**YALE UNIVERSITY**
**HUMAN INVESTIGATION COMMITTEE**

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

## SECTION I: ADMINISTRATIVE INFORMATION

| | | | |
|---|---|---|---|
| **Title of Research Project:** Investigating the role of the polyol pathway in the central nervous system production of fructose: an Intervention Study | | | |
| **Principal Investigator: Janice Hwang, M.D.** | | **Yale Academic Appointment:** Instructor | |
| **Department: Internal Medicine** | | | |
| **Campus Address:** Section of Endocrinology, TAC S-141 | | | |
| **Campus Phone:** 785 6222 | **Fax: 737-5558** | **Pager:** | **E-mail:** Janice.hwang@yale.edu |
| **Protocol Correspondent Name & Address (*if different than PI*):** | | | |
| **Campus Phone:** 785-6222 | **Fax: 737-5558** | **E-mail:** Janice.hwang@yale.edu | |
| **Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):** | | | |
| **Campus Phone:** | **Fax:** | **E-mail:** | |
| **Business Manager:** | | | |
| **Campus Phone :** | **Fax :** | **E-mail** | |

| | | | |
|---|---|---|---|
| **Faculty Advisor:** Robert Sherwin, MD | | C. N. H. Long Professor of Medicine (Endocrinology); Section Chief, Endocrinology | |
| **Campus Address:** Section of Endocrinology, TAC S-141 | | | |
| **Campus Phone:** 203.785.4183 | **Fax:** 737.5558 | **Pager:** | **E-mail:** robert.sherwin@yale.edu |

**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



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

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

☐ Yes X 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?

☐ Yes X 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:**

☒ 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]:**



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

☐ 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: 2/23/2016 |
| ☐ *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: 3/19/2016 |
| ☐ 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. 7years

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
   ☐ 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")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research

☐ Translational Research #2 ("Bedside-to-Community") ☐ 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: NCT03469492

:

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

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes X_ No ___ *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? Yes

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

c. Will a novel approach using existing equipment be applied? No

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 III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is “pending” at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note “Pending” in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.** This information is maintained in IRES

**NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.**

## SECTION V: RESEARCH PLAN

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

Growing evidence suggests that fructose is linked to the development of obesity and diabetes. Studies investigating the central nervous system (CNS) effects of fructose have shown that fructose and glucose have distinct metabolic effects in the brain. While intraventricular glucose infusion into the brain decreases feeding in rodents, intraventricular fructose infusion has the opposite effect to promote feeding. Moreover, our research group has shown using functional MRI in humans that ingestion of fructose and glucose has differential effects on cerebral blood flow in specific brain regions that influence eating behavior.

Recently, we have found that glucose is converted to fructose in the CNS via the polyol pathway (glucose→sorbitol→fructose). We found that fasting cerebrospinal fluid (CSF) fructose levels obtained at the time of spinal anesthesia in pregnant women undergoing elective

caesarean section are nearly 20-times higher than plasma levels. CSF sorbitol levels were also nearly 10-fold greater than plasma levels further supporting the presence of an active polyol pathway in the CNS. Furthermore, CSF fructose levels correlated positively with CSF glucose levels (ρ 0.453, $p = 0.02$).

**Specific Aim: To investigate whether longer-term improvement of glycemic control in poorly controlled diabetes patients with a 12-week intensification of their diabetic treatment regimen will lead to decreased polyol pathway activity.**
***Hypothesis:*** *Polyol pathway activity will decrease in diabetic individuals who undergo intensification of their diabetes treatment regimens as reflected by lower baseline brain intracellular fructose levels and higher intracellular glutathione levels. Furthermore, following longer-term improved glycemic control, patients may also have down-regulation of the pathway as reflected by decreased production of intracellular fructose in response to hyperglycemic clamp.*

15 T2DM subjects and 15 T1DM subjects with chronic hyperglycemia (HbA1C > 7.5%) will participate in a 12-week intervention study aimed at reducing their A1C levels. By lowering their glucose levels, we expect to also decrease activity through the polyol pathway. Subjects will receive exercise and dietary counseling in accordance to guidelines established by the American Diabetes Association. In addition, all patients will have their diabetes regimens adjusted on a weekly basis to achieve a target blood glucose level based upon data from the patients performing self-monitoring of blood glucose (SMGB).

At 0 and 12 weeks, subjects will undergo baseline MRS scan at 4T to measure intracerebral glucose, fructose, and glutathione. Participants may also be invited to participate in an overnight admission to normalize blood glucose levels, and a hyperglycemic clamp. During each of these two scans, plasma glucose, fructose, insulin, HbA1c, and fructosamine levels will be measured concurrently. One week prior to the week 0 and week 12 MRS scans, subjects will be asked to wear a CGMS (Free style libre) to continuously monitor their interstitial blood glucose levels and record their food intake in a food log. After first placing the CGM prior to the week 0 scan, the system is removed after 14 days and then reinserted for 14 days before the week 12 MRS scan.

2. **Background:** Describe the background information that led to the plan for this project.

The rising incidence of diabetes and obesity has paralleled the increased consumption of not just glucose, but also of fructose in the form of high fructose sweeteners and sucrose, which has been associated with numerous adverse metabolic effects including weight gain, insulin resistance, cognitive decline, and stroke [1-3]. While CNS glucose infusion decreases feeding in rodents, CNS fructose infusion has an opposite effect to promote feeding [4,5], which is due to differential effects on hypothalamic malonyl-CoA [5]. Furthermore, studies in humans have shown that, compared to glucose, fructose ingestion results in lower levels of satiety hormones such as GLP-1 [6] and insulin [7]. Glucose and fructose ingestion also result in distinct patterns of regional cerebral blood flow as assessed by functional MRI [8]. In rodents, high fructose diet results in impaired special memory [9,10], and epidemiological data in humans have noted an association between increased fructose consumption and lower score on the mini-mental status exam [11]. Taken together, these studies have generated considerable interest in the possible effects of fructose in the brain.

The polyol pathway is an alternate glucose pathway that bypasses glycolysis [3,4] and is present throughout the human body, including the brain [5,6]. While only a small percentage of glucose enters this pathway under normoglycemic conditions, during hyperglycemia up to 30%

of glucose enters the polyol pathway [7,8]. In addition to fructose generation, flux through the pathway also generates oxidative stress via production of NADH as well as through the competition between aldose reductase (AR) and glutathione reductase for NADPH resulting in decreased glutathione in its reduced form (GSH) [9]. In the periphery, this increased oxidative stress has been implicated in the development of peripheral neuropathy [10], diabetic retinopathy and cataracts [11-14], nephropathy [15], fatty liver [16], macrovascular disease [17] as well as platelet dysfunction [18,19].

In the brain, however, the role of this pathway (either normally or in states of hyperglycemia) remains unclear. In dogs, peripheral glucose infusion increases levels of fructose and sorbitol in the cerebrospinal fluid (CSF) [20,21]. Furthermore, dogs with experimentally induced diabetes have been reported to have 7-10 fold higher CSF fructose levels compared to non-diabetic animals [22,23]. In humans, CSF fructose levels were first reported to be higher than plasma levels in the 1930's [24], an observation later confirmed in the 1960's in a cohort of diabetic and non-diabetic individuals [25]. These studies were, however, limited by the technical inability to precisely measure fructose, the inclusion of both fasting and non-fasting subjects, and the lack of assessment of diabetes control or type of diabetes [25].

With a growing body of individuals exposed to increasing duration of hyperglycemia, understanding the impact of hyperglycemia on the brain is of critical clinical importance. The polyol pathway, through its effects on fructose production as well as oxidative stress, may be a novel mechanism through which glucose exerts its CNS effects.

## 3. Research Plan:

**Aim: To investigate whether longer-term improvement of glycemic control in poorly controlled diabetes patients with a 12-week intensification of diabetes treatment regimen will lead to decreased polyol pathway activity.**

**Study design:**

**Subjects:** 15 T2DM subjects and 15 T1DM subjects with HbA1C > 7.5% will be recruited from Yale New Haven Hospital and the greater New Haven area.

**Inclusion criteria:** Age 18- 65 yrs, BMI ≥18 kg/m$^2$ , and weight less than 285 pounds (upper limit of scanner),

**Exclusion criteria:** Creatinine > 1.5 mg/dL, Hgb < 10 mg/dL, hematocrit of 37 % for males participants and 33 % for female participants, ALT > 3 x ULN, , untreated thyroid disease, uncontrolled hypertension, known neurological disorders, untreated psychiatric disorders, malignancy, bleeding disorders, current or recent steroid use in last 3 months, illicit drug use; for women: pregnancy, actively seeking pregnancy, or breastfeeding; inability to enter MRI/MRS (per standard MRI safety guidelines).

**Screening visit:** Volunteers will be screened at the YNHH Research Unit (HRU) with a medical history and exam including detailed neurologic exam. Blood tests will be collected for A1C, ALT, TSH, Hematocrit. Less than 35 mL of blood will be drawn for blood work. Women will undergo urine pregnancy testing. Subjects will be required to give us information about their substance use/HIV status because this can affect brain glucose metabolism.

**Intensification of Insulin regimens:** The intensification of the diabetes regimens will be managed by Dr. Janice Hwang, a fully trained attending endocrinologist, and will follow the general strategies outlined in the Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. All participants will receive exercise and dietary counseling from Mary Savoye, a nutritionist and registered dietician with extensive



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

experience with working with individuals with diabetes and obesity. Participants will communicate with a nutritionist regularly over the course of the 12-week study.

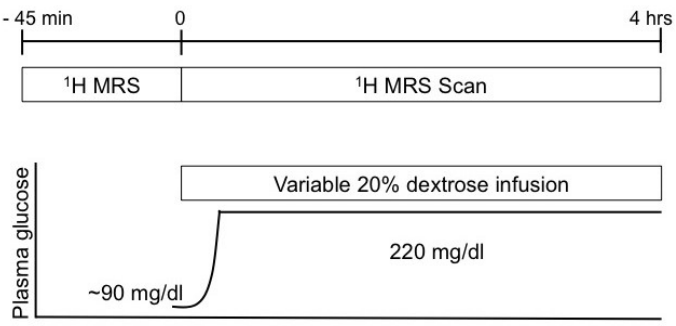
All individuals will be asked to perform SMBG at least 4 times a day (before breakfast, lunch, dinner, and bedtime). The daily SMBG records will be sent to Dr. Hwang weekly for review to guide adjustment of insulin regimens. Target blood glucose levels will be between 80-140 mg/dl before meals and between 100-160 mg/dl at bedtime. Individuals not at goal glycemic targets will undergo intensification of their regimen. Throughout the study, individuals will be contacted via telephone call, email or through additional clinic visits as deemed necessary for maintenance of glycemic control. All individuals will receive education regarding the detection and proper management of hypoglycemia.

**MRI and MRS scanning:**
Subjects will undergo MRS scanning at 4T at 0, and 12 weeks of the study. Scan time is ~45 minutes. After a T1 weighted MRI for anatomy (gray/white/CSF segmentation), glucose and fructose concentrations will be obtained from ~3X3X3 cc voxels. Signals from respective voxels are isolated using a MEGA PRESS-based sequence. Metabolite levels are measured by spectral fitting using a simulated basis set and referenced to total voxel water signal and creatinine to determine concentration.

During each of these two scans, plasma glucose, fructose, insulin, HbA1c, and fructosamine levels will be measured concurrently.

A nurse experienced with working in a MRS environment will be with subjects at all times. Vital signs including heart rate and blood pressure will be monitored prior to scanning. If patients express discomfort or anxiety and ask to be removed from the scanner, the session will be immediately terminated.

**Optional Hyperglycemic clamp**:
Prior to MRS scanning at weeks 0 and 12 Subjects may also be invited to participate in an optional overnight admission to normalize blood glucose levels the night before scanning and then a hyperglycemic clamp the following morning.




Subjects will be admitted in the evening prior to MRS scan day (~ 6 PM) to the YNHH research unit, all of their diabetic medications will be held and they will be placed on an insulin drip beginning at 8PM to maintain blood sugar levels at ~90-100 mg/dl until 7AM the next morning. The next morning, participants will be taken to the MRRC for MRS scanning. Following the 45 minute baseline scan, subjects will remain in the scanner for continuous scanning during the hyperglycemic clamp (see figure). An infusion of 20% dextrose at a variable rate to maintain plasma glucose levels at 220 mg/dL for 4 hours. Glucose infusion rates will be adjusted in response to plasma glucose levels measured every 5-10 minutes. Subjects will be able to take breaks as needed during the 3 hours hyperglycemic clamp and MRS scan. At baseline, 2 and 4 hours, plasma samples will also be obtained for fructose, sorbitol, insulin levels and other hormonal markers.



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

**Continuous glucose monitoring system (CGMS) and Food logs (at -1, and 11 weeks)**: One week prior to the MRS scans at 0 and 12 weeks, subjects will be asked to wear a CGMS (Free style libre) to continuously monitor their interstitial blood glucose levels and record their food intake

**Blood collection for platelet and inflammation analysis:** Participants will also have blood collected (~80 cc) for analysis of polyol pathway activity in platelets as well as for changes in inflammatory markers such as cytokines IL-6, TNF-alpha at weeks 0, and 12 weeks.

**Optional Specimens for Future Storage:** Subjects will be asked to give permission for the storage of any blood obtained during the study that will not be used for the above noted analysis

**4. Genetic Testing N/A** ☒

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

   15 T2DM subjects with HbA1C > 7.5%
   15 T1DM subjects with HbA1C > 7.5%

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

| | | |
|---|---|---|
| ☐ Children | ☐ Healthy | ☐ Fetal material, placenta, or dead fetus |
| X 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:**
15 Type 2 DM subjects with HbA1C > 7.5%
15 Type 1 DM subjects with HbA1C > 7.5%
Age 18- 65
BMI ≥18 kg/m2
Weight ≤ 285 pounds

**Exclusion criteria:** Creatinine > 1.5 mg/dL, Hgb < 10 mg/dL, hematocrit of 37 % for males participants and 33 % for female participants ,ALT >3 x ULN, untreated thyroid disease, uncontrolled hypertension, known neurological disorders, untreated psychiatric disorders, malignancy, bleeding disorders, current or recent steroid use in last 3 months, illicit drug use; for

women: pregnancy, actively seeking pregnancy, or breastfeeding; inability to enter MRI/MRS (as per standard MRI safety guidelines).

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.

**Hyperglycemia clamp:**
The infusion of glucose to achieve hyperglycemia (~220 mg/dl) for 3 hours is not associated with any specific symptoms or significant adverse effects. This modestly high glucose level can be seen in poorly controlled diabetic patients following a meal.

The overnight infusion of insulin to normalize plasma glucose levels is normally not associated with any specific symptoms. There is a small risk that plasma glucose may fall to lower levels resulting in symptoms of hypoglycemia.

**MRI/MRS:**
The major risk is the possibility of metal flying into the magnet. Subjects are asked to fill out a detailed MRI safety screening questionnaire (from the MRRC) to determine whether there are any contraindications to entering the magnet. Furthermore, subjects and all personnel are scanned with a metal detector before entering the magnet area and all metal objects are removed. Subjects with metal implants that cannot be safely removed, or pacemakers are not admitted to this study. Some subjects feel claustrophobic or experience physical discomfort inside the scanner. Communication is set up so that the subjects can talk to the investigators and may be removed from the scanner if they are uncomfortable. A RN will be present inside the scanner at all times with the subject.

**CGMS:**
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.

**12-week Intensification of Diabetes Regimen:**
The 12-week intensification of diabetes management poses minimal risks to the patient. All medical management strategies will follow the general strategies outlined in the Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes [48]. There may be slightly increased risk of hypoglycemia with improved glycemic control; however, as patients are all poorly controlled T2DM patients and we are targeting blood glucose levels to between 80-140 mg/dl before meals and between 100-160 mg/dl at bedtime, we expect that this risk will be minimal. In fact, participants may benefit from the free supplies and increased frequency of medical attention to lower their blood glucose into target ranges.



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

**Phlebotomy:**
Phlebotomy can result in anemia, although the amount of blood taken for these studies should not result in clinically-significant anemia because the blood drawn is spread out over the course of 3 months of participating in the study. Subjects are excluded if hemoglobin < 10 gms/dL or hematocrit of 37 % for males participants and 33 % for female participants.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.
    General:
    - Total blood loss in each subject will be approximately 549 cc over the 3 months of the study if subject completes the entire study (including the optional hyperglycemic clamp portions). Blood draws include: 35 cc at screen, 272 cc at week 0 visit,, and 272 cc at week 12. If the subjects choose not to do the optional hyperclamp portion of the study, the total blood draw will be approximately 202 cc over the course of the study. Blood draws include: 5 cc at screen, 98.5 cc at week 0 visit, , and 98.5 cc at week 12Subjects with Hgb <10 and hematocrit of 37 % for males participants and 33 % for female participants will be excluded from the study.
    - All subjects will be given a telephone number to enable immediate communication with the PI or one of the co-investigators to report any delayed adverse effects.
    - Physiological monitoring will be performed during each study.

    For glucose infusions:
    - Intravenous catheters will be placed under sterile conditions by experienced staff members.
    - During glucose infusions, 20% dextrose is used reducing the risk of thrombophlebitis normally associated with the use of excessively hypertonic glucose solutions.
    - To avoid hypoglycemia during the overnight insulin infusions, plasma glucose will be monitored closely using a bedside glucose analyzer (YSI). This will involve plasma measurements every 30 minutes and at more frequent intervals if plasma glucose is low (less than 4 mM, 70 mg/dl).
    - All studies will be performed under the direct supervision of a physician.
    - All solutions for infusion will be pyrogen free and prepared in a sterile environment.

    12-week Intensification of Diabetes Regimen:

    The 12-week intensification of diabetes management poses minimal risks to the patient. All medical management strategies will follow the general strategies outlined in the Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes [48]. There may be slightly increased risk of hypoglycemia with improved glycemic control; however, as patients are all poorly controlled T2DM patients and we are targeting blood glucose levels to between 80-140 mg/dl before meals and between 100-160 mg/dl at bedtime, we expect that this risk will be minimal. Subjects will be provided with free style libre sensors throughout the study (9 sensors are provided during the 12 weeks that the study last), and free style libre continuous glucose monitor reader. All participants will receive exercise and dietary counseling in accordance with ADA guidelines and increased frequency of medical attention to lower their blood glucose to target ranges. Throughout the study, individuals will be contacted via telephone call or through additional clinic visits as deemed necessary for maintenance of glycemic control. All individuals will receive education regarding the detection and proper management of hypoglycemia.



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

MRI/MRS:

- Subjects and all personnel are required to fill out an MRI safety questionnaire to ensure safety. Also, all subjects are scanned with a metal detector before entering the magnet area and all metal objects are removed.
- Subjects with metal implants or pacemakers are not admitted to this study.
- Some subjects feel claustrophobic or experience physical discomfort inside the scanner. Communication is set up so that the subjects can talk to the investigators and may be removed from the scanner if they are uncomfortable.
- A RN will be present inside the scanner at all times with the subject.
-

**Breach of Confidentiality:** It is possible that an unauthorized individual may gain access to subjects private information. We will make every effort to keep the data safe and private. For more information about how your data is protected, review the "Confidentiality and Security of Data paragraph on page 23.

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

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

**MODERATE RISK DSMP**

**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 MRRC have the authority to stop or suspend the study or require modifications.

**The risks associated with the current study are deemed moderate for the following reasons:**

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-

hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

**A. Attribution of Adverse Events:**

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (Dr. Janice Hwang) 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).
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).

**Plan for Grading Adverse Events:** The following scale will be used in grading the severity of adverse events noted during the study:
a) Mild adverse event
b) Moderate adverse event
c) Severe

**Plan for Determining Seriousness of Adverse Events:**
**Serious Adverse Events:** In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:
A is life-threatening OR
B. results in in-patient hospitalization or prolongation of existing hospitalization OR
C. results in persistent or significant disability or incapacity OR
D. results in a congenital anomaly or birth defect OR
E. results in death OR
F. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, OR
G. adversely affects the risk/benefit ratio of the study

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

**Plan for reporting Reportable Adverse Events and other unanticipated problems involving risks to subjects or others to the IRB**

The principal investigator will report the following types of events to the IRB: a) adverse events that are serious or life-threatening AND unanticipated (or anticipated but occurring with a greater frequency than expected) AND possibly, probably or definitely related to the



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

drug/device/intervention; and b) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website.

**Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s)**
For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

All Co-Investigators listed on the protocol.
National Institutes of Health

The principal investigator (Dr. Janice Hwang) 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.

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.
**Primary endpoints:** Primary endpoints include (a) HbA1C levels and CGM measures of glycemia; (b) baseline intracellular fructose and glutathione levels at 0, and 12 weeks; (c) intracellular fructose and glutathione levels following hyperglycemic clamp at 0 and 12 weeks.
**Secondary endpoints:** Concentrations of hormones and polyol metabolites will be correlated with structural changes/inflammatory changes on MRI.

**Sample size:** Because endogenous intracellular fructose production in the brain has never been shown in humans, the studies described in this proposal are exploratory studies. As such, sample sizes and statistical comparisons may not provide adequate power for definitive hypothesis testing. Because intracellular polyol levels will likely be equal to or higher than CSF levels, we expect that the percentage changes as measured by MRS will match those (or be even larger) than observed in CSF.
**Statistical analysis:** Before statistical testing, all variables will be tested for normality of distribution. For between-group comparison, ANOVA and t-tests will be used for continuous variables. Within subject comparisons at baseline and following hyperglycemia will be made with paired t-tests (parametric) and Mann-Whitney U (non-parametric) as well as repeated measures ANOVA as appropriate.

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

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

### A. 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).

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 for Insulin and Dextrose**
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

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.

Regular insulin is a polypeptide hormone structurally identical to human insulin synthesized through rDNA technology in a special non-disease-producing laboratory strain of Escherichia coli bacteria. Humulin R U-100 is a sterile, clear, aqueous, and colorless solution that contains human insulin (rDNA origin) 100 units/mL, glycerin 16 mg/mL and metacresol 2.5 mg/mL, endogenous zinc (approximately 0.015 mg/100 units) and water for injection. The pH is 7.0 to 7.8. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH.

CLINICAL PHARMACOLOGY
Regulation of glucose metabolism is the primary activity of insulin. Insulin lowers blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis, proteolysis, and gluconeogenesis, and enhance protein synthesis and conversion of excess glucose into fat. With intravenous use, the pharmacologic effect of regular insulin begins at approximately 10 to 15 minutes and terminates at a median time of approximately 4 hours (range: 2 to 6 hours) after administration of doses in

the range of 0.1 to 0.2 units/kg. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual.

CLINICAL STUDIES
Intravenous use of regular insulin
The intravenous administration of Humulin R U-100 was tested in 21 patients with type 1 diabetes. The patients' usual doses of insulin were temporarily held, and blood glucose concentrations were maintained at a range of 200 – 260 mg/dL for one to three hours during a run-in phase of intravenous Humulin R U-100 followed by a 6-hour assessment phase. During the assessment phase patients received intravenous Humulin R at an initial dose of 0.5 U/h, adjusted to maintain blood glucose concentrations near normoglycemia (100 to 160 mg/dL). All patients achieved near normoglycemia during the 6-hour assessment phase. At the endpoint, blood glucose was within the target range (100 to 160 mg/dL) for 20 of 21 patients treated with Humulin R U-100. The average time (± SE) required to attain near normoglycemia was 161 ± 14 minutes for Humulin R U-100.

INDICATIONS AND USAGE
Regular insulin is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 1 and type 2 diabetes mellitus. Regular insulin may be administered intravenously under proper medical supervision in a clinical setting for glycemic control

CONTRAINDICATIONS
Regular insulin is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Humulin R U-100 or any of its excipients.

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? Administer through invdrug pharmacy at yale, through funding

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** | ☐ **Yale Cancer Center** |
| ☐ **CMHC Pharmacy** | ☐ **West Haven VA** |
| ☐ **PET Center** | ☐ **None** |
| ☐ **Other:** | |

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

**B. DEVICES: N/A**



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

## SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

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

a. targeted for enrollment at Yale for this protocol: 30 subjects total

b. If this is a multi-site study, give the total subjects targeted across all sites: N/A

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

☐ Flyers
☐ Posters
Telephone☐ Letter
Television
☒ Medical Record Review
☒ Departmental/Center Newsletters
☒ YCCI Recruitment database
☐ Other (describe): Mychart, JDAT

☒ Internet/Web Postings
☒Mass E-mail Solicitation
☒ Departmental/Center Website
☒ Departmental/Center Research Boards
☐ Web-Based Clinical Trial Registries
☒ Clinicaltrials.gov Registry (do not send materials to HIC)

☐ Radio
☒
☐
☐ Newspaper

**3. Recruitment Procedures:**

a. Describe how potential subjects will be identified.

Potential subjects will be identified as indicated below using the methods identified in #2 above:
• Self-Identify
• Provider Referrals
• Study Team Members
• Existing registries, studies, and websites where participants have previously provided informed consent or a request to be contacted for research utilizing their preferred method of contact when known.
• Joint Data Analytics Team (JDAT)
How these options will be utilized is further described in section "b" below

b. Describe how potential subjects are contacted.

Self-Identify and Provider Referrals: Participants will self-identify using IRB approved recruitment materials that will be posted locally. Recruitment materials will display the contact information of the study team in addition to a description of the study. Potential participants may also be approached by their medical provider. Additionally, participants may be approached by study personnel at community events, or at various locations where potentially eligible patients are seen when facilitated through the participant's treatment team, including at Yale SOM, YNHH, YMG. These sites include the Adult Endocrine Clinic/Yale Diabetes Center (YDC), community clinics and Yale University Health.

• Recruitment through Existing Registries and Studies: In addition, the YDC diabetes registry will be used to identify eligible patients and contact them with IRB approved materials by phone, email, since this category of patients has already given their consent to be contacted for potential trials. Furthermore, participants will be recruited through the YCCI website/registry/Help Us Discover and ClinicalTrials.gov website. Participants may also be identified through their previous participation in HIC #0108012609, 2000021046, 2000020059, 2000020041 and 1408014461. Study personnel will use MyChart, traditional mail, telephone or email of patients recruited through this method. If the EPIC registration module provides a preferred method of contact, that method will be utilized. If the participant is not registered in

EPIC but has expressed interest in a research study by calling, emailing, filling out an online questionnaire, or speaking with study personnel face-to-face, the patient will be contacted by their means of preference, if stated.

- Recruitment through JDAT: The Joint Data Analytics Team (JDAT) will also be used to query eligible patients in EPIC based on the eligibility criteria. JDAT will also be used to identify potential subjects with the various permutations of diagnosis codes related to type 2 diabetes. JDAT will identify and send a study communication to potential participants based on these criterion that fall within the following time period: the last 2 years. Potential participants who do not use MyChart will receive a paper mailing including information about the study. JDAT will not identify the potential participants to the researchers, and therefore the researchers will receive no identifiable information from JDAT.

- Messaging to Study Participants: The following wording will be used in the letter or MyChart message patients receive via JDAT describing the study and inviting them to participate:

"You are receiving this [MyChart message or this letter] because you were diagnosed with type 1 or type 2 diabetes. You may be eligible to participate in a diabetes research study conducted by Yale University investigators to better understand the role of sugar in the brain. . The Yale New Haven Health electronic health record system has searched medical conditions to find people who may be good matches for research studies. No one has looked at your record and no information has been shared with any research doctor or research team member. Just because you received this message does not mean that you are in a research study or that you have to decide to be in this or any study. To opt-out of research, including opting out of receiving future messages about research studies, please email optout@yale.edu or call 1-877-978-8348 and select option #3."

The message/mailing will also include the following consent information:

"You are invited to take part in a research study designed to look at the role of sugar in the brain. Approximately 30 subjects with diabetes (type 1 and type 2) will be enrolled in this study. The study involves 12 weeks of one-on-one diabetes management with an endocrinologist with the goal of improving your diabetes control. It involves a screening history, physical exam, blood work, and MRI scans of your brain while blood sugar levels are adjusted. Participants will also receive exercise and dietary counseling and will be provided with the FreeStyle Libre continuous glucose monitor (CGM) during their time in the study".

Confidentiality and Privacy: No identifiable information will be obtained in connection with this study. Any personal health and financial data gathered will remain confidential and will be stored on a password-protected computer, only accessed by study personnel. When the results of the research are published or discussed, no information will be included that would reveal your identity. We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to participate, please contact the study coordinator at 203-785-6222.



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

Possible Benefits: Research is not designed to benefit you directly. However, knowledge gained from the results may help us to better understand Type 1 and Type 2 diabetes. In addition, you potentially might have better glycemic control at the end of the study, you will have personalized care/counseling and use of CGM.

Participation in this study is completely voluntary. You are free to decline to participate, to end participation at any time for any reason, or to refuse to answer any individual question at any time. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits).

Questions: If you have any further questions about this study, you may contact the investigator, Janice Hwang, at 203-785-6222. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688."

In MyChart, patient's will view this following message:

The Yale New Haven Health electronic health record system has searched medical conditions to find people who may be good matches for research studies. No one has looked at your record and no information has been shared with any research doctor or research team member. Just because you received this message does not mean that you are in a research study or that you have to decide to be in this or any study.

Title of study, Phase or type of study: Investigating the role of the polyol pathway in the central nervous system production of fructose
Principal Investigator: Dr. Janice Hwang
Study Coordinator: Jessica Leventhal Phone # 2037856222

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.

c. 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.

d. Who is recruiting potential subjects? All Research Team Members

**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.

**5. Future Request**

Subject that you will request the participants to agree to be contacted for future studies as indicated in the consent.

**6. 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 ii=021

☐ 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

**7. 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

**8. 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____



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

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

We will need the volunteers' full name, address, date of birth, and phone numbers to schedule a screening visit at the Hospital Research Unit. For volunteers who have signed up to be contacted through the YCCI and the Yale Diabetes Registry, we also would like to be able to review their medical records to determine whether they 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) to be greater than18 and their weight to be less than 285 pounds. By reviewing this information prior to contact, we will be able to avoid contacting subjects that may not be included in the study.

**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.*

9. **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
   ☐ HIPAA Research Authorization Form

10. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent. This information is maintained in IRES

11. **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.
    During the screening session the informed consent form and study details will be reviewed by a study physician. The study will be described to the subject in detail, including the purpose and potential risks associated with the study. The subject will be asked to read the informed consent form. All subjects who will be asked to volunteer are informed that no immediate personal medical benefits will be derived from participation. 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



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

physician will ask the subject to sign the informed consent form. 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 outlining the risks and benefits of participation in this study.

**12.** 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.

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.

**13. 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 Compound Consent and Authorization form for subjects that explains each part of the study.

**14. Non-English Speaking Subjects:** Our fluent Spanish speaking study member will provide potential subjects with a face-to-face interview. At that time, the study member 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. A certified Spanish translated consent form as well as any additional recruitment materials will be provided during interview.

**15.**

**16. 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?



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

☐ 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?
☐ 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? Waiver is for recruitment/screening purposes only
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 Entire Study (Note: If PHI is collected, information here must match Section VII, question 6.)**

## SECTION VIII: PROTECTION OF RESEARCH SUBJECTS



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

**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 hematocrit, A1c, LFTs, TSH, creatinine

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 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.

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting quarterly reviews. During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. All participants will be assigned a coded identification number, which will link their blood and CSF samples to their collected data.

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?

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.

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



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021

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? Yes, granted by the NIH.
h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? None

## SECTION IX: 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.)

Non-diabetic and diabetic subjects will have no direct benefit from the studies. However, this work will benefit the scientific community, and therefore society, as it will provide important insights into the CNS effects of hyperglycemia.

## 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.

$25 for the screening visit
$50 for wearing the CGMS at week -1
$150 for overnight admission/Hyperglycemic clamp/MRS scans at week 0 (Optional)
$50 for wearing the CGMS at week 11
$325 for overnight admission/Hyperglycemic clamp/MRS scans at week 12 (Optional)

Payments will be given via a Bank of America pre-paid debit card using the new Yale electronic payment service. After the first payment milestone (first study visit) subjects will receive a card in the mail which will need to be activated over the phone, any subsequent milestones

payments will automatically add additional funds to the subject's card. Reimbursement for incidental expenses will also be provided.

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 medical evaluation including physical examination and study related laboratory work will be performed at no additional cost to the study participant.

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?

   Medical treatment will be offered to the subjects for any physical injuries that they receive because of participating in this research. Yale School of Medicine and Yale-New Haven Health does not provide funds for treatment of research-related injury. However, the subject or his/her insurance company is responsible for the cost. Federal regulations require that subjects be told that if they are physically injured, no additional financial compensation is available. Subjects do not give up any legal rights by signing the consent form.



APPROVED BY THE YALE UNIVERSITY IRB 6/14/2021