IRB Minimal Risk Protocol Template

General Study Information

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Study Title: The Effect of Endoscopic Sleeve Gastroplasty on Long Term Gastric Emptying

Protocol version number and date: Version: 6, 1/8/2020

Research Question and Aims

Hypotheses:

1. The endoscopic sleeve gastroplasty will increase the amount of time needed for 50% of stomach contents to empty 60 minutes more than lifestyle interventions at 3 and12 months.
2. Larger induced changes in gastric emptying at 3 and 12 months will be associated with greater percent weight lost at 12 months

Aims, purpose, or objectives:

1. Identify the degree of gastric emptying delay produced by the endoscopic sleeve gastroplasty compared to lifestyle interventions at 3,12 months
2. Correlate the amount of weight loss at 3 and 12 months with the delay in gastric emptying delay 3 and12 months in both groups

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

Endoscopic sleeve gastroplasty is an endoscopic procedure for mild to moderate obesity (BMI 30-40). A recent multinational retrospective study was able to show 18% TBWL 24 months after the procedure. Our group investigated 4 patients with gastric scintigraphy prior to and 3 months after the ESG, showing an increase in T1/2 time of emptying for solids from 90 minutes to 180 minutes. This significant delay in gastric emptying is of significant physiological importance in light of the association between accelerated gastric emptying and obesity. If the ESG is able to produce long term effects on gastric emptying, the procedure may offset the compensatory responses that lead to weight regain and yield successful long term weight maintenance. Additionally, identifying the magnitude and duration of weight loss in those with delayed gastric emptying at baseline will allow us to tailor this therapy based of gastric emptying rates. In light of the recently approved office based gastric emptying breath test, this affords us the opportunity to better phenotype patients at the office, without the use of radiation or blood tests.
The mechanisms by which ESG delays gastric emptying are unclear. Potential explanations include a physical impediment to gastric emptying and/or impaired gastric motility, which may be related to the procedure and/or preexisting diabetes mellitus. In order to better understand these mechanisms, we propose to evaluate gastric motor functions (i.e., gastric accommodation and motility) with MRI before and after ESG.

Small studies suggest that the complications of hyperglycemia (eg, retinopathy) in diabetes mellitus are associated with epigenetic changes. Whether, and to what extent, these changes are potentially reversible with improved control of glycemia is unknown. Hence, we propose to study the effects of ESG and resultant improved glycemic control on epigenetic markers in these patients. In order to provide a control group, blood samples for epigenetic analyses will also be obtained before they start lifestyle changes in the lifestyle arm.

Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

Patient Selection: Subjects who have consented to participate in IRB 17-007934 will be approached to participate in this study. IRB 17-007934 is a multicenter randomized placebo-controlled clinical trial comparing the ESG with lifestyle interventions for patients with mild to moderate obesity. Potential study subjects will be consented during the screening process for the main study and will only be enrolled if they are eligible and randomized to the ESG arm of the main study.

Intervention (gastric emptying breath test, GEBT): Study subjects will receive an FDA-approved breath-based (Spiriluna) gastric emptying test within 2 weeks before ESG procedure (or at baseline if randomized to lifestyle intervention arm), 3 months into and 12 months into the main research study. One additional GEBT will be administered to participants that randomized to the treatment group at the end of year 2, month 24. The breath test will be performed during their main study followup appointments at the CRU. It takes total of 4 hours, with breath samples blown directly into glass test tube at specified time intervals. Study subjects can go to their appointments and do not need to stay inside the clinic during those four hours. However, they are not allowed to exercise, drink or eat anything outside of the kits contents for the duration of the test (4 hours). The kit needs to be returned to our study team at the conclusion of the four hours so we can mail it back to Cairn Diagnostics within 3 weeks.

Pre-meal breath samples are collected at the start of the test. Patients then eat a 230 calorie breakfast meal that's provided in the kit. After consuming the meal, additional breath samples are collected at 45, 90, 120, 150, 180 and 240 minutes after the meal. The special meal includes a precisely formulated scrambled egg mix containing pharmaceutical-grade Spirulina, a safe, nutritional blue green algae that, during manufacturing, has been enriched with carbon-13. Once the test meal is consumed, the carbon-13 in the Cairn GEBT test meal gives rise to carbon-13 labeled CO_2, or $^{13}CO_2$, which can be measured in the patient's breath samples. The kits will be mailed to Cairn (Brentwood, TN) with a unique identifier for analysis. Cairn will not have access to study subjects' protected health information

Data Collection (gastric emptying breath test, GEBT): Data will be collected in a protected REDCap database. Outside study center data
(not intended at this time) be directly sent from Cairns to our institution (in the same unique identifier fashion) to allow us to link the data with the protected REDCap database to obtain data from the study subjects in a protected fashion and inputted in a separate REDCap database for analysis.

Measurement of Gastric Accommodation by Dynamic MRI: Gastric MRI will only be performed in patients who can safely undergo MRI. Patients in whom a MRI exam cannot be safely performed will participate in other study procedures but not the MRI. The MRI will be performed at the time points (i.e., baseline, 3 months, and 1 year as the GEBT) for only ESG subjects (subjects randomized to treatment and subjects randomized to control who cross-over to receive the ESG). Subjects will be kept NPO after midnight and scanned with MRI using a torso phased array coil generally at the Opus building. If the 3T magnet (Phillips) is not available, a 1.5T magnet will be used. Before, and after a meal (296 ml Ensure mixed with 4ml gadolinium, i.e., 300 ml), static and dynamic imaging sequences will be acquired using available MR sequences to assess respectively gastric volumes and motility. No intravenous contrast will be administered. Postprandial accommodation will be calculated as the difference between postprandial and fasting volumes (Neurogastroenterol Motil 2009; 21:42–51; American Journal of Physiology. 2014;307:G582-G587). Likewise, gastric motility (i.e., contractile frequency, amplitude and velocity) will be analyzed with established approaches (Neurogastroenterol Motil 2011;23(7):617-e252) .

Blood sample for epigenetics – For both the ESG and control groups, a blood draw (50 ml) will be performed for assessing epigenetic markers in monocytes, will be obtained at baseline and at 12 months. The controls that elect to crossover at the 12 month period and receive an ESG, will have another blood sample 12 months after their ESG (around 24 months). These crossover subjects will follow the outlined tests for the ESG group. Based on scientific and budgetary considerations, we tentatively plan to evaluate epigenetic mechanisms by assessing activation of 4 histone marks (i.e., H3K27ac, H3K27me3, H3K36me3, H3K9ac) in monocytes with chromatin immunoprecipitation techniques that are available in the Epigenetic Core Laboratory at Mayo Clinic. This sample will be collected in a heparin tube and shipped to the lab on ice packs. Towards our long-term objective of uncovering associations between SNPs and dyspepsia and gastroparesis, we propose to extract DNA from 30 ml blood, to be drawn from study participants. Genome-wide analysis will be conducted using Illumina 610 QUAD microarray or comparable approaches. Genotype-phenotype correlations will be examined using these patients and other patients in ongoing studies. Hence, a total of approximately 80 mL and 50 ml of blood will be drawn respectively at baseline and 1 year visits. For participants in the main study (IRB 17-007934) and this sub-study, the total blood collection is well within safe limits.

Subject study activities:

	Baseline	**3 months**	**12 months**	**15 months**	**24 months**
ESG	Blood MRI GEBT	MRI GEBT	Blood MRI GEBT	N/A	GEBT
Control	Blood GEBT	GEBT	Blood GEBT MRI*	MRI* GEBT*	Blood* MRI* GEBT*

*if control crosses over to ESG at 12 months

Retesting: Re-testing will occur if test was not completed per guidelines or if deemed necessary by the Principal Investigator.

Remuneration: At this center, study subjects will receive $50 at the return of each completed GEBT kit (max 5) and $100 if they complete the GEBT study and the MRI at each visit.

Study Variables: Demographical, comorbidity data and weight loss outcomes will be used that will be collected by the main study to generate prediction models.

Resources:

This will be a substudy off the main study and will require minimal additional effort from the study team

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 80

Subject population Adults participating in the MERIT trial

Inclusion Criteria:

. The following are the inclusion criteria for the main study.

1. Age 21-65
2. BMI ≥ 30 and ≤ 40 kg/m^2
3. Willingness to comply with the substantial lifelong dietary restrictions required by the procedure
4. History of failure with non-surgical weight-loss methods
5. Willingness to follow protocol requirements, including signed informed consent, routine follow-up schedule, completing laboratory tests, completing diet counseling and undergoing adjustment procedure

6. Residing within a reasonable distance from the investigator's office and able to travel to the investigator to complete all routine follow- up visits
7. Ability to give informed consent
8. Women of childbearing potential (i.e., not post-menopausal or surgically sterilized) must agree to use adequate birth control methods

Exclusion Criteria:

1. History of foregut or gastrointestinal (GI) surgery (except uncomplicated cholecystectomy or appendectomy)
2. Prior gastrointestinal surgery with sequelae, i.e. obstruction, and/or adhesive peritonitis or known abdominal adhesions.
3. Prior open or laparoscopic bariatric surgery.
4. Prior surgery of any kind on the esophagus, stomach or any type of hiatal hernia surgery.
5. Any inflammatory disease of the gastrointestinal tract including esophagitis, Barrett's esophagus, gastric ulceration, duodenal ulceration, cancer or specific inflammation such as Crohn's disease.
6. Potential upper gastrointestinal bleeding conditions such as esophageal or gastric varices, congenital or acquired intestinal telangiectasis, or other congenital anomalies of the gastrointestinal tract such as atresias or stenoses.
7. A gastric mass or gastric polyps > 1 cm in size.
8. A hiatal hernia > 4cm of axial displacement of the z-line above the diaphragm or severe or intractable gastro-esophageal reflux symptoms.
9. A structural abnormality in the esophagus or pharynx such as a stricture or diverticulum that could impede passage of the endoscope.
10. Achalasia or any other severe esophageal motility disorder
11. Severe coagulopathy.
12. Insulin-dependent diabetes (either Type 1 or Type 2) or a significant likelihood of requiring insulin treatment in the following 12 months or a HgbA1C >= 9.
13. Subjects with any serious health condition unrelated to their weight that would increase the risk of endoscopy
14. Chronic abdominal pain
15. Motility disorders of the GI tract such as gross esophageal motility disorders, gastroparesis or intractable constipation
16. Hepatic insufficiency or cirrhosis

17. Use of an intragastric device prior to this study due to the increased thickness of the stomach wall preventing effective suturing.
18. Active psychological issues preventing participation in a life-style modification program as determined by a psychologist
19. Patients unwilling to participate in an established medically-supervised diet and behavior modification program, with routine medical follow-up.
20. Patients receiving daily prescribed treatment with high dose aspirin (> 80mg daily), anti-inflammatory agents, anticoagulants or other gastric irritants.
21. Patients who are unable or unwilling to take prescribed proton pump inhibitor medication
22. Patients who are pregnant or breast-feeding.
23. Subjects with Severe cardiopulmonary disease or other serious organic disease which might include known history of coronary artery disease, Myocardial infarction within the past 6 months, poorly-controlled hypertension, required use of NSAIDs
24. Subjects taking medications on specified hourly intervals that may be affected by changes to gastric emptying, such as anti-seizure or anti-arrhythmic medications
25. Subjects who are taking corticosteroids, immunosuppressants, and narcotics
26. Subjects who are taking diet pills
27. Symptomatic congestive heart failure, cardiac arrhythmia or unstable coronary artery disease.
28. Pre-existing respiratory disease such as moderate or severe chronic obstructive pulmonary disease (COPD), pneumonia or cancer.
29. Diagnosis of autoimmune connective tissue disorder (e.g. lupus, erythematous, scleroderma) or immunocompromised.
30. Specific diagnosed genetic disorder such as Prader Willi syndrome.
31. Eating disorders including night eating syndrome (NES), bulimia, binge eating disorder, or compulsive overeating
32. Known history of endocrine disorders affecting weight such as uncontrolled hypothyroidism.
33. Contraindications for MR imaging: i.e. pacemakers, aneurysm clips, cochlear implants.* [Patients in whom MRI is contraindicated can participate in remaining study procedures.]

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☒ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☒ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(3) Prospective collection of biological specimens other than blood:

Breath samples will be collected as dictated by the commercial kit and samples unusable/destroyed after analysis.

Review of medical records, images, specimens – Category 5

For review of existing data:

Date Range: From IRB IRB 17-007934 initiation to termination (projected 2021)

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☐ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☒ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☒ Data ☐ Specimens ☐ Data & Specimens **IRB 17-007934**

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☒ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name		
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number		
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.		
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☒ None

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement:

Primary Endpoint: The primary endpoint of our study is change in gastric emptying (delay) produced by the ESG vs placebo at 12 months. We will use a two sample t-test with a two sided alpha level of 0.05

Power Calculation: A sample size of 15 ESG and 23 LS subjects provides 90% power to detect a **clinically significant 33 minutes increase**(17, 21) in gastric emptying attributable to ESG, assuming a two-sided equal-

variances t-test at alpha=0.05 and with a standard deviation of 30 for the change in gastric emptying time from baseline to 3 (or 12) months. This SD of 30 is a more conservative than our preliminary findings of SD 15. (**Table 1).**

Exploratory Analysis: One exploratory analysis of our study is to identify the amount of weight loss observed at 12 months explained by changes in gastric emptying at 3 months. For this analysis we will use linear regression with the change in T ½ (time to empty 50% of food) at 3 months as a predictor and %TBWL at 12 months as the outcome, adjusting for age and baseline weight.

Table 1	Minimum Detectable Change at 3 and 12 months	Total Sample size needed with p < 0.05 at 90% power
Gastric emptying	61 min	13 subjects
Gastric emptying	42 min	25 subjects
Gastric emptying	**33 min**	**38 subjects**
Gastric emptying	29 min	50 subjects
Gastric emptying	22 min	80 subjects

Data Analysis Plan:

Primary:

We will use a two sample t-test with a two sided alpha level of 0.05

Secondary:

For the secondary endpoint of gastric emptying predicting weight loss, we will run exploratory linear regression models using percent total body weight lost at **1)** 12 and **2)** 24 months as the dependent variable and gastric emptying at baseline and 3 months (for models 1 and 2) and 12 months (for model 2) as the independent variables. Similar models will be used to assess the ability of fasting and postprandial gastric volumes and postprandial accommodation to weight loss.