Joslin Diabetes Center

Committee on Human Studies

Application for Review and Approval of Research and Training Projects Involving Human Research

Principal Investigator: Mary Elizabeth Patti, MD

Co-Investigator(s): Amanda Sheehan NP, Kathleen Foster, RN

Project Title: Determining the Efficacy of Continuous Glucose Monitoring to Reduce Hypoglycemia and Improve Safety in Patients with Hypoglycemia after Gastric Surgery

Funding: Dexcom

Study Contact: Mary Elizabeth Patti, MD x1966

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1. PURPOSE OF PROTOCOL:

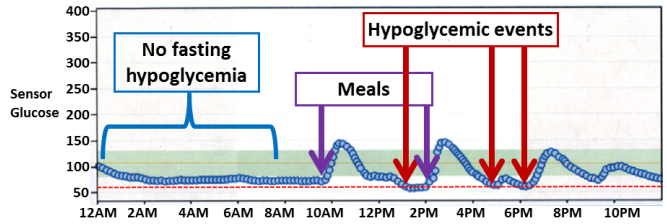
Obesity and related comorbidities, such as type 2 diabetes and cardiovascular disease, are increasingly recognized as major threats to individual and public health. Unfortunately, it is very difficult to achieve sustained weight loss with current medical approaches. Given these critical unmet needs, both clinicians and patients alike have embraced the results of recent controlled clinical trials demonstrating potent effects of bariatric surgical procedures to not only induce sustained weight loss but also to improve or normalize obesity-related comorbidities, including type 2 diabetes. Remarkably, surgery is superior to medical therapy for weight loss and diabetes, improves lifespan, and results in sustained improvement in glycemic control and reduced need for medications [1]. Such data have led to an explosion in the number of bariatric surgeries performed in the US – now over 200,000 annually [2]. While benefits of bariatric surgery are achieved with low operative mortality [3], longer-term intestinal and nutritional complications can occur.

One particularly challenging and sometimes severe complication of bariatric and other forms of gastric surgery (e.g. roux-en-Y gastric bypass, sleeve gastrectomy, gastrectomy for ulcer, fundoplication for reflux esophagitis) is hyperinsulinemic hypoglycemia [4]. While most commonly reported with roux-en-Y gastric bypass, hypoglycemia has also been observed with sleeve gastrectomy, a procedure increasingly employed in the US [5]. Prevalence estimates vary according to method of ascertainment, ranging from symptoms in 30% of patients to hospitalization required in <1%. However, studies utilizing continuous glucose monitoring suggest substantial hypoglycemia occurs even in completely asymptomatic patients post-RYGB, ranging from 29 to 71 min/day of sensor glucose values <60 mg/dL. In one study, 75% of 40

unselected patients following RYGB had sensor glucose values <55 mg/dL, compared with none in nonsurgical controls. Hypoglycemia during glucose or meal tolerance testing is also common (10–29%) after gastric bypass and is similarly observed after sleeve gastrectomy and other gastric procedures.

Hypoglycemia in this setting is defined as a documented plasma glucose level below 70 mg/dl in conjunction with symptoms and the relief of symptoms with the normalization of glucose levels. Hypoglycemia typically occurs within 1-3 hours after meals, particularly meals rich in simple carbohydrates, and is not present after prolonged fasting [6]. A typical pattern in the ambulatory state, as revealed by continuous glucose monitoring (CGM), can be seen in Figure 1. In this patient, there was no fasting hypoglycemia, as expected. By contrast, food intake and rapid emptying of the gastric pouch triggers a brisk and excessive rise in glucose (1st purple arrow), with subsequent rapid decline in glucose precipitating hypoglycemic events (red arrow). This pattern recurred after another meal (second purple, then red arrow), with treatment with glucose tablets resulting in temporary mild increase in glucose, then recurrent hypoglycemia (3rd arrow). Hypoglycemic symptoms may be autonomic (e.g., palpitations, lightheadedness, sweating) or neuroglycopenic (e.g., confusion, decreased attentiveness, seizure, loss of consciousness) in nature.

Figure 1. *CGM tracing in patient with PBH.*



Early in the post-operative period, hypoglycemia is usually mild, often associated with dumping syndrome, and effectively treated with low glycemic index diets. Such mild, often unrecognized, hypoglycemia is increasingly recognized as a potential contributor to increased appetite and weight regain after surgery [7]. A subset of post-bariatric patients develops very severe hypoglycemia with neuroglycopenia, with loss of consciousness, seizures and motor vehicle accidents, typically occurring 1-3 years following bypass. For these patients, a comprehensive multidisciplinary approach is required. Treatment of hypoglycemia, once it develops, requires rapid-acting carbohydrates, such as glucose tablets. Unfortunately, this treatment can contribute to rebound hyperglycemia, triggering further insulin secretion and recurrent hypoglycemia. Thus, prevention of hypoglycemia is essential.

Metabolic studies in patients with post-gastric surgery hypoglycemia reveal profound alterations in glycemic and hormonal patterns in the postprandial state occurring with altered gastric anatomy [8]. Plasma insulin concentrations are inappropriately high at the time of hypoglycemia, indicating dysregulation of insulin secretion as an important mechanism [9]. While initial reports demonstrated pancreatic islet hypertrophy, pancreatic resection does not cure hypoglycemia [4] [10, 11], and excessive islet number has not been observed in all series [4] [10, 12-14]. One candidate mediator of increased insulin secretion is GLP-1, an incretin peptide released from intestinal L-cells in response to meals, in turn stimulating insulin secretion in a glucose-dependent manner. Indeed, postprandial levels of GLP-1 are increased by >10-fold in post-bypass patients, are even higher in those with hypoglycemia, and correlate inversely with postprandial glucose levels [9, 15]. Furthermore, short-term pharmacologic blockade of the GLP-1 receptor markedly attenuates insulin secretion in post-bypass individuals [16], but increases GLP-1 levels in some studies [17, 18]. Interestingly, plasma levels of counterregulatory hormones such as cortisol and glucagon do not differ in the postprandial state in patients with symptomatic vs. asymptomatic hypoglycemia [9], but counterregulatory hormones are reduced during sustained hypoglycemia (hypoglycemic clamp) [19]. Additional gastrointestinal factors which could modify systemic metabolism include dietary composition, gut microbiota [20], bile acid composition [21], and intestinal adaptive responses [22]; these may influence absorption of glucose and other nutrients, intestinally-derived hormonal responses, and the magnitude of CNS-gut-liver regulatory loops. Finally, genetic variation could also contribute to altered hormonal responses and sensitivity [23].

A cornerstone of therapy is dietary modification, aimed at reducing intake of high glycemic index carbohydrates [24]. Both diet and pre-meal acarbose [25] aim to minimize rapid postprandial surges in glucose which are triggers for glucose-dependent insulin secretion. Additional therapies include octreotide (to reduce incretin and insulin secretion) [26], diazoxide (to reduce insulin secretion) [27], calcium channel blockade (to reduce insulin secretion) [28], gastric restriction or banding (to slow gastric emptying) [29], and providing nutrition solely through a gastrostomy tube placed into the bypassed duodenum [30]. Surprisingly, reversal of gastric bypass is not uniformly successful [4] [10, 11], suggesting the importance of underlying genetics and/or compensatory mechanisms which persist after surgical reversal. Finally, while pancreatic resection was initially employed for patients with life-threatening hypoglycemia [4], this procedure is not uniformly successful in remitting hypoglycemia and thus is not routinely considered at the present time.

Despite strict adherence to medical nutrition therapy and clinical use of multiple medical options above, usually in combination, some patients continue to have frequent hypoglycemia. While hypoglycemia most commonly occurs in the postprandial state, it can also be observed in response to increased activity and emotional stress. Importantly, patient safety is additionally compromised when hypoglycemia unawareness develops with recurrent hypoglycemia. Patients are often disabled by hypoglycemia which occurs multiple times per day, leading to inability to drive or maintain employment, and causing fear of eating and exercise due to potential provocation of hypoglycemic events, cardiac arrhythmias [31], syncope, falls, and seizures. Thus, there is an urgent need for improved approaches to the prevention and treatment of severe hypoglycemia to maintain health, allow optimal nutrition, and improve safety in individuals with PBH.

In our extensive clinical experience caring for patients with hypoglycemia after gastric surgery, we have observed that personal (unmasked) continuous glucose monitoring can improve patient safety and reduce hypoglycemia. CGM alarms, both glucose threshold and rate of change alarms, can alert the patient to treat to raise glucose - before severe hypoglycemia occurs. This is particularly helpful for those patients with hypoglycemic unawareness, who develop neuroglycopenia without any warning symptoms [4]. In this context, and recognizing the lag between capillary and sensor glucose values, we advise patients to respond to the rate of change alarm, so that treatment can occur before neuroglycopenia develops.

This approach is also similar to our strategy in ongoing studies of patients with post-bariatric hypoglycemia, in which we are testing the ability of CGM used in conjunction with algorithm-based prediction of hypoglycemia to guide delivery of glucagon. While this approach is still under study, use of CGM to predict hypoglycemia in this context has again reinforced the potential utility of CGM alone to provide patients with real-time sensor glucose values and predictive alarms, allowing patients to detect imminent hypoglycemia and self-treat to prevent severe hypoglycemia and dangerous neuroglycopenia. Moreover, real-time glucose information will also provide patients with information about glucose responses to specific food types and quantity, potentially allowing them to better individualize dietary choices in order to prevent postprandial glycemic spikes associated with excessive insulin secretion and subsequent hypoglycemia.

In parallel with glucose measures, we will assess activity (using a FitBit Charge 2) to define the relationship between activity measures and hypoglycemia risk and begin to provide guidance for patients about predicted glycemic responses to activity.

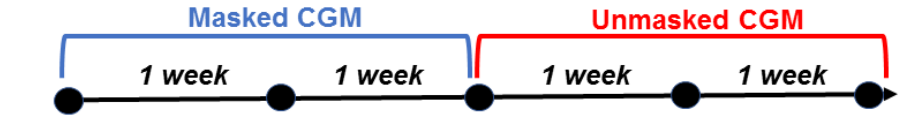
Our studies will also provide crucial data to guide next-step studies aimed at testing whether chronic CGM use could also reverse hypoglycemia unawareness, further improving safety and quality of life for this patient population.

The clinical relevance of severe hypoglycemia with neuroglycopenia is undeniable, as patient safety, cognition, and quality of life can be compromised. Given the continued increase in bariatric surgery and continued need for other forms of gastric surgery, the population of patients with hypoglycemia is expected to increase further, making the proposed studies essential for consideration of this approach to achieving safety.

2. *STUDY DESIGN:*

The proposed study is designed to assess the efficacy of unmasked personal CGM to reduce the frequency of hypoglycemia after gastric surgery. Specifically, we will analyze glycemic patterns during unmasked CGM wear, in comparison to the baseline of masked CGM wear. Initially study participants wore Dexcom G4 Professional (Pro) CGM devices, but as of July 2020 this has changed to the Dexcom G6 Pro. The Dexcom G6 Pro is worn for 10 days masked and 10 days unmasked, as this is the life span of the G6 sensor / transmitter pairs which are single use. Please note that we have chosen to have a consistent masked monitoring first, as providing unmasked data to participants first could alter their dietary or other patterns and reduce ability of the study to independently assess efficacy of the CGM intervention.

Figure 2. *Overview of Research Plan Through June 2020 (Dexcom G4 Pro)*



Visit 1
- Eligibility
- Consent
- History and Physical Exam
- Laboratory Studies
- CGM and HGM Instruction
- CGM insertion
- Hypoglycemia awareness scale

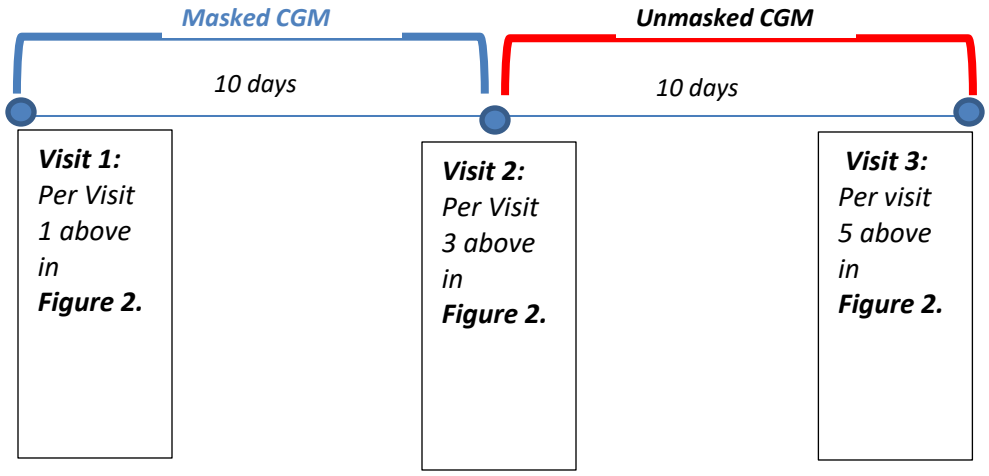
Visit 2
- Sensor insertion
- Hypoglycemia awareness scale

Visit 3
- Sensor insertion
- Hypoglycemia awareness scale

Visit 4
- Sensor insertion
- Hypoglycemia awareness scale

Visit 5
- Study equipment return
- Hypoglycemia awareness scale
- Data review and treatment modifications

Figure 3. *Overview of Research Plan July 2020 Onward (Dexcom G6 Pro)*



Visit 1:

Screening: We will recruit adult male or female patients with history of severe hypoglycemia after gastric surgery, defined as (1) symptoms of hypoglycemia with glucose <55 mg/dL [32] and resolution by glucose or food ingestion, (2) neuroglycopenia or (3) hypoglycemia requiring assistance of others. Potential participants will be identified from the hypoglycemia clinic at Joslin (directed by Dr. Patti). The study consent form will be reviewed in detail with potential participants, and patients consenting to participation will be asked to sign the IRB-approved consent form. Patients will undergo a history and physical examination, with particular emphasis on inclusion and exclusion criteria. Blood and urine samples will be obtained for screening laboratory testing including hemoglobin A1c, CBC, comprehensive chemistry, urinalysis, and pregnancy test (if applicable).

Participants will complete the following surveys:

1) HFS-II survey to assess fear of hypoglycemia and its impact on their daily routine Questions focused on insulin use will be omitted as participants do not have diabetes. (The modified survey has also been previously utilized for patients with hypoglycemia.)
2) The modified Clarke's hypoglycemia awareness questionnaire [33, 34] will be administered to all participants; score of ≥ 4 implies impaired awareness of hypoglycemia.
3) Edinburgh Hypoglycemia Scale to measure the intensity of hypoglycemic symptoms on a 7 point scale
4) Dumping Symptom Rating Scale to measure the severity and frequency of 9 different dumping symptoms.

CGM sensor placement and instruction: a continuous glucose monitor sensor and transmitter (Dexcom G4 or Dexcom G6) will be placed on the anterior abdominal wall. The CGM will be set to blinded mode. Participants will be provided a glucometer and instructed in sensor insertion, glucometer measurement of capillary glucose, and calibration techniques. Participants will be provided with and instructed in completion of a detailed log to record symptoms experienced, capillary glucose level and action taken (e.g. food, glucose type and quantity used, effectiveness), activity, and all food intake. The HypoMap tool may be utilized in parallel if the participant has access to a smart phone. Participants will be asked to email logs (identified with study acrostic only) on a daily basis to study staff.

Participants will be provided with a spare sensor in case the primary sensor is dislodged.

Participants will be provided with a fitness tracker (FitBit Charge 2) to be worn throughout the duration of the continuous glucose of monitoring, and will be instructed in its use (4 weeks for participants wearing the Dexcom G4 Pro and 20 days for participants wearing the Dexcom G6 Pro). This device will be used to assess activity level of each participant and to assess relationships between the timing of activity and hypoglycemia. This device will be returned at the end of the study.

Visit 2:

For participants wearing the Dexcom G6 Pro, insertion of second sensor: this visit will occur 10 days after visit 1. All other aspects of this visit are the same as were in place for participants wearing the Dexcom G4 Pro. Study staff will remove the sensor, and review participant diaries. A new sensor will be inserted. The study CGM will be unmasked, and alarms will be set for (1) sensor glucose <70 mg/dL, and (2) trend alarm for glucose drop of >3 mg/dL/min. Participants will be instructed in the meaning of alarms and suggested responses to alarms. Participants will be provided logs identical to those for visit 1, except that participants will also be asked to record alarms and action taken in response to alarms. The modified Clarke's hypoglycemia awareness questionnaire [33, 34] again will be administered to all participants.

Visit 3:

Return of study materials and removal of the 2nd sensor: this visit will occur 10 days after visit 2. Study staff will remove the sensor, download the sensor, and review logbooks to ensure data collection. Activity trackers will be returned to study staff. The modified Clarke's hypoglycemia awareness questionnaire [33, 34] will be administered. Frequency of hypoglycemia will be reviewed, and any recommendations for dietary or medication adjustments will be reviewed with the participant by the study physician.

Hardware Cleaning:

Dexcom G6 sensors and transmitters are single use and are worn only once per 10 day period by one participant.

3. INCLUSION / EXCLUSION CRITERIA

Inclusion Criteria

1. Males or females diagnosed with ongoing post-bariatric or post-gastric surgery hypoglycemia with prior episodes of neuroglycopenia
2. Age 18-65 years of age, inclusive, at screening.
3. Willingness to provide informed consent and follow all study procedures, including attending all scheduled visits.

Exclusion Criteria

1. Documented hypoglycemia occurring in the fasting state (> 12 hours fast);
2. Chronic kidney disease stage 4 or 5 (including end-stage renal disease);
3. Hepatic disease, including serum ALT or AST greater than or equal to 3 times the upper limit of normal; hepatic synthetic insufficiency as defined as serum albumin < 3.0 g/dL; or serum bilirubin > 2.0;
4. Congestive heart failure, NYHA class II, III or IV;
5. History of myocardial infarction, unstable angina or revascularization within the past 6 months or 2 or more risk factors for coronary artery disease including diabetes, uncontrolled hypertension, uncontrolled hyperlipidemia, and active tobacco use.
6. History of syncope (unrelated to hypoglycemia) or diagnosed cardiac arrhythmia
7. Concurrent administration of β-blocker therapy;

8. History of a cerebrovascular accident;
9. Seizure disorder (other than with suspect or documented hypoglycemia);
10. Active treatment with any diabetes medications except for acarbose;
11. Active treatment with octreotide or diazoxide;
12. Active malignancy, except basal cell or squamous cell skin cancers;
13. Personal or family history of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease);
14. Known insulinoma;
15. Major surgical operation within 30 days prior to screening;
16. Hematocrit < 33%;
17. Bleeding disorder, treatment with warfarin, or platelet count <50,000;
18. Blood donation (1 pint of whole blood) within the past 2 months;
19. Active alcohol abuse or substance abuse;
20. Current administration of oral or parenteral corticosteroids;
21. Pregnancy and/ or lactation: For women of childbearing potential: there is a requirement for a negative urine pregnancy test and for agreement to use contraception during the study and for at least 1 month after participating in the study. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence.
22. Use of an investigational drug within 30 days prior to screening.
23. Not having a smart phone compatible with the Dexcom G6 Pro CGM (in order to receive / view glucose data).

4. DATA ANALYSIS / SUBJECT SELECTION

Statistical and Analytical Plan

All participants who have consented to the study and completed at least one monitoring period of CGM use will be included in the data analysis set. Adverse events, vital signs, physical examination, and laboratory safety variables (Screening to Final Visit) will be reviewed and summarized on an ongoing basis during the study to evaluate safety. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Data will be stored using a secure, web-based application designed to support data capture for research studies (RedCap), providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data are stored and are backed up on a scheduled basis with data encryption for any regulated data types (private health data (PHI) which require backup media in an encrypted format. Data will be maintained in protected files at Joslin Diabetes Center. Only deidentified data will be transferred (via secure electronic file transfer) between collaborators.

CGM data, alarms, reported symptoms, need for assistance, hypoglycemia awareness scale, and timing of symptoms relative to sensor glucose levels will be recorded. We will also define CGM values, both during the day and night, using thresholds <55 (severe hypoglycemia)[32], 55-70 (moderate hypoglycemia), 70-180 (euglycemia), and >180 mg/dl (hyperglycemia).

CGM data will be analyzed in several ways: (1) minutes per day <70 mg/dl (primary analysis), (2) minutes per day <55 mg/dl, (3) number of episodes requiring assistance, (4) episodes of severe hypoglycemia (<55 mg/dl, (5) episodes of moderate hypoglycemia (55-70 mg/dl), and episodes of hyperglycemia (>180 mg/dl). In secondary analysis, data from days and nights (11 PM – 6 AM) will be analyzed separately. Activity measures, including total step number as well as duration of activity as defined by heart rate increment, will be analyzed to determine relationship to changes in sensor

glucose levels (Fitabase). For all data, paired analysis will be used to compare responses per participant for masked vs. unmasked periods.
Analyses will utilize either parametric (paired t tests) or non-parametric statistical tests (Wilcoxon signed-rank test), depending on data distribution for continuous variables, and chi square for categorical variables.

Sample Size and Justification
Approximately 40 subjects may be screened for this study, assuming approximately 30% will not meet inclusion criteria. To allow for potential drop-outs (assuming 20%), 28 subjects will be enrolled with goal for 20 subjects to complete all study visits.

Prior data from our group in patients with symptomatic post-bypass hypoglycemia (n=10, unselected for severity) demonstrate mean ± standard error of 63 ± 23 minutes/day for sensor glucose <70 [4]. This was a small cohort, (n=10), was unselected for severity, and utilized an early Medtronic diagnostic CGM system. The cohort proposed in this study is expected to have longer duration of hypoglycemia daily. However, we have used these data to estimate power for the current study. We estimate power of 98% to detect a 50% reduction (32 minutes) in time <70 with alpha 0.05 (2-sided) for paired comparison of masked and unmasked monitoring periods with a sample size of 20. As noted above, we expect power will be higher due to increased severity in this sample cohort; even with the conservative calculations, we should have adequate power (0.8) to detect differences between masked and unmasked periods as low as 23 minutes per 24 hours.

Data will be analyzed after 10 individuals have completed the paired analysis of response to masked vs. unmasked CGM analysis. At that time, power will be reassessed, and sample size will be adjusted if needed.

Local Interim Data Analysis/Data Monitoring Plan
Data will be stored using a secure, web-based application designed to support data capture for research studies (such as RedCap), providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data are stored and are backed up on a scheduled basis with data encryption for any regulated data types (private health data (PHI) which require backup media in an encrypted format.

Data will be maintained in protected files at Joslin Diabetes Center. Only deidentified data will be transferred (via secure electronic file transfer) between collaborators.

Data Safety Monitoring Plan: 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 study coordinator 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 trial inclusive of enrollment, oversight of informed consent, general conduct of the trial as well as reporting of any complications as needed to the NIH and IRB.

5. POSSIBLE BENEFITS:

The purpose of this study is to evaluate the efficacy of continuous glucose monitoring at reducing episodes of hypoglycemia in patients who experience hypoglycemia after gastric surgery. 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 following gastric surgery. Subjects enrolled in this study receive

comprehensive medical evaluation. As such, risks are appropriate in relation to the potential significant benefits for the large number of persons with or at risk for hypoglycemia after bariatric surgery. Thus, the potential benefits to society are likely to outweigh the risks to the individual subject.

6. *POSSIBLE RISKS:*

Risk of Device Reuse: This risk has been eliminated from this protocol as Dexcom sensors, transmitters and receivers will be used only by a single participant and thus do not require sterilization. Glucometers will not be cleaned or reused by subjects. A new meter will be given to each new participant.

Sensor inaccuracy:
Participants wearing the Dexcom G6 Pro CGM may take up to 1000 mg of acetaminophen every 6 hours (4 grams per 24 hours), without affecting sensor accuracy.

Sensor placement may cause bleeding, infection, clot formation (all minimal risk), bruising, or discomfort.

Phlebotomy may cause blood loss and discomfort. The total volume of blood sampling is approximately 15 ml for the screening visit. This should not pose significant stress to any individual. Volunteers will be requested not to donate blood within 2 months of the study. Any subject who has just donated blood will be asked to postpone entry into the study until 2 months have elapsed.

Screening Tests and Procedures: It is possible that as a result of the screening process a subject may learn that they have a health disorder that they were unaware they had. Every effort will be made to help the participant obtain the care that they need.

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 the clinical research project and can withdraw consent at any time.

7. *CONSENT PROCEDURES:*

Subjects will be recruited from the Joslin Hypoglycemia Clinic. The study will be explained to the potential subject initially in the clinical setting or during a subsequent telephone screening session. 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 unit. 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 IRB 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 the IRB to the patient throughout any study 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 IRB.

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.

8. RECRUITMENT / SOURCE OF SUBJECTS:

Patients with post-gastric surgery hypoglycemia will be recruited for this study from the weekly Hypoglycemia Clinic at Joslin Diabetes Center, directed by Dr. Patti. Post-gastric surgery hypoglycemia syndrome is the most common diagnosis within this clinic. More than 200 patients with this syndrome have been evaluated to date at Joslin, and over 50 patients have participated in research studies to date. Recruitment will be performed in the Hypoglycemia Clinic by the research fellow or study coordinator.

9. RIGHTS AND PRIVACY:

Storage of private health information is solely in locked offices or on secure access protected computer sites and portable devices that may be used for patient data are encrypted to protect privacy. All study staff are trained in privacy protection and the ethical conduct of clinical research. Records will be made available for inspection by the safety officer upon request.

Please answer the following questions:

- Will medical history/clinical information be obtained from the subjects' medical records for the purpose of this study? If yes, please list what information will be recorded.
  ν **YES** o NO
  - Age, gender, race
  - Date of surgery
  - Type of procedure
  - Pre-surgical BMI
  - Concomitant medical problems
  - Active and historical medications
  - History of hypoglycemia: first onset, symptoms, prior diagnostic testing and treatment approaches

- Will information resulting from this study (i.e. results of clinical/research lab tests, etc…) become part of the subjects' medical record or provided to the subject and/or others for clinical purposes? If, no, please list what information will not be given to the subject or recorded in their medical record and why.

ν **YES** o NO

- Will subjects' identifiable health information* be shared with others outside of Joslin Diabetes Center? If yes, list whom this information will be shared with (please be specific, include names of collaborators, study sponsor contacts)?

  o YES ν **NO**

10. OMIT PROCEDURES / LEAVE STUDY:

We will inform patients that they may discontinue the study at any time without consequence. *They will be informed that their decision will not affect how they are treated.*

11. INCENTIVES / REMUNERATION:

Participants will be given a payment of $200.00 (provided as check) upon the completion of five study visits. The study will also compensate participants for the cost of parking or taxi services up to $50 for each of the study visits.

Parking will be paid by vouchers on the participants are asked to come in for a study visit.

For participants wearing the Dexcom G6 Pro, as the sensors and transmitters are single use only, they cannot be kept and used again. Also, as a personal receiver is not needed for the Dexcom G6 Pro, a Dexcom G6 receiver is not provided to the participant.

Participants will not be able to keep the FitBit; it will be returned to study staff at the end of the study.

*** Identifiable Health Information**
Data that includes any of the following identifiers are considered identifiable health information:

- Name
- Social Security number
- Medical Record Number
- Address by Street Location
- Address by Town/City/Zip Code
- Date of Birth
- Admission or Discharge Date
- Date of Death
- Telephone Number
- Fax Number
- Electronic E-Mail Address
- Web URLs
- Internet Protocol (IP) Address
- Health Plan Beneficiary Number
- Account Number
- Certificate/License Number
- Vehicle Identification Number and Serial Number, including License Plate Number
- Medical Device Identifiers and Serial Numbers
- Biometric Identifiers (finger and voice prints)
- Full Face Photographic Image
- Any Other Identifier likely to identify the subject

Please answer the following questions:

12. Where and how will your project utilize the Joslin Diabetes Center?

- ❑ **General Clinical Research Center (GCRC)**
- ❑ Clinical Trials Unit (CTU)
- ❑ **Joslin Clinic**
- ❑ Eye Unit
- ❑ Other (please specify) _____

13. Will your project involve research on living human fetuses?

- ❑ Yes
- ❑ **No**

14. Does your project involve the use of any new drug or device?

- ❑ Yes IND# or IDE# _____
- ❑ **No**

15. Is review required by risk management foundation?

- ❑ Yes
- ❑ **No**

_____ _____

Signature of Principal Investigator ***Date***

I have read and reviewed this application for approval by the Committee on Human Studies

_____ _____

Signature of PI's Section Head ***Date***

Please bring the original and twenty-four (24) copies of
this form and the informed consent form for the above research project to
Leigh Read in the Office of Sponsored Research
by the appropriate CHS meeting deadline.

Approved by
JDC/CHS

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