HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: The Effect of Insulin Bolus Speed of Rapid-Acting Insulin Analog Absorption and Action in Individuals with Type 1 Diabetes

Principal Investigator: Laura Nally, MD

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(*If applicable*) Clinicaltrials.gov Registration #: NCT03542682

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.

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
   Unpredictable swings in post-meal blood glucoses are common for individuals with Type 1 Diabetes (T1D). They have long been instructed to bolus rapid-acting insulin (RAI) 15 minutes before meals to account for delays in insulin delivery time and onset of insulin action. The "Quick Bolus" insulin delivery feature has been introduced as a novel feature of the new generation insulin pumps with a bolus delivery rate 10 times faster than the conventional "Standard Bolus". The impact of this change in bolus delivery rate, that can potentially change insulin absorption and action leading to unexpected blood glucose fluctuations, on RAI pharmacokinetics and pharmacodynamics (PKPD) has not been examined in individuals with T1D.

   This study aims to address this gap in knowledge by investigating the effect of insulin bolus speed on insulin absorption and glucodynamic action in 15 adults (ages 18 – 30, inclusive) with T1D by a randomized order, cross-over, single blinded insulin action study. The PKPD properties of a 0.2unit/kilogram RAI bolus by "Standard Bolus" and "Quick Bolus" will be compared for each subject using the euglycemic clamp technique during two admissions. The 0.2unit/kg bolus of RAI is standard for euglycemic clamps and has been employed many times in previous studies.

   We hypothesize that RAI absorption and action measured by time to reach maximum insulin concentration and glucose infusion rate during the clamp study will be significantly faster when insulin bolus is delivered using the "Quick Bolus" feature as compared to the "Standard Bolus" eliminating the impractical need for an insulin bolus 15 minutes prior to meals and consequently, lowering the risk of hypoglycemia. Moreover, data derived from our study will be essential to model insulin PKPD to customize insulin delivery algorithms of future artificial pancreas systems with integrated "Quick Bolus" feature to improve the treatment safety and efficacy for individuals with T1D.

   This study is not intended to be submitted or held for FDA inspection, as it is not a device study, but rather a study of the bolus speed options available for individuals with Type 1 Diabetes. The effect of insulin bolus speed on RAI PKPD has not been studied by the manufacturer of the only pumps currently on the market offering this feature (Medtronic). Of note, the now-defunct pump company Animas Corporation, previously offered similar rapid speeds on their commercially available pumps, however there are no published studies on the effect of bolus speed on insulin PKPD using those older pumps that are no longer being manufactured.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   The study is expected to last 5 years.

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.
   Investigators have previously demonstrated that there are a number of factors that alter insulin absorption and action following insulin boluses given by insulin pumps, such as pump site duration (Swan et al., 2009) and temperature (Cengiz et al., 2014), alterations that contribute to unpredictable swings in blood glucose concentrations following meals. Thus, it is particularly noteworthy that the newest insulin pumps are equipped with a "Quick Bolus" option that delivers pre-meal bolus doses ten times faster than the "Standard Bolus" option. Despite the potential importance of this new feature, its effect on the pharmacokinetics (PK) and pharmacodynamics (PD) of relatively large boluses of rapid-acting insulin (RAI) in comparison to the Standard Bolus have not been investigated in individuals with T1D on insulin-pump treatment.

Overall aim of this study is to evaluate the effect of the faster speed of bolus delivery (the "Quick Bolus") on the absorption and action of RAI as compared to the conventional bolus delivery rate (the "Standard Bolus") in individuals with T1D and to determine whether alteration in speed of insulin delivery translates in to faster lowering of blood glucose concentrations after an insulin bolus.

Specific Aims are to compare the PK and PD of the same dose of RAI when the dose is delivered by the "Quick Bolus" and by the "Standard Bolus" in individuals with T1D during two separate study visits using the euglycemic clamp technique. We hypothesize that the RAI absorption and action will be significantly faster, as defined by an earlier time to reach 25%, 50% and maximum insulin levels and insulin action as compared to RAI bolus delivery by the "Standard Bolus". We also hypothesize that faster delivery of the insulin bolus will result in earlier clearance of exogenous insulin; i.e. faster in and faster out.

The results from this study have the potential to improve the safety and efficacy of daily insulin treatment by new generation insulin pump therapy and revise traditional treatment practices to keep up with the advanced features of diabetes technology.

The overall goal of insulin replacement in T1D is to mimic the function of beta cells to regulate blood glucose values during everyday activities. Despite the introduction of rapid acting insulin analogues (Garg, 2005), postprandial hyper- and hypoglycemia are still common in those with T1D (Boland et al., 2001). A major obstacle in optimizing after meal blood glucose has been the delay in insulin absorption and action after an insulin bolus that results from the subcutaneous route of insulin delivery. Previous studies have demonstrated that the peak plasma insulin concentration (CIns max) achieved after a 0.2 U/kg bolus dose of aspart insulin is not observed until 50 minutes after the dose and the peak action is not observed until 40 minutes later (GIRmax) in insulin pump treated patients when bolus is delivered at a rate of 1.5 units/min (Swan et al., 2008). In addition, the speed of insulin delivery has been described as "too slow" by many adolescents with T1D anecdotally, which is not surprising considering that the average insulin bolus delivery (0.2u/kg) is expected to last 8 – 10 minutes. Such delays in insulin delivery, absorption and action led to the common recommendation to take pre-meal boluses 15 minutes prior to eating to mitigate post-prandial hyperglycemia.

Recent advances in diabetes technology led to the development of high-tech insulin delivery devices with multiple new features. One of those features has been an accelerated rate of bolus delivery option in addition to the conventional bolus delivery rate option. For example, the two most recent Medtronic insulin pumps (630G and 670G models) offer two bolus speed options: the "Standard Bolus" default setting that delivers 1.5 units of insulin per minute, which is the same bolus speed as the OmniPod and Tandem T-slim, and also a "Quick Bolus" option that delivers 15 units of insulin per minute. While the rate of bolus delivery is increased by 10 fold when insulin is infused by the new Quick Bolus setting, the impact of accelerated bolus delivery on insulin PK and PD has not been investigated and could lead to unexpected blood glucose fluctuations or even hypoglycemia if the insulin bolus is delivered either 15 minutes prior to the meal or after finishing eating. On the other hand, earlier insulin action could eliminate the need for the impractical and cumbersome 15 minute pre-meal insulin bolus and it may limit the extent of hyperglycemia in patients who take their meal boluses after eating. Minimizing extreme variability in blood glucose responses to meals has been an important goal to optimize insulin treatment. Therefore, one of the main interests of Diabetes research in general has been to evaluate and explore factors that modulate the exogenous insulin absorption and action in children and young adults with T1D.

Early studies showed that mixing rapid-acting insulin analogs (lispro and aspart) with long-acting analogs (glargine and detemir) as was commonly done in practice, is associated with a delay in the absorption of insulin levels and a marked blunting of early insulin action, as shown in the Figures below (Cengiz, Tamborlane, Martin-Fredericksen, Dziura, & Weinzimer, 2010).

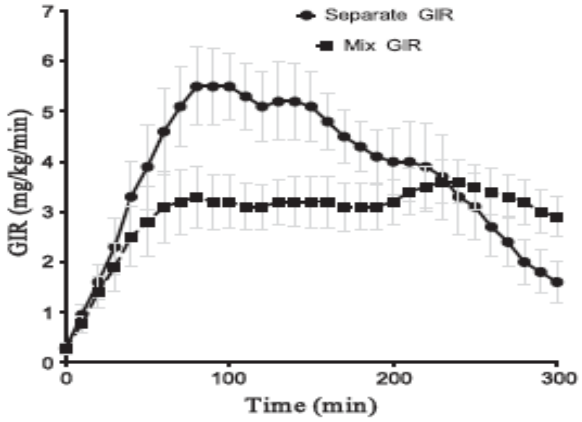

Figure 1—*Mean glucose infusion rate with SEM for separate (circles with solid line) and mixed (squares with dashed line) injections of aspart and detemir insulins.*

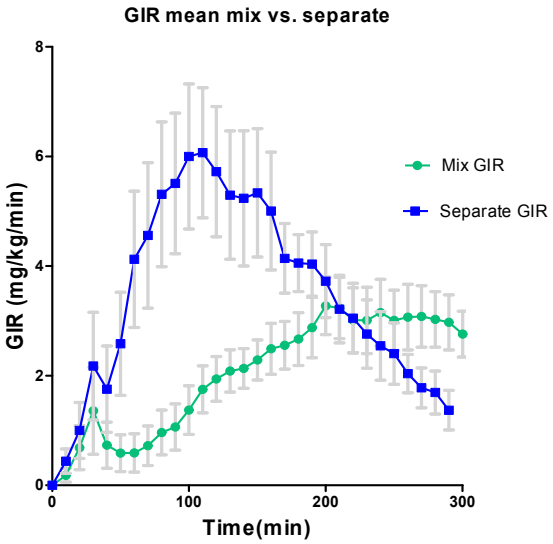

Figure 2. Insulin time action profile of RAI when RAI is injected separately and after mixing with Glargine insulin.

In 2014, a study investigating the effect on pump site warming using the InsuPatch (IP) device on insulin absorption (Cengiz et al., 2014) was performed. The InsuPatch is warming device used in conjunction with an insulin pump to warm the infusion site to 40 degrees Centigrade to help improve insulin absorption, as higher body temperature has been previously shown to accelerate insulin kinetics (Sindelka, Heinemann, Berger, Frenck, & Chantelau, 1994). Results of the InsuPatch study revealed that warming the infusion site resulted in earlier glucodynamic action, as reflected in the time to GIRmax and CIns max. It is particularly noteworthy that the accelerated rate of absorption with site warming in this study resulted in a time to GIRmax (TGIRmax) that was roughly 15 minutes earlier than that observed without site warming, roughly the time we tell people to bolus before eating, as seen in Figure 3 below.

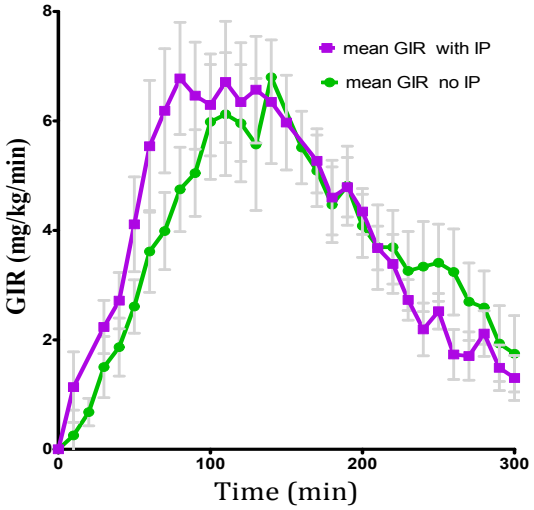

Figure 3. Time to mean GIR with InsuPatch (IP) and without InsuPatch

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

   Study Design: This study will be a cross-over, randomized order, single blinded clinical study in subjects with T1D, and will require two separate admissions per subject to the Yale-New Haven Hospital Research Unit (one admission with use of the Quick bolus option and one using the Standard bolus option).

   Study Protocol: The protocol will consist of an outpatient enrollment visit to obtain consent and confirm eligibility and two admissions at either the Hospital Research Unit (HRU) or Church Street Research Unit (CSRU). The procedures will be identical during both admissions, except for the speed of the insulin bolus delivery that will be used.

   Enrollment visit: At the enrollment visit, the risks and benefits of the study will be explained, the individuals will provide written consent. History and physical examination will be performed, hemoglobin A1c will be measured by DCA2000, hematocrit and serum potassium will be measured and urine will be tested for pregnancy in female subjects of reproductive potential. Subjects who are pregnant will not be eligible from the study. Pregnancy significantly changes the way a body uses glucose and insulin, which would be evident during the insulin clamp procedure. For subjects who are uncomfortable with pregnancy testing, we would not recommend they participate in the study. If all eligibility criteria are met, subjects will be entered into the study. Randomization with respect to the order of the studies will also be performed at the enrollment visit but subjects will not be informed regarding the order of randomization. Of note, potassium and hematocrit will not be measured again during the course of the study, as they are used as screening to check for chronic causes of hypokalemia and anemia. A normal potassium level is important, as insulin drives potassium into the cells. The insulin dose of 0.2u/kg used in the euglycemic clamp is a typical bolus amount individuals with T1D often administer at home for meals and is not considered excessive. The amount of blood drawn is about 40 mL, which is one-tenth the amount typically given when a healthy adult is donating blood.

   Preparation for the clamp: Study subjects will check blood glucose at 5 o'clock in the morning and they will call or text the on-call investigator for insulin dose adjustments before they come in for the insulin action study in order to begin the euglycemic clamp as close to the target blood glucose of 90 mg/dL as possible. Subjects will be admitted fasting to the HRU or CSRU the morning of each clamp and all female subjects of childbearing potential will be given another urine pregnancy test. A new subcutaneous infusion set compatible with the Medtronic 670G insulin pump will be inserted in the skin of the abdominal region before the clamp study, as insulin pump wearers are familiar with from their daily diabetes routine. The Medtronic 670G compatible infusion sets we will use will be the commercially available Mio and Sure-T infusion sets. Subjects will discontinue using their own pump and will be switched to the study pump programmed with their delivery settings in order to accommodate bolus speed delivery. Study staff will inspect the reservoir retainer ring of the study pump prior to each use in the study. It is important to note that, though the Medtronic 670G insulin pump is part of the only hybrid-closed loop insulin delivery system commercially available, we will only be using the pump in this study, not the accompanying sensor and glucose meter that

are used in conjunction with the insulin pump. The subjects will not be employing the hybrid closed-loop system Study pump will be used in research unit only. Subjects will not take the study pump home.

Clamp (Insulin Time-Action) Study Procedure: Two intravenous catheters will be inserted, one in each arm prior to the start of the study. One of the catheters will be used for variable rate infusion of dextrose during the study and the other will be used for frequent venous blood sampling for measurements of plasma glucose and insulin. After baseline glucose and insulin samples are obtained, the subjects will be given a 0.20 U/kg bolus of aspart insulin via either Standard or Quick Bolus through the insulin pump depending on the order of randomization. The insulin pump will be suspended after the bolus and disconnected from the study subject. Subjects will fast throughout the clamp procedure but will receive a variable rate of 20% dextrose solution to clamp the plasma glucose at the desired target (90+5 mg/dL) for 5 hours. Plasma glucose will be measured at the bedside every 5 minutes by the Yellow Springs Instrument. Blood samples for free insulin will be collected at 10 minute intervals for the first 90 minutes, then every 15 minutes until 3 hours, then every 30 minutes for the fourth and fifth hour. After the conclusion of the clamp, subjects will eat lunch and then be discharged from the HRU after receiving follow-up instructions. Subjects will insert their usual insulin set prior to lunch.

Visit	Procedures
Screening/Enrollment	• Review and sign consent • A1c • Venipuncture for eligibility labs • Pregnancy test (if applicable)
Research unit visit #1	• Subject reports BG @ 5:00 am, adjustments made if necessary so subject will be in good range prior to study start • Upon arrival at research unit, subject's personal pump is turned off, a new infusion site will be inserted, and study pump is activated • Two IV catheters will be inserted • Baseline glucose and insulin samples obtained • Bolus delivered through study pump using standard or quick bolus speed as per randomization • Clamp procedure completed as described • Subject returns to using personal pump, eats lunch • Discharge
Research unit visit #2	• Subject reports BG @ 5:00 am, adjustments made if necessary so subject will be in good range prior to study start • Upon arrival at research unit, subject's personal pump is turned off, a new infusion site will be inserted, and study pump is activated • Two IV catheters will be inserted • Baseline glucose and insulin samples obtained • Bolus delivered through study pump using standard or quick bolus speed as per randomization • Clamp procedure completed as described • Subject returns to using personal pump, eats lunch

	• Discharge

This project will provide the first data on the differences in the time/action profiles of bolus doses of RAI when administered by an insulin pump that has both Standard and Quick Bolus features. We have chosen to restrict eligibility for the study to young adults with T1D because most patients in this age group require relatively large pre-meal boluses of insulin, however in keeping with bolus amounts people with T1D generally give themselves at home. Hence, these patients with T1D are the group who are likely to receive a benefit from the Quick Bolus feature of new insulin pumps. Moreover, we don't anticipate any problems with enrolling a sufficient number of subjects because we have many patients and in our practice who have been actively engaged in past studies. Insulin aspart was selected as the RAI to be used in the study because we have a well-established assay for measuring plasma aspart levels and because the time/action profiles of insulin aspart and insulin lispro (the two most commonly used insulins in insulin pumps) are virtually identical.

5. 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 *Write here*

ii. the plan for the collection of material or the conditions under which material will be received *Write here*

iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*

iv. the methods to uphold confidentiality *Write here*

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*

C. Is widespread sharing of materials planned? *Write here*

D. When and under what conditions will materials be stripped of all identifiers? *Write here*

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*

F. Describe the provisions for protection of participant privacy *Write here*

G. Describe the methods for the security of storage and sharing of materials *Write here*

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.
Fifteen subjects ages 18 - 30 will be invited to participate in the study.

7. 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 ☒

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

Inclusion:

1. Age 18 – 30 (inclusive)
2. Clinical diagnosis of T1D of at least one year's duration
3. On CSII therapy for at least three months
4. HbA1c <10%
5. Minimum weight requirement of at least 37.9 kg
6. Ability to comprehend written and spoken English
7. Total daily requirement of insulin between 0.4 and 1.5 U/kg/day
8. Not have any other medical condition or disease known to affect insulin action and glucose control aside from T1D or treated hypothyroidism.
9. Not have evidence of insulin resistance based on clinical presentation or physical exam.

Exclusion

1. Medication besides insulin known to alter blood glucose or insulin action
2. Female subjects of reproductive potential that are pregnant or breast feeding, or not consistently using a barrier method or abstinence as contraception.
3. Inability to comprehend written and spoken English
4. Any other condition, which in the judgment of the investigators, would interfere with the subject's ability to provide informed consent or the investigator's ability to perform the study
5. Hematocrit less than 35% or a serum potassium less than 3.4 mmol/L

9. How will eligibility be determined, and by whom? Write here
Subjects will be screened during regular clinic visits. At the enrollment visit final eligibility will be determined. The ·study nurse or research associate will review eligibility requirements however, the PI will ultimately decide on the patients' eligibility to participate. The validity of HbA1c for enrollment is 8 weeks. The HbA1c will be repeated if the 8 week window expires.

10. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
The primary risks associated with the study are hypoglycemia from the insulin bolus, and potential discomfort and blood loss from the intravenous cannulation and phlebotomy.
In November2019 the pump manufacturer issued a safety notice describing a problem with a damaged reservoir retainer ring not locking the reservoir in place. In Feb 2020 (FDA) classified the November voluntary action as a Class I recall. It is important to note that this classification did not introduce any new issues or generate new instructions. Please note that a "recall" as defined by the FDA "does not always mean that you stop using the product or return it to the company." If the pump reservoir properly locks in place by the retainer ring and the pump is functioning, the pump may continue to be used.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
Hypoglycemia: The major risk associated with this study is hypoglycemia. Hypoglycemia is a common occurrence in individuals with T1D. It is estimated that, in individuals with well-controlled T1D, at least 15% of all readings may be in the hypoglycemic range (Boland, et al., 2001). All subjects will receive a standard bolus

of insulin aspart of 0.2 U/kg during the glucose clamp procedure. It should be noted, however, that bolus doses of insulin of this magnitude are commonly administered by subjects in the home environment before meals. In this case no meal will be given. Rather, the blood sugar will be clamped in the normal range at about 90 mg/dL by a variable rate of exogenous glucose infusion. Venous blood glucose levels will be checked every 5 minutes for the duration of the clamp procedure by the Yellow Springs Instrument, available at the patient bedside and capable of returning a value in 2 minutes. In previous studies, we determined that the maximum rate of fall of venous blood glucose following intravenous insulin is about 2 mg/dl/min (Tsalikian, et al., 2003). We expect that with subcutaneous administration of insulin, the rate of fall will be far slower, and glucose readings every 5 minutes will be more than adequate to monitor for and prevent any hypoglycemia.

Infusion Site and Insulin Pump: The pump reservoir retaining ring will be inspected to ensure that the reservoir will lock in place. The risks associated with the infusion site insertion are all the same as the patient encounters during routine diabetes care at home: bleeding, pain on insertion, and infection. There is also the risk of pump site failure, indicated by persistent hyperglycemia despite correction. If a pump site failure is not addressed, within hours an individual with Type 1 Diabetes may develop ketones. Persistent absence of insulin will cause diabetic ketoacidosis, putting the patient at risk for death. The Medtronic 670G is approved by the FDA for treatment of Type 1 Diabetes, and will have the patient's own insulin settings programmed into the device. The risk for any insulin pump is mechanical failure, which would be evident with hyperglycemia, subsequent ketones, and possible diabetic ketoacidosis. These are risks that patients face with their own insulin pump and infusion sets at home and they are mitigated by frequent monitoring of blood glucose and addressing any pump site or mechanical failures when they first present.

Phlebotomy: The major risks associated with intravenous cannulation and phlebotomy are pain, bruising, infection, inflammation, blood clot and blood loss. All intravenous lines will be inserted by nursing personnel in the HRU experienced with these procedures. Topical anesthetic creams will be used, if requested, to minimize discomfort. The IV sites will be monitored during the course of the clamp procedure for inflammation, swelling, or extravasation. The minimum volume of blood required for the proposed studies is 78.6 mL for the two clamp studies:

Clamp Study:

Insulin antibodies:	1.0 cc x 1 sample	= 1.0 mL
Glucose:	0.3 cc x 61 samples	= 18.3 mL
Insulin:	1.0 cc x 20 samples	= 20.0 mL
Total Blood Volume per admission		*= 39.3 mL*

The maximum blood volume in the blood draws will not exceed 3 mL/kg (considered to be less than/equal to minimal risk). This will be accomplished with the use of three-way stopcock assemblies, so that "waste" blood withdrawn to "clear the line" will be reinfused to the patient. We have previously demonstrated the feasibility of this procedure in patients with diabetes (DirectNet 2003) and can utilize blood volumes as low as 0.3 mL for the frequent glucose measurements. Using the 3mL/kg formula, subjects must weigh at least 37.9 kg in order to participate in the study.

12. 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.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? This study is considered to be greater than minimal risk and with no prospect of direct

benefit to individual subjects, but likely to yield generalizable knowledge of the subject's condition.

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://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for

i. Minimal risk
ii. Greater than minimal

All adverse events will be carefully monitored and documented using an adverse event form. The investigators will review the adverse event, determine its relationship to participation in the trial, and then grade the severity of the event, using standard definitions. An adverse event is any adverse change from the study participant's baseline condition that occurs following the screening visit, through the end of the study period. All adverse events will be documented in the study records, regardless of their relationship to the subject's participation in the study. Adverse events will be documented as a medical diagnosis or as a physical finding or symptom if no medical diagnosis is made. The investigators will assess each adverse event for severity and relationship to the study treatment. The investigators will provide an assessment of the relationship of the adverse event to study treatment, according to the following definitions:

Definite: Adverse event(s) will clearly be related to the investigational agent(s) or other intervention Probable: Adverse event(s) will likely be related to the investigational agent(s)

Possible: Adverse event(s) may be related to the investigational agent(s) Unlikely: Adverse event(s) will doubtfully be related to the investigational agent(s) Unrelated: Adverse event(s) will clearly not be related to the investigational agent(s)

The principal investigator will further grade the adverse event based on its severity, according to the following schedule:

0 No adverse event or within normal limits
1 Mild adverse event
2 Moderate adverse event
3 Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect
4 Life-threatening or disabling adverse event or Fatal adverse event

The principal investigator will make these assessments within 24 hours of notification that the event occurred. The adverse event forms will be collectively re-reviewed quarterly by the primary investigator, and the Yale University Human Investigations Committee (HIC) will be notified of Serious Adverse Events according to the guidelines for submission of such events. Serious anticipated and unanticipated adverse events (grade 3 or higher on the above scale) will be reported within 48 hours to the ***Yale HIC, and the YCCI Research Subject Advocate***. Serious AND unanticipated AND possibly, probably or definitely related events; and Anticipated Adverse Events occurring with a greater frequency than expected will be reported within 48 hours to the HIC whenever their magnitude or frequency exceeds expectations. The principal investigator will evaluate the adverse event and determine whether the adverse event affects the Risk/Benefit ratio of the study, and whether modifications to the protocol or

consent form are required.

Blood glucose levels <60 mg/dL and >400 mg/dL during the clamp procedure will be considered an adverse event.

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? *Write here*
   ii. What provisions are in place for management of interim results? *Write here*
   iii. What will the multi-site process be for protocol modifications? *Write here*

13. Statistical Considerations: Describe the statistical analyses that support the study design.
The primary hypothesis in this protocol is that the time to reach peak glucose infusion rate (TGIRmax), will be significantly shorter when the Quick bolus option is utilized compared to control conditions using a standard bolus option on the Medtronic 670G insulin pump. Using previous studies on mechanisms to affect insulin delivery speed (Cengiz, et al. 2014), we have determined that a group size of 15 will allow us to detect a difference with a two-sided type 1 error of 0.05 and a power of 80%, detecting a difference between means of roughly 15 minutes, which is the recommended about of time individuals with T1D are told to bolus before eating. Secondary analyses will compare the GIRmax. AUCGIR, and GIR30min during the clamp between the Quick bolus and standard control bolus. All comparisons will be made using paired t tests. As this is a crossover design, we will evaluate the period effect as well as the period by treatment interactions as describe by Pocock (1983).

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

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

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

4. **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 radiotracer is being administered to humans, include relevant data on animal models.
Write here

4. **Source:** Identify the source of the radiotracer to be used. *Write here*

5. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.
Write here

B. DRUGS/BIOLOGICS ☐N/A

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)*:

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.	☒
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.	☒
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	☒
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).	☒
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

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

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.
The study will involve the use of insulin aspart which is FDA approved and well-established as a first-line therapy in CSII treatment of adults and youth with T1D. The most common risk of insulin injection is hypoglycemia. However, it should be stressed that subjects will have blood sugar levels monitored every 5 minutes for the duration of the clamp procedure, and the dosage of bolus chosen for the study, 0.2 U/kg, is of a magnitude commonly administered by patients at home during typical living conditions. Blood glucose levels will also be monitored closely during the study and increased IV Dextrose given if the BG level falls below the targeted blood glucose of 90 mg/dL during that study. The Medtronic 670G insulin pump is FDA-approved for use in individuals with Type 1 Diabetes ages 14 and over who require eight or more units of fast-acting insulin (aspart or lispro) per day. For this study, insulin aspart (Novo Nordisk) will be the allowed medication. Vials of insulin aspart will be provided by the investigator, as will the Medtronic 670G insulin pump. Dextrose is also used as part of the clamp procedure.

3. Source: Identify the source of the drug or biologic to be used. Investigator

a) Is the drug provided free of charge to subjects? ☒YES ☐NO
If yes, by whom? Investigator

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.
N/A

Check applicable Investigational Drug Service utilized:

☐ YNHH IDS ☐ 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.*

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

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. *Write here*

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

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

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

6. 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. *Write here*

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

B. DEVICES ☐N/A

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

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.
Medtronic 670G is an FDA approved device-
3. Source:
a) Identify the source of the device to be used. Medtronic manufactures the pump
b) Is the device provided free of charge to subjects? ☐Yes ☐No N/A pump is used in research unit only not given to subjects

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:
N/A – not an investigational device

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): *Write here*

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): *Write here*

c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*

d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*

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

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: The targeted enrollment is 15 subjects.
   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 email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☐ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrails.gov
☐ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	
☒ Other: Patients of the Yale Diabetes Clinic		

* 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. Diabetes clinic visits, at their request to be included in T1D research. If they express interest, clinicians will discuss potential enrollment with eligible subjects (as determined by inclusion/exclusion criteria). We will not require advertising or recruitment of subjects not already under our care. Subjects who express interest in the study will be given a copy of the Consent Form, asked to review it, and then given the opportunity to discuss the study with the investigators in detail. It will of course be stressed that participation is voluntary and that non-participation will not affect continuing care at the Yale Diabetes Program, and that consent may be withdrawn at any time without ill effect. Additionally, potential participants will be recruited through diabetes social media groups (facebook, twitter).

b. Describe how potential subjects are contacted. See above

c. Who is recruiting potential subjects? Physicians and mid-level providers in the Yale Diabetes clinic.

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. Potential subjects may be patients of the PI or other members of the research team. Other potential subjects may contact the team after seeing the protocol on ClinicalTrials.gov.

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.

   i. Describe why it would be impractical to obtain the subject's authorization for use/disclosure of this data: We will get verbal authorization to ask some basic eligibility questions to see if potential subjects are qualified before scheduling an in-person visit to review the consent form and perform screening procedures. This information will not be retained for subjects who do not enroll in the study.

   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: Potential subjects may call or email after seeing the study on ClinicalTrials.gov. We can ask some basic eligibility questions to see if they are qualified before scheduling an in-person visit to review the consent form and perform screening procedures.

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 investigators will approach prospective participants about participation in the study during routine medical visits. They will have a face-to-face meeting with the Investigator and Study Coordinator to address questions about the study rationale, procedures, risks and benefits. The process of assuring that individuals are making an informed decision about participating in this study includes both verbal and written communication. The consent form will be reviewed with participants and the participant will be given time to review the written consent form and ask questions. The enrollment/consent process may be

completed on the HRU at the time of admission for the first visit. The participant will be given a copy of his/her signed consent forms.

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. Written informed consent will be obtained from all subjects. As part of the informed consent process, the participant will also be required to answer an open-ended question about this study designed to ensure that the participant understands the study, as well as what is being asked of him/her.
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 *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

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

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:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of 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? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? Protected health information that will be collected and used for the research will include subject name, DOB, address, telephone number, the research study records, medical and laboratory records of only those services provided in connection with this study, the entire research record and any medical records held by Yale New Haven Hospital and the Yale School of Medicine, medical history of diabetes and other conditions that may affect eligibility for study participation. Research material will consist of measurements of C-peptide, insulin antibodies, hematocrit, plasma HbA1c, plasma glucose, and insulin concentrations obtained every 5-30 minutes over all of supervised research center study periods. Study forms will be generated for each subject, and clinical data will be transcribed to the study form. Each study participant will be assigned a code number that will be associated with all study data. No such data will be labeled with, or otherwise include the name or identifying information other than the assigned study code number. The list of names of the study subjects and their assigned code numbers will be kept in a locked file cabinet or password-protected computer file by the Clinic Coordinator. Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Legally required inspection of study data by the

sponsors and this organization's Institutional Review Board (HIC) will be done in such a way as to safeguard patient confidentiality to the maximum possible extent. It is likely that data from this study will be published in scientific and medical journals and presented at scientific and medical conferences. In all such cases, project data will be presented in such a way that no participant could possibly be identified.

2. How will the research data be collected, recorded and stored? Data will be collected from physical examination, laboratory testing, and patient report.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☐Desktop Computer ☒Other Scanned paper forms

4. 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? Upon enrollment, all study subjects will be assigned a unique study number. The study number-and no personal identifiers-will be used as labels for study records and samples and any other related research documentation. Any study obtained information that must be entered in the subject's medical record will not contain the study subject ID number. A key linking the individual study numbers to the study subjects will be kept by the Project Coordinator as an excel spreadsheet file on a separate computer from study information, which will be password protected and maintained in folder on a secure server. All electronic and digital files will be stored on the secure Yale network and the PC accessing the network will be password protected. Individual identifiable data or the key cited above will not be stored on moveable media [e.g. laptops, compact discs, jump drives, thumb drives, personal digital assistants (PDA), Blackberry, etc.] unless encrypted. If identifiers are stored on moveable media, then investigators must use encryption methods to protect access to these files or other methods as appropriate for the types of information stored on these devices. Any research information intended for submission to the sponsor will be transcribed onto case report forms (CRF) and will contain no identifiers. All paper files will be stored in a locked file cabinet in a locked office and access is limited to members of the study research team.

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

5. 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. All people who are involved in the conduct of this research study, including those involved in the study design, performance, data acquisition or analysis, will be trained on HIPAA regulations and will receive human subject protection training. The PI will periodically monitor the methods and procedures herein to ensure proper use and that continued protections are in place and being followed. In the case that the PI leaves Yale University, s/he will make appropriate arrangements for the secured transfer of data. Research data will be stored indefinitely following the completion of the study.

   Research data containing protected health information will be de-identified and archived in Yale approved archival storage. When destroying paper records of research data with protected health information, it will be shredded. All electronic media will utilize methods for disposal such as zeroing or degaussing to remove personally identifiable research data from electronic sources as specified in "Disposal of Media Containing Confidential or Protected Health Information" under Procedure 1609: Media Controls found at http://www.yale.edu/ppdev/Procedures/its/1709/1609PR.01DisposaiMediaPHI.pdf

6. If appropriate, has a Certificate of Confidentiality been obtained? *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.)
There is no direct benefit to subjects participating in this study, however, it is possible that the subjects in this study may benefit if the study data reveal an effective means to increase the rate of absorption of subcutaneously administered rapid-acting insulins. Subjects may receive pharmacokinetic and/or pharmacodynamic information about insulin action that could improve their own diabetes care.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   The alternative to participating in this study is non-participation. Subjects who choose not to participate may continue their current regimen of insulin pump therapy, as prescribed by the physicians and nurse practitioners of the Yale Diabetes Program. There are no risks of non-participation.
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.
   Screening and enrollment visit: $30
   Clamp study visit: $100; subjects will undergo two clamps for a total of $200 per participant
   Total payment per subject for completed study: $230, visits ***will be paid as milestones using a Bank of America debit card.***

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.
   The inpatient stay and all associated study procedures will be provided at no cost to the subject. The funding for the costs of all study-related procedures, including the supplies and personnel for the clamp procedures, is pending. Costs of tests and supplies that are part of usual diabetes care, such as the A1c tests ordered as part of a regular health visit, will be covered by subjects and their insurance companies. Patients will pay for gas, car mileage and parking or public transportation fares. Subjects will be responsible for travel and may need to take off of work, as all visits take place on weekdays.

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? In the case of injury, medical care will be provided at the Yale-New Haven Hospital. However, subjects will be responsible for the costs of such medical care that is not covered by their own health insurance. Additional compensation will not be provided in the case of injury. Subjects do not waive any of their legal rights by signing the permission forms.

   b. Where and from whom may treatment be obtained? *Yale New Haven Hospital*
   c. Are there any limits to the treatment being provided? *N/A*

d. Who will pay for this treatment? Subjects will be responsible for the costs of such medical care that is not covered by their own health insurance.
e. How will the medical treatment be accessed by subjects? Medical treatment will be available on site at the hospital, minimal transport would be required.

IMPORTANT REMINDERS

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

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.**