or re-sterilize.
- Store infusion sets in a cool, dry place. Do not leave infusion sets in direct sunlight or inside a vehicle.
- Only use reservoir and infusion sets manufactured or distributed by Medtronic Diabetes. The pump has undergone extensive testing to confirm appropriate operation when used with compatible reservoirs and infusion sets manufactured or distributed by Medtronic Diabetes. We cannot guarantee appropriate operation if the pump is used with reservoirs or infusion sets offered by third parties. We are not responsible for any injury or malfunctioning of the pump that may occur in association with such use.
- Use aseptic techniques when temporarily disconnecting the set and consult your healthcare provider on how to compensate for missed medication when disconnected.
- If infusing insulin, carefully monitor your blood glucose levels when disconnected and after reconnecting.
- Reservoir and transfer guard are sterile, non-pyrogenic, and for single use only.
- Do not clean or re-sterilize. Reuse of the reservoir may lead to insulin degradation, infection, inaccurate medication delivery, and/or leaks which may cause damage to the pump. • Inaccurate medication delivery, infection and/or site irritation may result from improper insertion and maintenance of the infusion site.
- If using this infusion set for the first time, do the first set-up in the presence of your healthcare professional.
- Do not leave air in the infusion set. Prime completely.
- Replace the infusion set every 48 to 72 hours according to Centers for Disease Control guidelines, or per your healthcare professional’s instructions.

- If infusing insulin, do not change the infusion set just before bedtime unless you can check your blood glucose 1 to 3 hours after insertion.
- Do not use if package has been opened or damaged.
- Ensure sterility by checking that the sterile paper and tamper-proof seal are not damaged.
- This device is sterile and non-pyrogenic unless the package has been opened or damaged. Do not use if the package has been opened or damaged. Do not use the infusion set if the tubing connector needle has been damaged.
- Do not use the infusion set for more than 3 days. Insulin is not labeled for more than three days when it is used in an infusion set. If insulin is used in the infusion set for more than three days, it may increase the risk of set occlusions and cause problems with insulin absorption, which may lead to severe hyperglycemia and DKA.
- Before insertion, clean the insertion site with isopropyl alcohol.
- Check frequently to make sure the soft cannula remains firmly in place as you may not feel pain if it pulls out. The soft cannula must always be completely inserted to receive the full amount of medication.
- Release the tubing with caution as a hard pull of the tubing can result in damage to the infusion set/introducer needle. Ensure that the infusion set is properly in place when the tubing is fully released.
- If the infusion site becomes inflamed, replace the set, and use a new site until the first site has healed. Replace the infusion set if the tape becomes loose, or if the soft cannula becomes fully or partially dislodged from the skin.
- Failure to remove trapped air from reservoir may result in inaccurate delivery of medication
- Never point a loaded insertion device towards the body part, where insertion is not desired.
- Remove the needle guard before inserting the infusion set.

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3. **Source:**
   a) Identify the source of the device to be used.
   b) Is the device provided free of charge to subjects? ☒Yes ☐No

4. **Investigational device accountability**: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

      Device shipments will be verified against the packing slip and logged in the study regulatory binder. The dispensing and return of the study devices to the subjects will be recorded in the study regulatory binder.

   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

   c) Lot and/or serial numbers are recorded on the packing list sent with equipment shipments

   d) Study equipment will be stored according to manufacturer's instructions in locked areas of the research office as appropriate for the required storage conditions. Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

      Study equipment will be stored according to manufacturer's instructions in locked areas of the research office as appropriate for the required storage conditions.

   e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

      Equipment will only be distributed to subjects who have signed an approved consent and have met all eligibility criteria for study participation.

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**

   a. Targeted for enrollment at Yale for this protocol: 30
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/Web Postings	Radio
☒ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☐ Letter	☒ Departmental/Center Website	☐ Television
☒ Medical Record Review*	☒ Departmental/Center Research Boards	☐ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	☐
☒ YCCI Recruitment database	☒ Clinicaltrials.gov Registry (do not send materials to HIC)	

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☒ Other (describe): Yalestudies.org and yalestudies social media Facebook and Twitter

*** Requests for medical records should be made through JDAT as described at**
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Some subjects will be identified through their previous participation in HIC #1009007394: "Effect of a long-term Medium Chain Triglyceride diet on cognitive function and brain activation.", HIC #0505000079: "Effect of Medium Chain Fatty Acids in cognitive function during acute hypoglycemia in patients with type 1 diabetes." And HIC#1208010648 "Impact of Hypoglycemia on Brain Ketone and Neurotransmitter Metabolism in Type 1 DM".
In addition, we will collaborate closely with the YNHH JDAT group to identify subjects that match our specific inclusion and exclusion criteria.

b. Describe how potential subjects are contacted.

Possible study participants will be approached by their caregivers or study staff at the different locations where Type 1 Diabetic patients are seen at Yale SOM, YNHH and YMG. These sites include the Adult Endocrine clinic (Yale Diabetes Center, YNHH), Veterans Affairs Hospital, West Haven, community clinics and Yale University Health. We will also accept referrals from outpatient clinics in the community. Flyers will be put up on notice boards at and around Yale University and Yale New Haven Hospital. Study volunteer listings will be requested from the YCCI volunteer database (HIC#0805003779) to assist with recruitment of subjects. Brief screenings will take place either over the telephone or email and subjects will then be invited to a full screening at the HRU (see Appendix 6 – Phone script for recruitment).

Epic MyChart will identify and notify potential candidates for a study. Patients who have an Epic MyChart account and meet basic inclusion /exclusion criteria will be notified of the study through a MyChart message (see Appendix 7 – MyChart message). The notification will provide an overview of the study and a phone number for additional information. Within MyChart, patients can indicate whether or not they are interested in the study. If a patient is interested, research coordinators may contact the patient for eligibility screening. If a patient selects no- they are not interested in the study, they will not receive any additional messages about the study within Epic, and their information will not be shared with the research coordinator.

c. Who is recruiting potential subjects?

Caregivers or study staff.

The text to appear on yalestudies.org is as follows:

Purpose (healthcare version): The goal of this proposal is to implement a Predictive Low Glucose Suspend (PLGS) system in older patients with type 1 diabetes mellitus (T1DM) in order to reverse brain metabolic adaptations and restore metabolic sensitivity, hypoglycemia awareness and appropriate

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hormonal counterregulatory responses (CRR). For purposes of this study we are looking to enroll aged T1DM subjects.

Purpose (subject friendly version): We are trying to demonstrate that a new insulin pump system can prevent low glucose episodes and improve brain function in aged T1DM subjects.

Inclusion Criteria:

1. Type 1 Diabetes Mellitus >10 years duration
2. HbA1c <8%
3. Age 50 years and older
4. Male or female
5. A person in good health

Exclusion Criteria:

1. Significant Systemic Disease or diabetic complications
2. Pregnancy
3. Significant Anemia
4. Excessive Exercise
5. Vegetarian Diet
6. Excessive Alcohol Use
7. Substance Abuse

Compensation offered: **Up to $800**

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☒ Yes, some of the subjects
☐ No

If yes, describe the nature of this relationship.

Subjects with type 1 diabetes will be recruited from the surrounding area. Therefore it is possible that some patients may be under the care of the principle investigator, Dr Herzog, in the setting of the Yale Diabetes Center or Dr Weinzimer in the Pediatric Diabetes Clinic.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

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i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

We are requesting a waiver of HIPPA Authorization in order to utilize the YNHH admission lists that would indicate patients we may not be able to contact prior to their discharge from the hospital. Such cases may be admissions that are over the weekends and holidays that may meet our criteria for inclusion. We would like to be able to identify Type 1 diabetic potential subjects that may be interested in participating, but were discharged prior to being able to discuss the study in person. We will contact the clinician that the patient is scheduled to see for follow up care and ask that they assist with referring the potential subject to contact us, or will allow us to speak to the subject at their next visit directly if the subject agrees when asked by their clinician.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

The study will be described to the subject in detail, including the purpose and potential risks associated with the study. This will be explained by the physician, including the intervention and process for the study day. The subject will be required to read and sign the consent form approved by the HIC, and the patient will retain a copy of this consent to review. Additionally, the patient will sufficient time to ask questions during the screening and will be encouraged to contact investigators with further questions or concerns.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

In this study, we are not using vulnerable subjects. Subjects will be asked open-ended questions in order to evaluate their understanding of the research protocol and the risks involved.

8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

   N/A

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐**Not Requesting any consent waivers**

☒**Requesting a waiver of signed consent:**

☒ **Recruitment/Screening only**

☐ **Entire Study (**Note that an information sheet may be required.)

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For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? **YES ☐ NO ☐**
- Does a breach of confidentiality constitute the principal risk to subjects? **YES ☐ NO ☐**

OR

- Does the research pose greater than minimal risk? **YES ☐ NO☐**
- Does the research include any activities that would require signed consent in a non-research context? **YES ☐ NO ☐**

☐ Requesting a waiver of consent:

☐ <u>Recruitment/Screening</u> only
☐ <u>Entire Study</u>

For a waiver of consent, please address the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? **YES ☐ NO☐**
- Why would the research be impracticable to conduct without the waiver?
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Protected health information will include all blood work, urine pregnancy in women, medical history, physical examination, cognitive test and questionnaire results.

b. How will the research data be collected, recorded and stored?

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To comply with HIPAA standards, patient identification will be kept confidential. Subjects will be identified by code number, not by name during the data analysis. This data will be stored in computer files by code number, and their names will appear only on the initial form. Data that links the subject's number to the subject will be kept in password protected documents and kept on a secured server. Any data that contains patient's identifying information will be released only with written consent from the patient.

All subjects who enroll in studies conducted at the HRU, such as this study, will have a medical record created for them at YNHH. In addition, the researchers and HRU staff will have access to records of any prior admissions to YNHH, including the details of those admissions.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☐ Secured Server ☐ Laptop Computer ☐ Desktop Computer ☒ Other: ITS maintained secure server.

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

The documents will be password protected and held on a secured server which will only be available to the principle investigator and the co-investigators.

> All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Individual's names will appear only on the initial forms and these will be kept under on a secured server. All data files that could link a code number to an individual study subject will be password protected. Once the study is completed zeroing will be used to remove any identifiable subject information.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

Principle investigators, co-investigators , and the Food and Drug Administration (FDA).

g. If appropriate, has a Certificate of Confidentiality been obtained?

N/A

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h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

N/A

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Study subjects will derive no direct medical benefits from the study. However, the potential benefits of this study to older T1DM population are substantial in that the knowledge gained from this work should provide important information concerning the effects of recurrent, antecedent hypoglycemia on CNS responses to hypoglycemia and the potential benefit provided by PLGS system.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   Standard insulin pump therapy.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

For completion of this entire study subjects will receive up to $800, as follows:
Screening visit: $50
1st Questionnaire and PLGS training session: $100
1st Hypoglycemic session: $250
2nd Questionnaire session: $50
2nd Hypoglycemic session: $350

Payment will be issued in the form of a Bank of America pre-paid debit card using the Yale electronic payment service. The subject's name, address, and telephone number will be shared with Bank of America for ePayments. After the first payment milestone (the screening visit) the subject will receive a card in the mail which he/she will need to activate over the phone. Completion of subsequent study visits will automatically add additional funds to the card. Participants may also be reimbursed for incidental expenses for parking.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

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Subjects will not be responsible for any costs associated with the study or the screening portion prior to the study, including blood work, history and physical examination, or urine pregnancy test. We believe that given the length and number of procedures performed, the remuneration is fair and is not an excessive inducement for people to volunteer for the study.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs?
   b. Where and from whom may treatment be obtained?
   c. Are there any limits to the treatment being provided?
   d. Who will pay for this treatment?
   e. How will the medical treatment be accessed by subjects?

If injury were to occur, we will provide any care or treatment required. Our study has no provision for additional compensation.

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Appendix 1

TIMELINE and Blood Drawing Schedule for Hypoglycemic clamp study and recovery

Time	Real Time	Label	Glucose 0.5cc q5 min YSI	Insulin 2cc LTT	Glucagon 2cc Spec. tube	Catechol's 3cc Spec. epi tube: RTT	Acetate Enrichment 3cc GTT	Lactate, Ketones, Cortisol, GH 3cc LTT	Cells/ Plasma 10cc Na Heparin GTT	Meta-bolites 3cc Citrate BTT	Blood volume ALL TUBES ON ICE	Notes
A.1.____	**Baseline**	1.000	X	X	X	X	X	X	X	X	26	
B.1.____	**Start insulin / start clock**	2.000	Glucose is checked every 5 minutes	X	X	X				X	10	Enter scanner
B.2.____	B.1 +30	2.015	X	X	X	X		X		X	13	
B.3.____	B.1 +60	2.030	X	X	X	X			X	X	20	
B.4.____	B.1 +90	2.045	X	X	X	X				X	10	
C.1.____ Acetate baseline	**Start Acetate infusion**	3.000	Glucose is checked q5 min	X	X	X	X	X	X	X	26	Target glucose ~55mg/dl
C.2.____	C.1 +5	3.015	↓				X			X	6	
C.3.____	C.1 +10	3.030	↓				X		X	X	16	
C.4.____	C.1 +15	3.045	↓				X			X	6	
C.5.____	C.1 +30	3.060	↓	X	X	X	X	X	X	X	26	
C.6.____	C.1 +60	3.075	↓	X	X	X	X	X		X	16	
C.7.____	C.1 +90	3.090	↓	X	X	X	X	X	X	X	26	
C.8.____	C.1 +120	3.105	Glucose check	X	X	X	X	X	X	X	26	End clamp
TOTAL VOLUME			**18 cc**								**227cc**	**∑250cc**

Appendix 2

Schedule of Events

	Screening Visit	Cognitive assessment 1	MRS scan 1	Cognitive assessment 2	MRS scan 2
Informed Consent	X				
Medical History	X				
Physical Exam	X				
EKG	X				
Hematocrit (3 mLs)	X (3mLs)				
Creatinine (2 mLs)	X (2mLs)				
Liver Function Tests (3mLs)	X (3mLs)				
HbA1c (3mLs)	X (3mLs)				
Inclusion/Exclusion Check list	X				
Record Blood Sugar Levels 5x daily *	X				
CGM reading		X		X	
Schedule two MR sessions	X				
Urine Pregnancy (females)	X	X			
IV Placement			X		X
Hypoglycemic Clamp			X		X
Cognitive battery (screening)	X				
Cognitive battery (test)		X		X	
MRS scan			X		X
Hypoglycemia questionnaires	X	X	X	X	X
Satisfaction questionnaires		X		X	
Blood Volume per visit	11 ml	none	< 250ml	none	< 250ml

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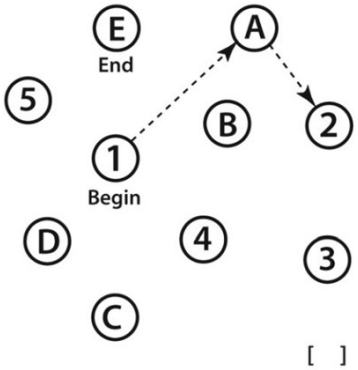
Appendix 3

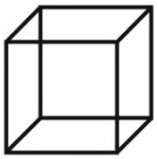
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



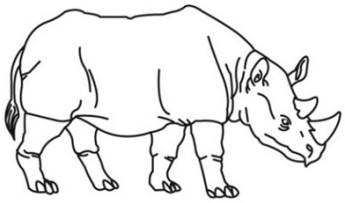
[ ] [ ]

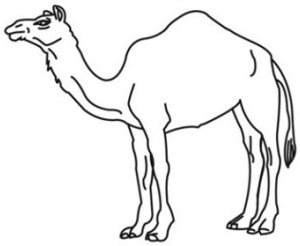
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING





[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

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The Hypo Awareness Questionnaire

These questions are about your recent experience of hypoglycaemia, also known as low blood glucose, having a 'hypo' or going 'low'. Please tick the one box ☑ on each line that best describes your experience. There are no right or wrong answers. We just want to know about your experiences.

1. In the past week, how often have you had any hypo (mild or severe, day or night)? ____ times *(please enter a number)*

2. In the past 6 months, how often did you have a hypo where …

   a) ... you needed help / were unable to treat yourself? ____ times *(please enter a number)*

   b) ... emergency services were called to help you? ____ times *(please enter a number)*

   c) … you were taken to hospital (A&E) for treatment? ____ times *(please enter a number)*

   d) … you were admitted to hospital (overnight or longer)? ____ times *(please enter a number)*

A. 'Hypos' when you are awake

		Never	Once or twice	Three or four times	About once or twice a month	About once a week	More than once a week
3.	In the past 6 months, how often have you had any 'hypo' when awake?	☐	☐	☐	☐	☐	☐
4.	In the past 6 months, how often have you had any 'hypo' when awake where you …	Never	Once or twice	Three or four times	About once or twice a month	About once a week	More than once a week
	a) … had symptoms and were able to treat yourself?	☐	☐	☐	☐	☐	☐
	b) … had symptoms and were unable to treat yourself?	☐	☐	☐	☐	☐	☐
	c) … needed someone else to give you sugar by mouth (e.g. a drink, carbohydrate, glucose gel)?	☐	☐	☐	☐	☐	☐
	d) … needed someone else to give you a glucagon injection?	☐	☐	☐	☐	☐	☐

			If yes, how often did you have hypo symptoms?				
5.	In the past month, have you had blood glucose readings (in mmol/l) …		Never	Rarely	Sometimes	Often	Always
	a) … 3.5 to 3.9?	Yes ☐ No ☐ Don't know ☐	☐	☐	☐	☐	☐
	b) … 3.0 to 3.4?	Yes ☐ No ☐ Don't know ☐	☐	☐	☐	☐	☐
	c) … 2.5 to 2.9?	Yes ☐ No ☐ Don't know ☐	☐	☐	☐	☐	☐
	d) … less than 2.5?	Yes ☐ No ☐ Don't know ☐	☐	☐	☐	☐	☐

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6. How low does your blood glucose usually need to be before you feel any of the following symptoms?	4.0mmol/l or above	3.5-3.9 mmol/l	3.0-3.4 mmol/l	2.5 -2.9 mmol/l	Below 2.5mmol/l	I do not have these symptoms
a) Trembling, shakiness, pounding heart, warmth, sweating, hunger	☐	☐	☐	☐	☐	☐
b) Weakness, lack of coordination, confusion, dizziness, inability to concentrate, difficulty speaking, blurred vision, drowsiness, tiredness, irritability, odd behaviour	☐	☐	☐	☐	☐	☐
c) Nausea, tingling, headache	☐	☐	☐	☐	☐	☐

	Never	Rarely	Sometimes	Often	Always
7. I have symptoms when my blood glucose is low	☐	☐	☐	☐	☐
8. I 'just know' when I am going hypo by the way that I feel	☐	☐	☐	☐	☐
9. I check my blood glucose level if I feel 'low'	☐	☐	☐	☐	☐
10. Other people recognise I am hypo before I do	☐	☐	☐	☐	☐

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
11. I am less aware of my hypos coming on than I used to be	☐	☐	☐	☐	☐
12. I have lost symptoms I used to have when my blood glucose is low	☐	☐	☐	☐	☐
13. In the past 6 months, I have been more aware of my hypos coming on than I used to be	☐	☐	☐	☐	☐

14. Is there anything else you would like to mention about your hypos or your awareness of hypos when you are awake? If so, please write it in this box.

B. 'Hypos' when you are asleep

Never	Less than one a	About once or twice a	About once a week	About twice a	Most days

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		Never	Less than one a month	About once or twice a month	About once a week	About twice a week	Most days
15.	In the <u>past 6 months</u>, how often have you had a hypo <u>during your sleep</u>?	☐	☐	☐	☐	☐	☐

		Never	Less than one a month	About once or twice a month	About once a week	About twice a week	Most days
16.	In the <u>past 6 months</u>, how often have you had a hypo <u>during your sleep</u> …						
	a) ... and were <u>unable</u> to treat yourself when you woke up?	☐	☐	☐	☐	☐	☐
	b) ... and someone else gave you sugar by mouth (e.g. a drink, carbohydrate, glucose gel)?	☐	☐	☐	☐	☐	☐
	c) … and someone else gave you a glucagon injection?	☐	☐	☐	☐	☐	☐
	d) … which led to a major problem (e.g. a fit, tongue biting, fall, collapse, incontinence)?	☐	☐	☐	☐	☐	☐
	e) … where you stayed asleep and only later realised that you had been hypo?	☐	☐	☐	☐	☐	☐

During my sleep...		Never	Rarely	Sometimes	Often	Always	Not Applicable
17.	... I have symptoms which wake me when my blood glucose is low	☐	☐	☐	☐	☐	
18.	... other people recognise that I am hypo before I do	☐	☐	☐	☐	☐	☐
19.	… my insulin pump / monitoring device wakes me when my blood glucose is low	☐	☐	☐	☐	☐	☐

20. Is there anything else you would like to mention about your hypos or your awareness of hypos when you are <u>asleep</u>? If so, please write it in this box.

Thank you. Please check that you have answered all the questions.

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Appendix 4 - Hypoglycemia symptom questionnaires

Hypoglycemic symptoms during the hypoglycemic clamp

Please rank your experience of the following SYMPTOMS on a scale from 1 to 7 where "1" means that you do not experience the symptom at all, while "7" means that you experience the symptom a great deal. Please place an "X" in ONLY ONE of the 7 boxes for each symptom.

SYMPTOM INTENSITY	Not at all	→	→	Moderate	→	→	A great deal
Inability to Concentrate	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Blurry Vision	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Anxiety	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Confusion	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Difficulty Speaking	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Double Vision	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Drowsiness	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Tiredness	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Hunger	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Weakness	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Sweating	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Trembling	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Warmness	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Heart Racing	**1**	**2**	**3**	**4**	**5**	**6**	**7**

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Appendix 5 - Hypoglycemia questionnaires

The Gold Score

1. Do you know when your hypos are commencing? Please circle a number:

	Always aware						Never aware
Awareness	1	2	3	4	5	6	7

Edinburgh Hypoglycaemia Survey

2. Please score the extent to which you experience the following symptoms during a typical daytime hypoglycaemic episode (circle a number for each symptom)

	Not present						Present a great deal
Confusion	1	2	3	4	5	6	7
Sweating	1	2	3	4	5	6	7
Drowsiness	1	2	3	4	5	6	7
Weakness	1	2	3	4	5	6	7
Dizziness	1	2	3	4	5	6	7
Warmth	1	2	3	4	5	6	7
Difficulty Speaking	1	2	3	4	5	6	7
Pounding heart	1	2	3	4	5	6	7
Inability to concentrate	1	2	3	4	5	6	7
Blurred vision	1	2	3	4	5	6	7
Hunger	1	2	3	4	5	6	7
Nausea	1	2	3	4	5	6	7
Anxiety	1	2	3	4	5	6	7
Tiredness	1	2	3	4	5	6	7
Tingling lips	1	2	3	4	5	6	7
Trembling	1	2	3	4	5	6	7
Headache	1	2	3	4	5	6	7

Comments:

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Guy's and St Thomas' Minimally Modified Clarke Hypoglycaemia Survey

2. Tick the category that best describes you (tick one only):
   - ☐ I always have symptoms when my blood sugar is low
   - ☐ I sometimes have symptoms when my blood sugar is low
   - ☐ I no longer have symptoms when my blood sugar is low

2. Have you lost some of the symptoms that used to occur when your blood sugar was low?
   - ☐ Yes
   - ☐ No

9. In the past 6 months, how often have you had hypoglycaemic episodes, where you might feel confused, disorientated, or lethargic and were unable to treat yourself?
   - ☐ Never
   - ☐ Once or twice
   - ☐ Every other month
   - ☐ Once a month
   - ☐ More than once a month

10. In the past year, how often have you had hypoglycaemic episodes, where you were unconscious or had a seizure and needed glucagon or intravenous glucose?
   - ☐ Never
   - ☐ 1 time
   - ☐ 2 times
   - ☐ 3 times
   - ☐ 4 times
   - ☐ 5 times
   - ☐ 6 times
   - ☐ 7 times
   - ☐ 8 times
   - ☐ 9 times
   - ☐ 10 times
   - ☐ 11 times
   - ☐ 12 or more times

11. How often in the last month have you had readings <3.5mmol/l with symptoms?
   - ☐ Never
   - ☐ 1-3 times
   - ☐ 1 time/week
   - ☐ 2-3 times/week
   - ☐ 4-5 times/week
   - ☐ Almost daily

12. How often in the last month have you had readings <3.5mmol/l without any symptoms?
   - ☐ Never
   - ☐ 1-3 times
   - ☐ 1 time/week
   - ☐ 2-3 times/week
   - ☐ 4-5 times/week
   - ☐ Almost daily

13. How low does your blood sugar need to go before you feel symptoms?
   - ☐ 3.4-3.9mmol/l
   - ☐ 2.8-3.3mmol/l
   - ☐ 2.2-2.7mmol/l
   - ☐ <2.2 mmol/l

14. To what extent can you tell by your symptoms that your blood sugar is low?
   - ☐ Never
   - ☐ Rarely
   - ☐ Sometimes
   - ☐ Often
   - ☐ Always

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Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

most of the time	6	5	4	3	2	1	0	none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

most of the time	6	5	4	3	2	1	0	none of the time

4. How convenient have you been finding your treatment to be recently?

very convenient	6	5	4	3	2	1	0	very inconvenient

5. How flexible have you been finding your treatment to be recently?

very flexible	6	5	4	3	2	1	0	very inflexible

6. How satisfied are you with your understanding of your diabetes?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

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Insulin Treatment Satisfaction Questionnaire (ITSQ) – abridged version

People who take insulin can have many different experiences with their treatment. Some people who take insulin may find it difficult and burdensome, while others feel that it is not much of a bother at all. The following questions are about your perceptions of your current insulin treatment and how it affects you in your daily life. When you think of your insulin treatment, please keep in mind the type of insulin you take, the dose or amount of insulin, your schedule for taking insulin, and the device or method you use to give yourself insulin.
Please think about your experiences during the **past 4 weeks** when you answer the questions.
Please answer each question by circling the number ① that best represents your answer. If you are unsure about how to answer a question, please give the best answer you can.

1. **How confident are you that you can avoid symptoms of low blood sugar (such as sweating, trembling, dizziness, blurred vision) with your current insulin treatment?**

Extremely confident						Not at all confident
1	2	3	4	5	6	7

2. **How confident are you that you can avoid severe episodes of low blood sugar that result in loss of consciousness (fainting or passing out) with the insulin you currently use?**

Extremely confident						Not at all confident
1	2	3	4	5	6	7

3. **In general, how bothered are you by symptoms of low blood sugar (such as sweating, trembling, dizziness, blurred vision) due to the insulin you currently use?**

Not at all bothered						Extremely bothered
1	2	3	4	5	6	7

4. **How much do you feel that the insulin you are currently using increases the chances that you will experience low blood sugar?**

Not at all						Extremely
1	2	3	4	5	6	7

5. **How worried are you about experiencing low blood sugars during the night with the insulin you currently use?**

Not at all worried						Extremely worried
1	2	3	4	5	6	7

The following questions are about your perceptions of your **current method of taking insulin** and how it affects you in your daily life. For these questions, you should only think about the device or method you use to give yourself insulin.

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6. **How easy is it for you to take the correct amount of insulin each time with your current method of taking insulin?**

Extremely easy						Not at all easy
1	2	3	4	5	6	7

7. **How convenient is your current method of taking insulin when you are away from home?**

Extremely convenient						Not at all convenient
1	2	3	4	5	6	7

8. **How much pain or other physical discomfort do you experience with your current method of taking insulin?**

No pain or discomfort						A tremendous amount of pain or discomfort
1	2	3	4	5	6	7

9. **How comfortable are you taking insulin in a public place (where people might see you with your current method of taking insulin)?**

Extremely comfortable						Not at all comfortable
1	2	3	4	5	6	7

10. **How much emotional distress or anxiety do you experience related to your method of taking insulin?**

No distress or anxiety						A tremendous amount of distress or anxiety
1	2	3	4	5	6	7

11. **Overall, how satisfied are you with your current method of taking insulin?**

Extremely satisfied						Not at all satisfied
1	2	3	4	5	6	7

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EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care
- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)
- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain / Discomfort
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety / Depression
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

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Your Quality of Life

Please think about your life right now. Whether your life is good or bad, we still want to know. Think about your blood glucose control and what you currently need or don't need to do (eg blood tests, insulin, waiting for a transplant, anti-rejection medication). Please tick one box ☑ on each line.

My blood glucose and what I need to do to manage it mean …	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree	N/A
1. …I can have the sort of relationship I would like with my family eg parents, brothers, sisters, children, grandchildren	☐	☐	☐	☐	☐	☐
2. …I can have the sort of relationship I would like with friends eg visiting, mutual support, shared interests / experiences	☐	☐	☐	☐	☐	☐
3. …I can go out or socialise as I would like eg cinema, concerts, eat or drink with friends, go to busy or crowded places	☐	☐	☐	☐	☐	☐
4. …I can have the sort of relationship I would like with a partner / spouse eg mutual support, sharing interests / experiences	☐	☐	☐	☐	☐	☐
5. …I can enjoy sexual activity as I would like eg spontaneity, frequency, ability	☐	☐	☐	☐	☐	☐
6. …I can be as physically active as I would like eg walking, gardening, shopping, sports	☐	☐	☐	☐	☐	☐
7. …I feel as well as I would like eg feel fit and healthy, no symptoms, healthy weight, enough energy	☐	☐	☐	☐	☐	☐
8. …I feel as in control of my body as I would like eg no highs and lows, can start a family	☐	☐	☐	☐	☐	☐
9 …I look as good as I would like eg look healthy, wear the clothes I want (no worries about hiding pump)	☐	☐	☐	☐	☐	☐
10. …I can have the holidays I would like eg accommodation, location, travelling	☐	☐	☐	☐	☐	☐
11. …I can work as I would like eg have responsibility, earn money, progress in my career, full- or part-time	☐	☐	☐	☐	☐	☐
12. …I have enough money	☐	☐	☐	☐	☐	☐

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My blood glucose and what I need to do to manage it mean …	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree	N/A
eg to pay bills, transport costs, food, gifts						

My blood glucose and what I need to do to manage it mean …	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree	N/A
13. …I can drive as much as I would like eg to go shopping, give lifts to people, get to work, go out alone	☐	☐	☐	☐	☐	☐
14. …I can practise my religion / follow my beliefs as I would like eg go to my place of worship, be part of the community	☐	☐	☐	☐	☐	☐
15. …I can look after my home as I would like eg cooking, cleaning, decorating, repairs	☐	☐	☐	☐	☐	☐
16. …I can enjoy relaxing pastimes as I would like eg TV, hobbies, reading, computer games	☐	☐	☐	☐	☐	☐
17. …I can sleep as I would like eg get to sleep, stay asleep, feel rested	☐	☐	☐	☐	☐	☐
18. …I can eat as I would like eg when, where, what, as much or as little as I want	☐	☐	☐	☐	☐	☐
19. …I can look after or be as useful to others as I would like eg family, friends, colleagues, pets / animals, volunteering	☐	☐	☐	☐	☐	☐
20. …I can enjoy being with my pets / animals as much as I would like eg exercising, grooming, playing	☐	☐	☐	☐	☐	☐
21. …I can be as independent as I would like eg look after myself, go out alone, work or stay at home alone	☐	☐	☐	☐	☐	☐
22. …I can control my life as I would like eg freedom, choices, planning ahead, keeping appointments	☐	☐	☐	☐	☐	☐
23. …I can be as spontaneous as I would like	☐	☐	☐	☐	☐	☐

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	eg go out without notice, stay out as long as I want						
24.	…I can do “normal” things eg enjoy everyday life, do what other people do without worry	☐	☐	☐	☐	☐	☐
25.	…I am treated as “normal” eg trusted to look after myself, capable, like any other person my age	☐	☐	☐	☐	☐	☐
26.	…I have the confidence I would like eg alone or with others, able to take on challenges	☐	☐	☐	☐	☐	☐

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Adult Low Blood Sugar Survey (University of Virginia) / Fear of Hypoglycaemia Survey

I. Behaviour: Below is a list of things people with diabetes sometimes do in order to avoid low blood sugar and its consequences. Tick the box that best describes what you have done during the last 6 months in your daily routine to AVOID low blood sugar and its consequences. (**Please do not skip any!**).

To avoid low blood sugar and how it affects me, I …	Never	Rarely	Sometimes	Often	Almost always
1. ate large snacks	☐	☐	☐	☐	☐
2. tried to keep my blood sugar 4mmol/L or above	☐	☐	☐	☐	☐
3. reduced my insulin when my blood sugar was low	☐	☐	☐	☐	☐
4. measured my blood sugar six or more times a day	☐	☐	☐	☐	☐
5. made sure I had someone with me when I go out	☐	☐	☐	☐	☐
6. limited my out of town travel	☐	☐	☐	☐	☐
7. limited my driving (car, truck or bicycle)	☐	☐	☐	☐	☐
8. avoided visiting friends	☐	☐	☐	☐	☐
9. stayed home more than I liked	☐	☐	☐	☐	☐
10. limited my exercise / physical activity	☐	☐	☐	☐	☐
11. made sure there were other people around	☐	☐	☐	☐	☐
12. avoided sex	☐	☐	☐	☐	☐
13. kept my blood sugar higher than usual in social situations	☐	☐	☐	☐	☐
14. kept my blood sugar higher than usual when doing important tasks	☐	☐	☐	☐	☐
15. had people check on me several times during the day or night	☐	☐	☐	☐	☐

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Worry: Below is a list of concerns people with diabetes sometimes have about low blood sugar. Please read each item carefully (do not skip any). Tick the box that best describes how often in the last 6 months you WORRIED about each item because of low blood sugar.

Because my blood sugar could go low, I worried about…	Never	Rarely	Sometimes	Often	Almost always
16. not recognising / realising I was having low blood sugar	☐	☐	☐	☐	☐
17. not having food, fruit or juice available	☐	☐	☐	☐	☐
18. passing out in public	☐	☐	☐	☐	☐
19. embarrassing myself or my friends in a social situation	☐	☐	☐	☐	☐
20. having a hypoglycaemic episode while alone	☐	☐	☐	☐	☐
21. appearing stupid or drunk	☐	☐	☐	☐	☐
22. losing control	☐	☐	☐	☐	☐
23. no-one being around to help me during a hypoglycaemic episode	☐	☐	☐	☐	☐
24. having a hypoglycaemic episode while driving	☐	☐	☐	☐	☐
25. making a mistake or having an accident	☐	☐	☐	☐	☐
26. getting a bad evaluation or being criticised	☐	☐	☐	☐	☐
27. difficulty thinking clearly when responsible for others	☐	☐	☐	☐	☐
28. feeling lightheaded or dizzy	☐	☐	☐	☐	☐
29. accidentally injuring myself or others	☐	☐	☐	☐	☐
30. permanent injury or damage to my health or body	☐	☐	☐	☐	☐
31. low blood sugar interfering with important things	☐	☐	☐	☐	☐
32. becoming hypoglycaemic during sleep	☐	☐	☐	☐	☐
33. getting emotionally upset and difficult to deal with	☐	☐	☐	☐	☐

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Appendix 6 – Phone script for recruitment

HIC #2000020059

Phone script for recruitment for Counterregulatory failure and hypoglycemia unawareness in intensively treated older adult type 1 diabetic patients.

This is XXX calling from the Yale Diabetes Center about a research study opportunity. I was looking at your pre-screen questionnaire through the Yale Center for Clinical Investigation database you had agreed to participate in. I would like to tell you about our current research to see if you might be interested in participating.

This research study is designed to demonstrate that a new closed loop insulin pump system can prevent low glucose episodes and enhance brain function in older patients with type 1 diabetes mellitus. We are looking for participants with Type1 Diabetes Mellitus, or T1DM, and who are over the age of 50, who have a history of frequent and/or severe episodes of low glucose values. Based on your pre-screen/screen information, you may be eligible.

Here is a little bit of a background information: As of right now, the best current treatment for T1DM is a sensor-augmented insulin pump therapy (so called "predictive low glucose suspend"; PLGS), which consists of an insulin pump that can "talk" with a continuous glucose monitor and can stop insulin injection in the presence of low glucose values. This feature limits duration and extent of hypoglycemic episodes that can frequently occur with traditional systems of insulin delivery.

In this study we will focus on the potential benefits of 2 FDA approved PLGS systems (Medtronic Minimed 670G and Tandem t:slim X2). These systems have been shown to effectively prevent hypoglycemia in the general patient population. Our hypothesis is that it would be safe and effective in reducing low glucose episodes specifically in older diabetic people.

To demonstrate this hypothesis, we will compare two groups of T1DM subjects for 8-10 weeks. As needed in this kind of scientific investigations, you will have the same probability to be assigned in one group or another and this decision will be independent from your or our determination. The intervention group consists of treatment with a PLGS-enabled insulin pump/CGM combination (Medtronic MiniMed 670G pump with Guardian sensor, or Tandem t:slim X2 pump with Dexcom sensor) in auto mode for Medtronic users and with Basal-IQ for Tandem users; subjects in the control group will use the same PLGS-enabled insulin pump/CGM combination but in manual mode for Medtronic users or without Basal-IQ for Tandem users. For subjects who use multiple daily injections as part of their standard insulin therapy or for subjects who do not use the MiniMed 670G pump or t:slim X2 pump, a loaner MiniMed 670G system will be provided.

To become a volunteer in this study, we'll first have to schedule a 1-hour screening visit at the Yale New Haven Hospital Research unit. As part of this visit, we'll go over the consent form with more details about

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the study; you will have a blood draw, an EKG, a brief physical and a short cognitive test for our baseline information. If you qualify for the study, we'll be able to schedule your trial days at that point.

The trial itself consists of several sessions, of which two are 2 "questionnaire sessions", each 8 weeks apart, where you will be asked to complete a battery of tests to measure your cognitive abilities, quality of life and satisfaction of current insulin therapy. These take 2.5 hours each. Then there are 2 "hypoglycemic sessions" in an MRI machine, each 8-10 weeks apart and 2 days immediately after the 2 questionnaire sessions. There will be 7 brief weekly visits in between, either by phone or in person if needed, to check your glucose values and to ascertain that everything is going well.

The hypoglycemic sessions will take place in the early morning and you'll be asked to arrive fasting. The visit will last no longer than 4 hours and the time in the MRI scanner will be no longer than 130min. At the end of first of the 2 sessions you may be asked to continue your standard insulin pump therapy or to receive the new AC/AP pump for 8-10 weeks. You will be discharged home during the early afternoon.

For completion of this entire study you may receive up to $800. If you complete the screening visit, you will receive $50 as a reimbursement for your time and possible parking fee.

Do you have any questions at this point? I would be happy to go ahead and look at possible days for you to come in for the screening.

Thank you, I'll send you a confirmation along with this information to your Email.

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Appendix 7 – MyChart message

You are receiving this MyChart message because you were diagnosed with Type 1 Diabetes and you have a history of frequent and/or severe episodes of low glucose values. You may be eligible to participate in a Type 1 Diabetes research study conducted by Yale University investigators to demonstrate that new insulin pump systems (so called "closed loop" or "artificial pancreas" systems) can prevent low glucose episodes and enhance brain function.

Study Information:
HIC Study #: 2000020059
Title: Restoring brain metabolism and function in older adult T1DM patients using an artificial pancreas system.
PI: Raimund Herzog, MD

What the study involves:
Study participants will be asked to:

- Have a brief screening visit to obtain detailed health information.
- Wear a PLGS system for 8-10 weeks
- Wear a continuous glucose monitor and have brief weekly visits for 12 weeks to assess glucose control and number of low glucose episodes
- Have two visits in which a battery of tests and questionnaires will be completed to measure brain abilities (such as attention and memory), quality of life and satisfaction of current insulin therapy (8-10 weeks apart).
- Have two visits in which blood samples and brain images will be taken during a controlled hypoglycemic event (8-10 weeks apart)

The study pays up to $800 as applicable as compensation for your participation.

This message is automatically generated by the electronic medical record system Epic and no one on the research team has been notified, nor has your name or personal information been shared with any investigator. To opt-out of research, including opting out of receiving future messages about research studies, please email optout@yale.edu or call 1-877-978-8348 and select option #3.

If you are interested in learning more about this study, please call us at (203)-737-4777 to speak to a study coordinator. You can also contact us by email at diabetes.research@yale.edu.

Future research opportunities:
You may also create a volunteer profile through the Research Tab in MyChart.

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