YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2013-1)

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://www.yale.edu/hrpp/forms-templates/biomedical.html Submit the original application and one (1) copy of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	**HIC OFFICE USE ONLY**	

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Investigation into the Effects of blood glucose levels upon eating behavior in lean and obese non-diabetic and diabetic subjects. -			
Principal Investigator: Renata Belfort De Aguiar		**Yale Academic Appointment:** Assistant Professor	
Department: Internal Medicine			
Campus Address: Section of Endocrinology, TAC S-135			
Campus Phone: 785-2440	**Fax:** 737-5558	**Pager:**	**E-mail:** Renata.Aguiar@yale.edu
Protocol Correspondent Name & Address (*if different than PI*):			
Campus Phone:	**Fax:**	**E-mail:**	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

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Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI
o Yes ☒ No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?
o Yes ☒ No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as con-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form:
http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s of the Study:

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☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☐ Yale-New Haven Hospital
☐ Cancer Data Repository/Tumor Registry
☐ Specify Other Yale Location:

☐ Yale University PET Center
☒ YCCI/Church Street Research Unit (CSRU)
☒ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:

☐ APT Foundation, Inc.
☐ Connecticut Mental Health Center
☐ Clinical Neuroscience Research Unit (CNRU)
☐ Other Locations, Specify:

☐ Haskins Laboratories
☐ John B. Pierce Laboratory, Inc.
☐ Veterans Affairs Hospital, West Haven
☐ International Research Site (Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. December 2019

3. **Research Type/Phase: (Check all that apply)**

a. **Study Type**

☒ Single Center Study
☐ Multi-Center Study

Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐

☐ Coordinating Center/Data Management
☐ Other:

b. **Study Phase** ☐ **N/A**

☒ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV

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☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☐ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒
Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
Yes ☐ No ☐

7. Will this study have a billable service? A Billable Service is defined as a service or procedure that will be ordered, performed or result in charging in EPIC for individuals who are enrolled in a clinical research study, regardless if the charge is intended to be paid by the subject/their insurance or the research study.

Yes ☐ No ☒

If you answered "yes", this study will need to be set up in OnCore Support
http://medicine.yale.edu/ymg/systems/ppm/index.aspx

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8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ___ No __X_ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

c. Will a novel approach using existing equipment be applied?

If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

_____ _____

PI Name (PRINT) and Signature Date

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As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions Prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.

_____ _____

Advisor Name (PRINT) and Signature Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____

Chair Name (PRINT) and Signature Date

_____

Department

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YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____

YNHH HSPA Name (PRINT) and Signature Date

For HIC Use Only

_____ _____

Date Approved **Human Investigation Committee Signature**

This protocol is valid through _____

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

To investigate whether the daily glucose profiles as assessed by continuous glucose monitoring for 1 week of normal weight, obese, and diabetic individuals relate to hunger levels and food intake.

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.

The rising incidence of type 2 diabetes (T2DM) and obesity has paralleled the increased consumption of sugar, which has been associated with numerous adverse metabolic effects including weight gain, insulin resistance, cognitive decline, and stroke [1-3].

Human studies using nuclear magnetic resonance spectroscopy (MRS), a powerful, non-invasive tool to determine the concentration of metabolites in living tissue, have shown that glucose transport across the BBB is not rate limiting during hyperglycemia [4,5]. Furthermore, in previous

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work from our lab, brain glucose levels remain elevated in chronically hyperglycemic diabetic rats suggesting that there is very limited protective adaptation by the BBB [6]. We have also shown using microdialysis probes and hyperglycemic clamp in human subjects undergoing electrophysiological evaluation for epilepsy that brain microdialysate from non-epileptogenic brain areas showed a 200% rise in glucose levels from baseline during a hyperglycemic clamp [7].

Glucose has traditionally been considered a satiety signal in the brain. More than 50 years ago, Jean Mayer proposed the glucostatic theory of feeding where elevated glucose levels act as a satiety signal in the brain while falling glucose levels exert the opposite effect to stimulate hunger and subsequent food consumption [8-12]. While our knowledge of the signals from the periphery to the brain that regulate eating behavior has expanded exponentially, much remains unknown about the mechanisms by which glucose regulates feeding behavior and how these pathways are altered in diabetes and obesity.

Furthermore, previous published data from our lab[13], subjects using a 2-step clamp, i.e. euglycemia (~90 mg/dL) followed by mild hypoglycemia (~65 mg/dL) in conjunction with fMRI and visual stimuli of food/non-food, showed that euglycemia was associated with activation of prefrontal cortex (PFC) and anterior cingulate ($p<0.05$), while during hypoglycemia there was activation of hypothalamus, nucleus accumbens, insula, caudate and putamen in response to visual food cues ($p<0.05$). In addition, hunger was increased during hypoglycemia as compared to the euglycemic phase (5.7 ± 0.5 vs 4.5 ± 0.5; $p<0.01$). The study also included a small group of obese subjects (n=5). When this group was compared to lean subjects, they failed to show activation of the medial pre-frontal cortex during euglycemia and showed greater bilateral activation of the hypothalamus, striatum and insula in response to high-calorie food images during mild hypoglycemia ($p <0.05$). Taken together the data suggest that during euglycemic phase of the clamp study there was activation of PFC in lean individuals, a region involved in complex cognitive behaviors, decision making and moderating correct social behavior[14], whereas during hypoglycemic phase limbic regions were activated; which are involved in physiological and emotional responses[15]. Of particular interest these preliminary data suggest that the neural response to food consumption and food cues is altered in obese individuals in a way that could contribute to overeating behavior, namely increased stimulation of reward centers in response to nutrients (glucose) and/or food cues. This differentiated brain response could be a contributing factor to the pathogenesis of human obesity. We also plan to study patients with diabetes, who have chronic high glucose levels. Preliminary work from our group showed that obese unlike lean subjects suppressed activity in the ventral medial PFC (executive-control area) in response to food images; with a preferential liking/wanting for high-calorie food during hyperglycemia[16]. Therefore, we want to investigate if changes in circulating glucose levels can interfere with eating behavior and food intake in lean, obese subjects and patients with diabetes.

Continuous glucose monitoring (CGM) is used in people with diabetes for better glycemic control as well as in non-diabetic individuals to characterize glucose patterns [17-19]. No study thus far has looked into glucose profiles normal weight, obese, and diabetic individuals in a normal, outpatient setting in relation to hunger and food intake. In a preliminary study of 8 individuals who wore a CGMS for 1 week and recorded their food intake and hunger levels, we found that increasing subjective hunger levels are more related to pre-prandial glucose peaks as opposed to nadirs. Furthermore, declines in glucose are correlated with caloric intake as well as the

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macronutrient content of subsequent meals. Our findings suggest that glycemic excursions following a meal may play a role in hunger and food choices for the subsequent meal.

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

Continuous Glucose Monitoring System (CGMS): To evaluate the effect of blood glucose levels on eating behavior in a population of patients with diabetes in a free-living environment; we plan to study 15 lean healthy control subjects (BMI <25 kg/m2), 15 obese non-diabetic subjects (BMI > 30 kg/m^2), 15 T2DM subjects who will be age and BMI-matched to obese, non-diabetic subjects, and 15 T1DM subjects who will be age and BMI matched to control, non-diabetic subjects. The participants will come to the research unit for a screening visit to review their medical history and receive a physical examination. Blood tests will be collected for exclusion of anemia (hematocrit), diabetes (A1c), untreated thyroid disease (TSH), or any other major health problems (liver enzymes and creatinine). The total amount of blood drawn will be less 1 table spoon. All female subjects will undergo a urine pregnancy test at the time of screening. These blood and urine tests will not be performed if they have been done within the 3 months prior to the screening visit. The participants who qualify will be invited to use the CGMS (DEXCOM G4 Platinum) for up to 7 days. On the visit for placement of the CGMS: 1) the participants will be explained by one of the study physicians how to use a glucometer (FreeStyle or Accu-Check), 2) they will have the CGMS inserted under the skin, and 3) they will be instructed how to fill up the food log (using informational brochures). On the second visit (up to 7 days after the initial visit) the CGMS will be removed from the skin and the glucose meter and food log will be returned to the investigators. The first visit will last approximately 1 hour and the second visit about 30 minutes. The CGMS consists of 3 parts: sensor, transmitter and monitor. The small sensor measures the glucose levels from the interstitial tissue. The transmitter is attached on top of the sensor and connects wirelessly to the monitor. The sensor is sterile and comes in an unopened package. It has a plastic wire-like tip that is placed under the skin and continuously measures the glucose levels. One of the study physicians will insert the CGMS wire-like tip under the volunteer's skin with the use of the DEXCOM sensor insertion kit. The transmitter is snapped to the sensor pod and the sensor/transmitter unit will be attached to the skin with an adhesive patch. The monitor is the size of a small hand-held device with a digital screen that displays a graph showing the glucose levels from the previous 4-24 hours. While using the CGMS, the volunteers will need to check their glucose levels with a glucose meter twice a day to calibrate the device. One of the investigators will teach the volunteers how to use the glucose meter, which will be loaned to the volunteers during the CGMS session. The monitor and transmitter should be kept 6 meters apart for adequate wireless communication. While using the CGMS the participants will be asked to fill up a food record. The Food Record will ask about amount and type of food consumed throughout the day. The participants will also register how hungry they are before the meal and how full they feel after they ate, and type and duration of physical activity After completing the CGMS session, the sensor will be removed by one of the investigators. To remove the sensor, the adhesive patch will be gently peeled off from the skin, together with the sensor pod and transmitter. Removal of the sensor is a painless procedure. The sensor and sensor

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pod will be discarded after use. The transmitter and receiver and glucose meter will be disinfected with a bleach solution and 70% isopropyl alcohol wipes to remove any disinfectant residue.

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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.

15 lean, healthy control subjects (BMI <25 kg/m2)
15 obese, non diabetic subjects (BMI > 30 kg/m^2)
15 T2DM subjects who will be age and BMI-matched to obese, non-diabetic subjects
15 T1DM subjects who will be age and BMI matched to control, non-diabetic subjects.

6. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> 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 (If yes, see Instructions section VII #4 for further requirements)

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

Inclusion criteria (for both diabetic and non-diabetic participants):
-Age 18-65 years
- A1c < 10.5 %

Exclusion criteria:
BMI <18 (no upper limit), Creatinine > 1.5 mg/dL, Hgb < 10 mg/dL, ALT > 2.5 X ULN, untreated thyroid disease, uncontrolled hypertension, known neurological disorders, untreated psychiatric disorders, use of antidepressants and psychiatric medications, use of weight loss medications in the 6 months prior to the study, malignancy, smoking, current or recent steroid use in last 3 months, history of current illicit drug use; for women: pregnancy, or breastfeeding.

8. How will **eligibility** be determined, and by whom?
Eligibility will be determined by a qualified physician associated with the research protocol and will be based upon the above inclusion/exclusion criteria

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
The CGMS poses no major risks to the subjects. Participants may feel a mild discomfort (pin prick sensation) during the sensor insertion. Some individuals may experience black and blueness of the skin at the insertion site of the CGMS sensor, which resolves by itself in a few days. Redness and discomfort (inflammation) can occur at the sensor insertion site. Rarely sensors may fracture and a small piece may remain under the skin which will need to be removed by the physician. This may cause mild discomfort, bruising, or temporary bleeding.

Blood samples will be obtained with a needle inserted into a vein which results in mild discomfort, bruising and temporary bleeding.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.
CGMS catheter will be placed under sterile conditions by experienced staff members. In case of signs of inflammation or bruise at the sensor insertion site, the sensor will need to be removed immediately and standard care should be applied. The participants will be given one of the study physician's cell phone number to contact for any questions, concerns or problems.

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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.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? greater to minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
    c. Copy, paste, and then tailor an appropriate Data and Safety Monitoring Plan from http://www.yale.edu/hrpp/forms-templates/biomedical.html for
        i. Minimal risk
        ii. Greater than minimal/moderate risk
        iii. High risk

Greater Than Minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or [*enter the names of other oversight bodies that have this authority, e.g.,* Yale Cancer Center Data and Safety Monitoring Committee (DSMC)] have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)

1. We do not view the risks associated with the CGM and Glucose monitoring _____ as minimal risks.

Although we have assessed the proposed study as one of greater than minimal 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:

3. 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 (*Insert Investigator Name*) according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).

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c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. 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

5. 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 results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, 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.

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 IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND

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3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), 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):

X All Co-Investigators listed on the protocol.

☐ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)

☐ National Institutes of Health

☐ Food and Drug Administration (Physician-Sponsored IND #_____)

☐ Medical Research Foundation (Grant_____)

☐ Study Sponsor

☐ Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigator (*Insert Investigator Name*) 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.

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Please note: For any study that may be considered high risk, the IRB will be more focused on the safety requirements for the study and a DSMB will likely be required.

For more guidance on Adverse Event reporting and DSMPs, see **IRB Policy 710 Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events**

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency [*e.g., monthly, quarterly, etc*]. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator or the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A
   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?

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

This is a pilot project. We estimate that a sample size of 15 subjects per group will provide 80% power to detect within group differences of of 1.1 standard deviations. For changes in hunger ratings of liking, wanting and hunger we will have at least 80% power to detect between group differences across all glycemic conditions (i.e. main effect of group) of 1.0 standard deviation and within each condition of 1.25 standard deviations.

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

N/A

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

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a. What is the Investigational New Drug (IND) **number** assigned by the FDA?
b. Who holds the IND?
c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____
Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, 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:

i. 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
ii. 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
iii. 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
iv. 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
v. 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

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☐ 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.

3. **Source:** a) Identify the source of the drug or biologic to be used.

   b) Is the drug provided free of charge to subjects? ☐ Yes ☐ No
   If yes, by whom?

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.
   Check applicable Investigational Drug Service utilized:
   - ☐ **YNHH IDS**
   - ☐ **CMHC Pharmacy**
   - ☐ **PET Center**
   - ☐ **Other:**
   - ☐ **Yale Cancer Center**
   - ☐ **West Haven VA**
   - ☐ **None**

   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.
   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.

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6. **Use of Controlled Substances:**
Will this research project involve the use of controlled substances in human subjects?
☐ Yes ☐ No *See HIC Application Instructions to view controlled substance listings*.

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **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.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at YNHH, e.g., YNHH Operating Room or YNHH Heart and Vascular Center? Yes ☐ No ☒
If Yes, please be aware of the following requirements:

a. A YNHH New Product/Trial Request Form must be completed;

b. Your request must be reviewed and approved by a Hospital Committee before patients may be scheduled; and

c. The notice of approval from YNHH must be submitted to the HIC for the protocol file.

Please contact Gina D'Agostino, gina.d'agostino@ynhh.org or 203-688-5052, to initiate the process.

2. What is the name of the device to be studied in this protocol?

Has this device been FDA approved? ☐ Yes ☐ No
If yes, state for what indication.

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3. **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.

4. **Source:**

   a) Identify the source of the device to be used.

   b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

   ☐ **Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

   Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

   What is the **IDE number** assigned by the FDA?

   Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

   Who holds the IDE?

   ☐ **Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions,* Section VI.B.4 at http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf *to determine if these pertain to this study.*

   ☐ **Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. **Investigational device accountability**:

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a. 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:

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):

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

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

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

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

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. targeted for enrollment at Yale for this protocol__60_

b. If this is a multi-site study, give the total number of subjects targeted across all sites___

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)	

☒ Other (describe): Yale Diabetes Registry (HIC# 0911005973)

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Subjects will be recruited by flyers that will be posted locally. The flyer will display the contact information of the study team. They may also be identified at the Adult Endocrine Clinic and Yale University Health Services and approached through their caregiver. In addition the diabetes registry will be used to identify eligible patients and contact them by phone or letter, since this category of patients have already given their consent to be contacted for potential trials. Furthermore, they will be recruited through YCCI website, ClinicalTrials.gov website and community clinics. They will then be offered to contact one of the research team members or if they give their approval, to be contacted by the team by phone or e-mail and they will provide the subject with additional information about the study and the investigator will determine the eligibility of the subject for the study. The purpose and potential complications of the study will be explained to each subject in detail.

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During the screening session, the informed consent form and study details are reviewed in detail by one of the project investigators and the subject will be asked to read the informed consent form (approved by the Yale Human Investigations committee). The subject will be given time to ask questions and only after that will the subject be asked to give informed consent to participate. The informed consent form and study details will again be reviewed with the subject on each study day prior to beginning the study.

b. Describe how potential subjects are contacted.

The consent process is a two-step process, whereby the subject initiates contact via telephone or in person presentation and will undergo a phone or in person screen with a member of the research team. Thereafter, potentially eligible candidates will be scheduled for a face-to-face interview.

c. Who is recruiting potential subjects? See IRES IRB

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

☒ Names

☒ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☒ Telephone numbers

☐ Fax numbers

☒ E-mail addresses

☐ Social Security numbers

☐ Medical record numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☒ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web Universal Resource Locators (URLs)

☐ Internet Protocol (IP) address numbers

☐ Biometric identifiers, including finger and voice prints

☐ Full face photographic images and any comparable images

☐ Any other unique identifying numbers, characteristics, or codes

5. 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.

An investigator may be the treating clinician for subjects recruited from the Endocrine Clinic.

6. 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 purposes only: __X____

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
We will need the volunteers' full name, address, date of birth, and phone numbers to schedule a screening visit at the Hospital Research Unit. We also would like to be able to review clinic appointments to see if any of the scheduled patients meet the inclusion criteria prior to calling them on the phone. This would include reviewing their diagnosis for DM, their age to be between 18-65 years, and their Body Mass Index (BMI). By reviewing this information prior to contact, we will be able to avoid contacting subjects that may not be included due to BMI and age.

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.

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.

7. Required HIPAA Authorization: If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

☒ Compound Consent and Authorization form

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☐ HIPAA Research Authorization Form

8. **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 have sufficient time to ask questions during the screening and will be encouraged to contact investigators with further questions or concerns. All subjects who will be asked to volunteer are informed that no immediate personal medical benefits will be derived from participation. Any subject who appears incapable of providing informed consent (e.g., due to apparent cognitive impairment) will be excluded. Subjects will be informed that they can decline to participate in the study without penalty, and given the opportunity to withdraw from the study prior to analysis of their data. All subjects will be given a copy of the consent form enclosed with this protocol outlining the risks and benefits of participation in this study. Following the resolution of any questions, the subjects will be asked to sign the consent form, if he/she agrees to participate.

9. E**valuation 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.

   We do not plan to recruit subjects with limited decision-making capacity. Potential subjects will undergo a face-to-face interview. At that time, a study physician will meet the subject, review the informed consent form, explain the purpose of the study and risks associated with participation, and will be available for questions. To ensure that the study subject understands the study, the subject will be asked questions about the study procedures and the risks associated with participation. If any concern arises that the study subject did not fully understand the study, the study physician may decide that the subject is not suitable for participation. If the subject is still interested after all questions have been answered, a study physician will ask the subject to sign the informed consent form.

10. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

    There will be a specific Compound Consent and Authorization form.

11. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

    N/A, we do not plan to recruit non-English speaking subjects.

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12. 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 a consent waiver**
☒ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☒ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☒ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☒ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☒ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☒ No

☐ **Requesting a waiver of signed consent for the Entire Study (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. **Full waiver** of consent: (No consent from subjects will be obtained for the activity.)

☒ **Requesting a waiver of consent for Recruitment/Screening only**

a. Does the research activity pose greater than minimal risk to subjects?

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☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☒ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☒ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the <u>Entire Study</u> (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

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

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

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

- Name
- Address
- Phone number
- Age
- Medical record number
- Race
- Past medical, and surgical history, allergies, medications taken.
- Family and social history
- Body mass index, vital signs
- Labs, including A1c, ALT/AST, creatinine, TSH, pregnancy test, and CGMS results

b. How will the research data be collected, recorded and stored?
Research data will be collected directly from the subject as well as via the electronic medical record. Subjects will be assigned a study number. The principal investigator will create a computer worksheet where the name of the subject's medical information is linked to the coded information. This will be housed on a password protected computer on a secured network. Only the investigators will have access to the computer records, which include the subject's identity, in order to evaluate the information generated by the study. No further

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public disclosure of this information will be made. One copy of the consent form will be kept in a secured and locked cabinet in the PI's office (which is also locked). The subject's name will be kept separate from the results.

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

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?
Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

All identifiable subject information that is collected during recruitment, screening, and participation will appear only on the initial paper forms, which will be kept under lock and key in the academic office of one of the study investigators. All digital files that could link a code number to an individual study subject will be password protected and stored on CD, which will be kept locked in the PI's office.

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.

Procedures to ensure confidentiality follow the regulations and policies of the Yale University School of Medicine. The security mechanisms specified above in section **d** will continue to be in place to protect study data.

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)

The NIDDK will be the only external agency that will have access to de-identified study data. Only the investigators will have access to PHI and de-identified data. The Yale University HIC will have access to study files.

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

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 IX: POTENTIAL BENEFITS

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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.)
Healthy non-diabetic subjects will have no direct benefit from the studies. Diabetic subjects will benefit by learning about their blood glucose levels while using the CGM.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   The alternative is to decline participation in the study.

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.
   Participants will be paid $150 for using the CGM, upon completion of the study. Compensation may be provided in the form of check or through Bank of America card issued through YCCI. In addition parking will be complementary.

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.
   There will be no additional cost to the study participants.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   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?

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