Principal Investigator	**Mary Elizabeth Patti, M.D.**
Study Title	**Pilot Study – Cognition in Patients with Hypoglycemia, without Diabetes**

I. Objectives

The goal of this study is to evaluate the effect of recurrent hypoglycemia on cognitive function in patients who do not have diabetes. This pilot aims to identify the cognitive domains of interest, as well as inform the development of a future battery of assessments, which could be replicated in a larger sample. Ultimately, this information may have important implications for assessment of risk, patient teaching methods, and treatment, to help avoid potential cognitive decline. We will test the hypotheses that (1) recurrent hypoglycemia in patients without diabetes is associated with impairment in cognition, and (2) patients with a history of post-bariatric hypoglycemia (PBH) have impaired performance on cognitive tests as compared with patients without known hypoglycemia.

II. Background

Hypoglycemia in the absence of diabetes is generally classified in relation to its timing, and can manifest in the fasting state, with exercise, or most commonly, after meals (reactive hypoglycemia). Some patients present with predominantly one type, while others may present with mixed patterns. While there are conditions which have been identified that cause, or contribute to hypoglycemia, diagnosis can be challenging, and for some the precise etiology of hypoglycemia remains unknown.

Despite the heterogeneity of this population, hypoglycemia yields similar symptoms and may result in some common long-term outcomes. When hypoglycemia is severe it causes not only distressing adrenergic and cholinergic symptoms, but also neuroglycopenia, with symptoms including changes in thinking, memory impairment, brain fog, headaches, and difficulty concentrating or maintaining attention. When recurrent, hypoglycemia unawareness can develop, impairing safety and increasing risk for disability, syncope, arrhythmias, seizures, coma, and death. Patients often report multiple episodes with alteration in, or loss of consciousness. Impaired cognition during acute hypoglycemia may result in inability to self-treat, thus, requiring assistance from others to both procure and administer treatment. Moreover, many individuals with recurrent hypoglycemia are disabled due to inability to perform job-related tasks, or endorse difficulty in meeting the cognitive demands of their profession, or activities of daily life.

Hypoglycemia has been extensively studied in the population of patients with diabetes; however, there is a paucity of literature describing cognition in patients with hypoglycemia, without diabetes. For patients with diabetes, hypoglycemia is induced by medications, often in combination with behavioral factors such as reduced food intake or increased activity. Hypoglycemia in the absence of diabetes can be unpredictable, even when patients are following all recommendations provided. Management of this condition can be onerous for patients. Options for therapy are limited, and medications available are not always well tolerated. Even with the best-available treatment, hypoglycemia can be a chronic, lifetime condition. Thus, the effect that this repeated neurologic insult exerts on cognition is important to understand to assess risk, improve patient teaching methods, and optimize treatment, to help avoid potential cognitive decline.

Preliminary Data:

Studies of cognition in relation to hypoglycemia have generally been focused on diabetes. For example, in patients with type 1 diabetes, recurrent hypoglycemia is associated with impaired memory, executive function, language, and psychomotor speed. It is notable that severe hypoglycemia in patients with type 1 diabetes has been positively correlated with the severity of depressive symptoms, and that a bi-directional relationship has been shown to exist between severe hypoglycemia and depressive symptoms. Depression is known to have a deleterious effect on cognition. In patients with obesity, BMI is negatively correlated with performance on cognitive assessments. Moreover, obesity is an independent risk factor for poorer neurocognitive outcomes, and is associated with increased risk for dementia. Inflammation, vascular effects, and higher adipose-derived cytokine / hormones have been implicated as potential mechanisms implicated in the white matter changes, disturbances of blood-brain barrier integrity, and brain atrophy observed in this population.

Research has shown relatively prompt improvements in memory, executive function, and language with weight loss after bariatric surgery. However, at least two studies have failed to show any improvement in cognition after bariatric surgery. One limitation to the current literature is duration of follow-up, with most studies assessing cognition at one year or less post-surgery. The longest duration of follow-up is in the Longitudinal Assessment of Bariatric Surgery (LABS) cohort; one study in this cohort reported improvements in executive function and attention after weight loss; contrary to expectations, post-operative improvements in HbA1c were not associated with improvements in cognitive function. The authors acknowledged that hypoglycemia following bariatric surgery could have been an unmeasured contributor to cognitive dysfunction.

Thus, for patients who have hypoglycemia without diabetes, whether induced by bariatric surgery or due to other conditions, there is a paucity of data. There are no known published studies specifically investigating the potential effect of recurrent hypoglycemia on cognition in these patients. Also, the presence of depressive symptoms, as well as their potential relationship with cognitive function, has not been reported on in individuals with PBH, or in those with hypoglycemia in the absence of diabetes.

Hypoglycemia Effect on the Brain:

The brain is particularly vulnerable to the effects of hypoglycemia, as it is the organ in the body with the highest demand for glucose. Neuronal function is compromised whenever the supply of glucose is not sufficient to meet the demand. Within the brain, the areas which are the most metabolically active have been found to be the most susceptible to the effects of low glucose, such as the hippocampus and prefrontal cortex – areas critical for memory, executive function, and attention.

In healthy individuals hypoglycemia induces an adaptive neurohormonal, counterregulatory response, that results in alterations in metabolism aimed to restore normoglycemia. Low glucose levels are sensed in the ventromedial hypothalamus, ultimately triggering release of counterregulatory hormones and activation of the parasympathetic and sympathetic nervous system.

Research in animal models has revealed that when glucose depletion is sustained, cascade of impaired mitochondrial respiration, excitotoxicity, oxidative stress, generation of reactive oxygen species (ROS), lipid peroxidation, and microglial activation can result in cell death. While the entire cortex is affected, the hippocampus has been found to be significantly more vulnerable to these effects. Cellular damage can also occur during reperfusion with rising glucose concentrations.

Hypoglycemia also induces a pro-inflammatory, pro-thrombotic state, as evidenced by increases in pro-inflammatory mediators (IL6, IL-8, IL-1B, TNF-alpha), enhanced platelet activation, platelet aggregation, p-

selectin, and decreased fibrinolysis. Acutely, vasoconstriction, endothelial dysfunction, and white blood cell activation, also occur and may have cumulative effects on atherogenesis and thrombotic complications, including central ischemia. Recurrent / moderate hypoglycemia has been found to aggravate brain damage in post-ischemic rats.

Collectively, these data highlight several important points: 1) recurrent hypoglycemia can result in unawareness, with episodes possibly more frequent than appreciated by patients, leading to clandestine damage; 2) hypoglycemia can directly result in cell damage or death, neuroinflammation, and a pro-thrombotic state; 3) hypoglycemia in patients with diabetes has been shown to have serious and detrimental cognitive consequences, both for short-term patient safety and long-term cognition; 4) it is possible that patients undergoing bariatric surgery may have a pre-existing neural vulnerability due to prior history of obesity, with subsequent hypoglycemic insults; 5) understanding the impact of recurrent hypoglycemia on cognition in this understudied group is essential for risk assessment, raising provider awareness, developing more effective patient teaching strategies, and informing treatment, to help avoid potential cognitive decline.

In this study, we will assess and compare cognitive function in patients with hypoglycemia without a history of diabetes, as well as in RYGB patients with and without PBH. We will also assess and compare depressive symptoms between groups, and their potential relationship to cognition.

III. Study Design

a. Recruitment Methods

Participants will be recruited into 4 groups: (1) patients with hypoglycemia after upper gastrointestinal surgery, recruited from the Joslin Hypoglycemia Clinic, (2) asymptomatic post-bariatric patients, recruited from postoperative surgical clinics at Brigham and Women's Hospital, (3) patients with hypoglycemia and no history of upper gastrointestinal surgery, and NO current diagnosis of diabetes or pre-diabetes, recruited from the Joslin Hypoglycemia Clinic, (4) participants without hypoglycemia or upper gastrointestinal surgery (controls), recruited by local advertisement. Some participants may be recruited from other hypoglycemia studies at Joslin.

The Joslin Hypoglycemia Clinic has emerged as a referral clinic for patients with hypoglycemia from around the country, and particularly the New England region. Over 300 individuals have been evaluated in this clinic since its inception, and new patient referrals continue to increase as the awareness of hypoglycemia is increasing among patients and physicians alike. Thus, we have immediate access to a large pool of highly motivated patients.

Under a HIPAA waiver, a list of all potential candidates will be generated from the Joslin Electronic Medical Records every three months. Candidates will be sent a letter explaining the study in simple terms, including a phone number to call in order to "opt-out". The letter may be mailed or given to the patient at the time of a clinic visit by clinic personnel. If the potential research subject does not decline further contact in two weeks, the study staff will invite him/her to participate in the study by telephone or at the time of their next visit. Prospective study subjects may also be informed of the study by their Joslin clinicians, who may provide them with information on how to contact study coordinators. Patients who agree to participate will be screened by telephone or in person to determine eligibility. Subjects who meet screening criteria will be mailed or given an informed consent form and will be invited to come to the Joslin CRC for the study visit. Written consent will be obtained after explaining again the purpose and procedures of the study. In the initial contact and

again at the time of the screening visit, study subjects will be encouraged to ask questions and they will be reassured that they may withdraw from the study at any time without impact on clinical care.

Participants will also be recruited via Research Match, a secure online recruitment tool. Research Match allows for recruitment searches for individuals who have registered on their site and are interested in being contacted with research opportunities. An informational email about the study is then sent out through the Research Match portal to the potential participants whose information is de-identified in the initial search. For those who respond to the initial email that they are interested (by clicking within the message), their contact email will be sent to the study specific Research Match portal (password protected), and the study team will respond to each person individually with a follow-up email to schedule phone screening. For those that are not interested, they are able to click "not interested" and opt out of further communications, or not respond at all to the initial recruitment email.

The hypoglycemia patient population is highly motivated by the frustration of this disease; we anticipate no difficulty in recruitment or retention for this population. As involvement will include initial telephone or in-person screening and a single study visit with history and testing, we do not anticipate significant attrition in this protocol. Our study team has extensive experience with recruitment and retention of post-bariatric patients in the context of the SLIMM-T2D and ARMMS-T2D longitudinal clinical trial, and in prior studies of post-bariatric hypoglycemia.

b. Inclusion and Exclusion Criteria

Initial general screening will be performed during an initial phone or in person visit (e.g. during a clinical visit), which will include administration of the Patient Health Questionnaire-2 (PHQ-2).

Individuals who appear to meet criteria will be invited for the study visit, when a detailed history will be performed by study clinicians. Inclusion and exclusion criteria will be reviewed after the visit to determine study eligibility.

Inclusion criteria:

1. For PBH group: Males or females diagnosed with ongoing post-bariatric hypoglycemia with prior episodes of neuroglycopenia, unresponsive to dietary intervention (low glycemic index, controlled carbohydrate portions).
2. For post-RYGB without hypoglycemia: Males or females with history of RYGB and no history of symptomatic hypoglycemia.
3. For hypoglycemia without a history of upper gastrointestinal surgery group: Males or females diagnosed with ongoing hypoglycemia with prior episodes of neuroglycopenia, and without a history of prediabetes or diabetes
4. For non-surgical controls only: Males or females with no history of upper gastrointestinal surgery and no history of hypoglycemia, prediabetes, or diabetes.
5. Age 18-70 years of age, inclusive, at screening.
6. Willingness to provide informed consent and attend one study visit.

Exclusion criteria:

1. Active treatment with any diabetes medications, except for acarbose.
2. History of cerebrovascular accident.
3. History of a traumatic brain injury not related to hypoglycemia.
4. A score of 6 on the PHQ-2.

5. Active alcohol abuse or substance abuse.
6. Known insulinoma, gastrinoma or other neuroendocrine tumor.
7. Having undergone same / similar cognitive assessments within the last calendar year.

There will be no involvement of special vulnerable populations such as fetuses, neonates, pregnant women, children, prisoners, institutionalized or incarcerated individuals, or others who may be considered vulnerable populations.

Please note that duration of hypoglycemia will not be included in either inclusion or exclusion criteria, but will be included as a covariate in our analyses.

c. Number of Subjects

Participants will be recruited into 4 groups, (1) patients with PBH, recruited from the Joslin Hypoglycemia Clinic, (2) asymptomatic post-RYGB patients, recruited by advertisement flyers at postoperative surgical clinics at local hospitals (e.g. Brigham and Women's and Beth Israel Deaconess Hospitals), (3) patients with hypoglycemia and no history of upper gastrointestinal surgery, and NO current diagnosis of diabetes or pre-diabetes, recruited from the Joslin Hypoglycemia Clinic, (4) controls, recruited by local advertisement. We anticipate screen failure and drop out rate of 20% each. We plan to enroll patients with hypoglycemia continuously over the next 4 years. We anticipate performing cognitive testing in up to 20 participants in each of the four groups, based on availability of grant funding.

d. Study Timelines

The total duration of the study will be one to three weeks: one screening call and one study visit. We anticipate recruitment to continue for up to 4 years, concurrent with grant funding.

There is no plan in the current study to re-contact patients after the study has been completed.

e. Study Endpoints

Primary endpoints:

- Assessment of memory

Secondary endpoints:

- Assessment of executive function, language and psychomotor speed
- Assessment of depressive symptoms using the Beck Depression Inventory (BDI)
  Analysis to assess the effects of participant group, and BDI scores (depressive symptoms), on standardized quantitative scores for each cognitive domain assessed (memory, executive function, language and psychomotor speed).

f. Study Procedures

An initial pre-screening phone call will occur with focus on inclusion, and exclusion criteria. The PHQ-2 will be administered as part of the screening process to assess for the presence, on a nearly daily basis, of both of the two cardinal symptoms of major depressive disorder. Individuals will be told that as part of the screening process they will be asked 2 questions about symptoms related to their mood. For individuals who

are ineligible due to their PHQ-2 score, the study physician or nurse practitioner will offer to contact their primary care physician and recommend referral for mental health assessment. PHQ-2 forms completed via phone for those who are not eligible or who do not want to participate will be disposed of in a secure waste bin (for shredding) immediately after screening.

The study visit will then be scheduled for eligible participants. At this visit, we will test the hypothesis that hypoglycemia is associated with changes in cognitive function in the domains of memory, language, executive function, and psychomotor speed. Secondarily, we will also test the hypothesis that recurrent hypoglycemia is associate with higher scores on the BDI (depressive symptoms), and that BDI scores will be negatively correlated with cognitive function.

Sites: Participants will be recruited at Joslin Diabetes Center and via advertisement. All clinical evaluation will be performed on the clinical research unit of the Joslin Diabetes Center.

Study Visit: After informed consent, patients will undergo a history, and EKG, with emphasis on inclusion/exclusion criteria. Blood glucose will be assessed by capillary glucose. Prior to cognitive testing, participants will also be asked to complete the BDI, measuring depressive symptoms. Participants will be offered breaks of up to 10 minutes between components of the assessment.

Cognitive Testing: Prior to cognitive assessment, blood glucose levels will be assessed by capillary glucose testing. If glucose level is less than 70 mg/dL, glucose tablets and a snack will be provided, and glucose levels will be rechecked every 15 minutes until levels exceed 80 mg/dL. If during the course of testing a patient develops symptoms of hypoglycemia, blood glucose levels will be checked, and if needed, treated as above. Testing will not be resumed until glucose levels exceed 80 mg/dl.

The neuropsychological tests include:

a) Intelligence

The National Adult Reading Test (NART) is composed of a list of 50 words that progress in level of difficulty. The participant is instructed to read each word aloud while the examiner tracks the number of errors made. This test was designed in order to estimate premorbid intelligence based on the test taker's word familiarity.

b) Working Memory and Attention

To assess working memory, we will use the Letter-Number Sequencing subtest from the Wechsler Memory Scale III. In this task, the examiner instructs the participant to repeat a string of mixed letters and digits back in alphabetical and ascending numerical order. This string gets progressively longer and thus more difficult as the participant has more digits and letters to sort using working memory.

c) Rey Auditory Verbal Learning Test

The Rey Auditory-Verbal Learning Test (RAVLT) is a cognitive task aimed at assessing verbal memory and delayed memory. During this task, a list of 15 words is repeated 5 times. The participant is asked to recall as many words from the list as possible in no specific order. After the fifth cycle of repeating and recalling the first list, a second list of 15 words is read. The participant must recall as many words from the second list as possible. A delayed recall trial then occurs 20 minutes following the end of the previous trial where the participant is asked to recall as many words as possible from the first list.

d) Delis-Kaplan Executive Function System

The Delis-Kaplan Executive Function System (DKEFS) measures executive function and focuses on verbal and nonverbal concept formation, flexible thinking, and problem solving. We will administer Trail Making tests tasks (with Number-Letter Switching condition), the Stroop Task, and Verbal Fluency Task. Trail making tasks

are scored by time to complete the task plus errors, and allow us to assess cognitive flexibility and multitasking.

e) Grooved Pegboard

The grooved pegboard is a task to assess psychomotor speed and efficiency. It is scored according to time for completion combined with the number of dropped pegs. The validity of this task as a measure of motor speed and psychomotor processing comes from its demonstrated relationship to other tests of motor speed as well as to measures of attention and perceptual speed and nonverbal reasoning.

Data Collection and Storage: Research material for this study will consist of data obtained during the study visit, including medical history, and cognitive testing. Data will be recorded on case report forms, as well as cognitive testing forms, and stored in participant-specific binders. Data will be stored at the Joslin Diabetes Center in locked cabinets and rooms accessible only to study staff. All study participants will be assigned a unique study identifier. Publications or public presentations will not provide any information which could identify individual study participants or their families. Data analysis will commence once the entire cohort has been studied.

g. Data and Specimen Banking

After study completion, primary written materials (cognitive battery scoring and answer sheets) will be stored in locked filing cabinets accessible only to current study team members, and data will be stored on shared drives accessible only to current study team members approved by IRB. Identifiers will not be shared with anyone beyond the study team.

h. Data Management

Study Records Retention and Storage

Study documents will be retained for at least 10 years following study conclusion.
Each participant will be assigned a unique study ID acrostic and number. Study data will be identified with this study ID, not with participant's names. Study documents will be stored in locked file cabinets or locked storage rooms and only authorized study staff will have access to these files. Electronic data will be stored on a password-protected network accessible only to authorized staff. Only deidentified information will be transferred between sites. All data transfer between study sites will be performed via secure encrypted file transfer (e.g. MoveIt).

Data Monitoring

Designated personnel from the study site will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the study is conducted, and data are generated, documented, and reported, in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

Analysis plan for the primary study endpoints

(1) The distributions of relevant variables will be examined for outliers and to determine appropriate statistics for use. χ^2, Kruskal-Wallis, and ANOVA tests will be used to examine categorical differences.
(2) ANOVA tests will be used to assess the effects of group standardized quantitative score on each of the assessed cognitive domains.
(3) Cohen's delta (*d*) may be used to assess effect size between groups

Sample size and power.

Since the cognitive assessments represent a pilot study, and no data are available in a similar population to guide power analysis, our sample size is guided by anticipated feasibility of recruitment.

i. Confidentiality

Representatives of the IRB or authorized representatives from Joslin Diabetes Center, and the NIH may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study team will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

j. Provisions to Monitor the Data to Ensure the Safety of Subjects

Data safety and monitoring plan. This plan will be implemented and strictly followed. The PI will be responsible for ensuring that recruitment and phenotypic analyses are conducted in accordance with the IRB-approved protocol and will review all adverse events and serious adverse events. The Joslin PI will also perform a periodic review of all data from phenotypic analyses. The members of the study team will conduct regularly scheduled meeting approximately weekly as well as on an as-needed basis to review status of the study inclusive of enrollment, oversight of informed consent, general conduct of the study as well as reporting of any complications as needed to the IRB. Safety data (including AE/SAE logs and protocol deviations) will be collected and reviewed every 3 months or as needed.

Data quality. Interim analyses will be conducted on a quarterly basis to assess the quality of data through descriptive statistics. Attempts will be made to fill missing data, verify outliers, and reconcile data discrepancies by assessing medical records or recontacting participants. If data quality is not satisfactory, the need to follow GCP guidelines for data collection will be reinforced with study staff and retraining will be performed as needed. Once a year, study staff will conduct an internal clinical monitoring to assess database accuracy relative to source documents, as well as adherence to regulatory and study procedures and maintenance of the study regulatory binder. Emphasis will be placed on the process of consenting participants, compliance with regulatory requirements and study protocol, values of key endpoints, and identification of AE that may not have been reported. Source documents will be stored for at least 10 years after the study ends.

Definition of Adverse Events. Adverse events (AE's) will be defined as untoward medical events related to the procedures done during the study visits. A Serious Adverse Event (SAE) is any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability, or is a congenital anomaly/birth defect. Important medical events that do not fall into the above categories may also be considered an SAE when, based on medical judgment, such events may jeopardize the patient's safety and require medical/surgical intervention to prevent one of the outcomes listed in the SAE definition. The term SAE is not intended as a measure of severity or intensity. All AE or SAE that occur after the time of informed consent will be reported. The seriousness of adverse events will be ascertained by the study staff according to the criteria above and the

need for further evaluation, follow-up, or referral. The relationship between study participation and AEs will be determined according to the following criteria:

- **Not related** – temporal relationship of the onset of the event, relative to study participation, is not reasonable or another cause can by itself explain the occurrence of the event.
- **Possibly related** – temporal relationship of the onset of the event, relative to study participation, is reasonable but the event could have been due to another, equally likely cause.
- **Probably related** – temporal relationship of the onset of the event, relative to study participation, is reasonable and the event is more likely explained by the study treatment than by another cause.
- **Definitely related** – temporal relationship of the onset of the event, relative to study participation, is reasonable and there is no other cause to explain the event.

Reporting of AE and safety analyses. AE and SAE will be recorded on an ongoing basis in an AE/SAE log, and tabulated yearly at the time of the annual report to the Joslin Committee on Human Studies (CHS), unless an SAE meets the criteria for immediate report to the CHS (i.e., an unexpected SAE that is deemed to be possibly/probably/definitely related to study participation). Since this is an observational study, we do not anticipate an excess of AEs/SAEs in one treatment group as compared to another. Nonetheless, if the number of AEs/SAEs occurring in relation to the study visit appears to be excessive in comparison to what one would reasonably expect, we will thoroughly review our study operations to identify and rectify possible problems and will report results to the Joslin CHS.

Protocol Deviations and Violations. A Protocol Deviation is defined as any change, divergence, or departure from the approve study protocol that does not affect the participant's safety, rights, welfare or the integrity of the study and its resultant data. A Protocol Violation is defined as a protocol deviation that may affect the participant's rights, safety, or wellbeing and/or the completeness, accuracy, and reliability of the study data. Deviation will be reported to the Joslin CHS at the time of continuing review whereas violations will be reported as soon as study personnel are aware of the event. The PI will keep an internal protocol deviation and violation log that will be forwarded to the IRB at the time of continuing review.

Data and Safety Monitoring Board. Since this is a low-risk, single-center observational study, the oversight of an external Data Safety and Monitoring Board is not deemed necessary.

Rules for stopping the trial. The trial may be stopped by the study team or CHS if the number of unanticipated study-related SAE appears to be excessive in comparison to expected numbers.

k. Withdrawal of Subjects

Subjects will be withdrawn from the research study without their consent for any of the following reasons:

a. Subject decision to withdraw consent for study participation
b. New diagnosis of exclusionary medical condition
c. Intolerable adverse event as judged by investigator and participant
d. If the PI feels the subject is not following the study protocol / instructions provided at the study visit

Participants will be notified of the reasons for the termination. Data collected until the point of withdrawal will be analyzed, unless the participant specifically requests that data be removed from analysis.

IV. Risks to Subjects

Potential risks regarding participation include risks associated with:

Depression Assessment:

PHQ-2: There may be a small potential risk of some discomfort or sadness when answering the 2 questions of the PHQ-2 during eligibility screening; however, investigators believe that the benefit of identifying symptoms of severe depression allowing for referral to treatment outweighs this risk.

BDI: Reading / responding to questions on the BDI about the presence and severity of depressive symptoms may cause sadness or be mildly distressing for some participants. If concerns for depression are revealed during the study visit, the study physician or nurse practitioner will offer to contact the participant's primary care physician so that they may work together on a mental health follow-up plan.

Cognitive Testing: Certain assessments may be challenging, and possibly mildly distressing for some patients related to perception of their performance. Patients will be reassured during the testing that it is expected that the tasks they are asked to perform may be difficult, and their best effort is all that is required.

Screening Tests and Procedures: It is possible that as a result of the screening process a subject may become aware of a health disorder. Every effort will be made to help the participant obtain the care that they need. Results will be shared with participants, and if they consent, with their primary care providers.

Breach of Confidentiality: While every effort will be made to protect the confidentiality of participant identifiable information, there is the potential loss of confidentiality by participating in this study.

Inconvenience and Unknown Risks: Participants may be inconvenienced by the time commitment involved in participation in the study. There may be other risks from this study not yet identified.

Participants can choose not to participate in this study and can withdraw consent at any time.

V. Potential Benefits to Subjects

The purpose of this study is to evaluate the effect of recurrent hypoglycemia on cognitive function in patients without diabetes. This project is not designed to be of direct benefit to any individual subject, although it is hoped that through the knowledge gained from these studies there will be general benefit to persons with or at risk of development of hypoglycemia, and in particular for those who report concerns about cognitive changes. Patients will not be provided results of cognitive testing. . As such, risks are appropriate in relation to the potential significant benefits for the significant number of persons with or at risk for hypoglycemia.

VI. Provisions to Protect the Privacy Interests of Subjects

The participants will be provided adequate time and private space to review the consent document and as much time as needed to ask questions about procedures. All study procedures will be performed in a private space. When reviewing participants' medical records, study staff will access the minimum necessary information needed for the study.

VII. Compensation for Research-Related Injury

There is no compensation provided to participants in the event of a research-related injury.

VIII. Economic Burden to Subjects

There will be no costs for subjects to participate in this study.
Participants will receive a parking voucher for the study visit and will receive $20 compensation for completing study procedures. If this testing is performed during a screening visit for another protocol, the $20 will be provided in addition to stipends from other studies.

IX. Consent Process & Documentation

Subjects will be recruited from the Joslin Hypoglycemia Clinic, and from local advertisements. The study will be explained to the potential subject initially in the clinical setting (in a private location) or during a telephone screening session by the study coordinator/recruiter. The informed consent process will be inclusive of various types of education and counseling opportunities including an in-person or telephone screening, allowing for general overview of the procedures as well as options available for all subjects expressing interest in participation.

Those still interested after in person or telephone screening will be scheduled for screening visit(s) at the clinical research center. The consent process will involve initial discussion of the purpose and scope of the research as well as risks and benefits. Ample opportunity will be provided for participants to read consent, share with family or other health care providers as well as have all questions answered by the Principal Investigator or their designated study staff prior to obtaining written informed consent using CHS- approved documents. The consent form will include a description of risks and benefits, alternative possible procedures, the availability of the investigating physicians throughout any study to discuss any concerns, the availability of CHS to discuss any concerns, and the fact that the patient can withdraw from the study at any time with no change in his/her standard treatment. There can be no changes in the protocol without the prior agreement of the CHS.

If the patient consents to enroll in the study, and the consent form is signed, further evaluation in the form of the medical and screening visit will take place to determine eligibility. One copy of the consent form will be retained by the principal investigator and one copy will be provided to the subject.

X. Vulnerable Populations

Vulnerable populations will not be studied.

XI. Drugs and/or Devices

Not applicable.

XII. Sharing of Results with Subjects

If screening history reveals new medical diagnoses of clinical significance, information will be shared with the participant and primary care physician. Results of cognitive testing will not be shared with participants or primary care physicians.

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