Multi-center ESG Randomized Interventional Trial (MERIT-Trial)

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Study Title: Multi-center ESG Randomized Interventional Trial (MERIT Trial)

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The undersigned have read and understand the Protocol specified above and agree on its content. I agree to conduct the study according to this protocol, its amendments, the clinical trial agreement and the applicable regulatory requirements. I understand that said study will not be initiated without appropriate Institutional Review Board (IRB) approval and that the administrative requirements of the governing body will be fully complied with.

_____	_____
Principal Investigator's Printed name and Signature	Date
_____	_____
Site Name	Site Number

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

1. ABSTRACT

More than one-third of U.S. adults are obese[1]. The increasing prevalence of obesity in the U.S. has been accompanied by an increasing prevalence in its associated comorbid conditions including hypertension, diabetes, dyslipidemia, coronary heart disease, stroke, sleep apnea, osteoarthritis, gallbladder disease, GERD, nonalcoholic fatty liver disease (NAFLD/NASH), and cancer. Obesity is associated with an increased risk of all-cause and cardiovascular mortality and accounts for about 2.5 million preventable deaths annually[2-4]. Patients with mild to moderate obesity (BMI 30-40 kg/m_2), who do not qualify for bariatric surgery are left without an effective management approach to their disease; considering the modest effects seen with medications or lifestyle intervention alone and their ability to achieve >10% total body weight loss (TBWL) only in the minority of patients. Therefore, there is ***significant management gap*** for patients with mild to moderate obesity (BMI between 30-40 kg/m_2). **Endoscopic sleeve gastroplasty (ESG) is an endoscopic, minimally invasive intervention that is well positioned to fill the obesity management gap** since it results in more than 10% TBWL in the majority of patients, has excellent safety profile, and is roughly one quarter the cost of bariatric surgery. Clinical data from both the United States (US) and outside the US (OUS) demonstrates a 19.8% TBWL at 18 months after ESG with excellent safety profile. ESG is performed using an FDA approved and commercially available endoscopic suturing device. Despite the excellent clinical experience with ESG, no randomized clinical trials have been performed to evaluate the long-term efficacy of the technique over life-style intervention in producing significant long-term weight loss and improving obesity associated co-morbidities. Level 1 evidence is needed to further advance this promising technique and inform global adaptation. Therefore, we are proposing a randomized controlled trail to evaluate the long-term safety and efficacy of ESG in meeting efficacy endpoints set forth in a consensus statement by relevant societies (American Society or Gastrointestinal Endoscopy [ASGE] and American Society of Metabolic and Bariatric Surgery [ASMBS]) and its impact on obesity related co-morbidities in patients with obesity and body mass index (BMI) between 30-40 kg/m^2.

2. INTRODUCTION

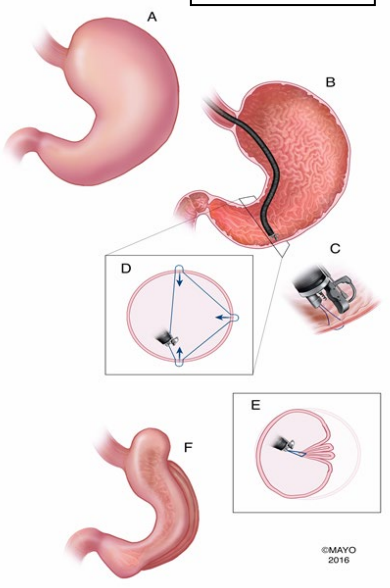
2.1 Background

The National Institutes of Health, the World Health Organization, and numerous other scientific organizations including the America Medical Association (AMA) recognize obesity as a chronic disease requiring primary therapy. More than one-third of United States adults are obese. [1] The increasing prevalence of obesity in the U.S. has been accompanied by an increasing prevalence in its associated comorbid conditions including hypertension, diabetes, dyslipidemia, coronary heart disease, stroke, sleep apnea, osteoarthritis, gallbladder disease, GERD, nonalcoholic fatty liver disease (NAFLD), and cancer. Obesity is associated with an increased risk of all-cause and cardiovascular mortality and accounts for about 2.5 million preventable deaths annually. [2-4] The economic consequences of obesity are enormous, and projected increases may threaten the integrity of our health care system. Recent analyses estimate that 147 to 210 billion dollars are spent annually to treat obesity-attributable medical problems in the United States, accounting for about 21% of health care expenditures.[5, 6]

Current treatment options for patients with obesity include lifestyle intervention, obesity pharmacotherapy, and bariatric surgery. The components of lifestyle intervention include diet, exercise, and behavior modification and should be considered the cornerstone of any obesity treatment. [7] However, as a stand-alone therapy, even intensive lifestyle intervention is only modestly effective with an expected percent total body weight loss (%TBWL) < 3%. [8-10] The available pharmacological approaches for the treatment of obesity increase weight loss by 3% to 9% compared with lifestyle therapy alone, but some can be associated with unfavorable side effects, significant cost, and weight loss achieved by pharmacotherapy is rarely maintained upon withdrawal of the medication. [11]

The scientific literature is clear in showing that the magnitude of weight loss is strongly associated with improvement in obesity related co-morbidities such as diabetes, blood pressure, hyperlipidemia, obstructive sleep apnea, and fatty liver disease. The odds of clinically significant improvements in obesity related co-morbidities are much higher when %TBWL exceeds 10%. [12, 13] Bariatric surgery, such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy, can achieve significant and durable weight loss that exceeds the 10% TBWL threshold in the majority of patients; however, it is estimated that less than 1% of patients with severe obesity (body mass index [BMI] ≥ 40 kg/m_2) undergo surgical interventions given high costs, patient preference, access to care, and the morbidity and mortality associated with surgery. [14] More importantly, the majority of patients with mild to moderate obesity (BMI 30-40 kg/m_2) who do not qualify for bariatric surgery are left without an effective management approach to their disease, considering the modest effects seen with medications or lifestyle intervention alone and their ability to achieve >10%TBWL only in the minority of patients. Yet, according to the global

Figure 1.



disability-adjusted life-years and deaths study, patients with mild to moderate obesity are the highest contributors to the burden on disease both in terms or co-morbidities and overall mortality[15]. Therefore, both government agencies (the Agency for Healthcare Research and Quality [AHRQ][16]) and national societies (American Society of Bariatric and Metabolic Surgery [ASMBS][17], and American Society of Gastrointestinal Endoscopy [ASGE][18]) now recognize that a significant management gap exists for patients with mild to moderate obesity (BMI between 30-40 kg/m_2) and have defined safety and efficacy thresholds for endoscopic weight loss interventions to achieve societal recommendations. Recently the FDA has approved endoscopic bariatric therapies (EBTs) such as intragastric balloons (IGB) for the management of obesity. [19] These endoscopic therapies can achieve >10%TBWL in the majority of patients with excellent safety and lower cost (roughly one quarter of the cost of bariatric surgery). Furthermore, they are anatomy preserving, reversible, repeatable, and are thus well positioned to fill the gap in the management of obesity.

Endoscopic Sleeve Gastroplasty (ESG) is an endoscopic minimally invasive weight loss procedure where a commercially available, FDA approved, full-thickness endoscopic suturing device (Overstitch; Apollo Endosurgery, Austin, TX) is used to reduce the stomach volume by 80% through the creation of a restrictive endoscopic sleeve (figure 1). This is accomplished by a series of endolumenally placed full-thickness sutures through the gastric wall, extending from the antrum to the gastroesophageal junction.

2.2 Clinical Data to Date

The feasibility of ESG was first demonstrated in humans in the US in 2013.[20] Since then, the technique has gained wide clinical adoption in the US and world-wide with more than 2000 cases performed. Multiple single-arm prospective and retrospective studies have demonstrated the safety and minimally invasive nature of the technique and reported %TBWL of about 18% at 12 months.[21, 22] Furthermore, studies have demonstrated physiologic perturbations resulting from creation of the ESG and its association with increased satiation and metabolic effects that are potentially important to control the metabolic dysregulation associated with obesity.[23] In a recent multicenter study of 248 patients enrolled at Mayo Clinic, Cornell Medical Center, and Madrid Hospital, ESG was associated with 18% and 20% TBWL at 12 and 18 months, respectively [23]. More importantly, in this large series, incidence of serious adverse events (SAE) was only 2% and none of these SAEs required any surgical intervention. No mortality was reported.

2.3 Rationale

A joint task force convened by the ASGE and the ASMBS defined safety of efficacy threshold that endoscopic bariatric therapies, such as ESG, need to meet before societies recommend their wide-spread adoption. These thresholds are as follows: EBTs intended as a primary obesity intervention in patients with mild to moderate obesity should achieve a mean minimum threshold of 25% excess weight loss (%EWL) measured at 12 months (calculated based on an ideal BMI of 25mg/kg²). In addition to the absolute threshold of weight loss, the mean %EWL difference between the procedure and control should be should be a minimum of 15% EWL and be statistically significant. Finally, the risk associated with EBT should equate to a 5%

incidence of serious adverse events or less. Based on this consensus statement, an endoscopic intervention that meets these established thresholds should be considered appropriate to incorporate into wide-spread clinical practice presuming that the appropriate training and credentialing in that EBT has been achieved [24, 25].

Despite the excellent clinical experience with ESG, no randomized clinical trials have been performed to evaluate the long-term efficacy of the technique over life-style intervention in producing significant long-term weight loss, improving obesity associated co-morbidities, and meeting the societal thresholds. Furthermore, Level 1 evidence is needed to further advance this promising technique and achieve wide-spread adoption. Therefore, we are proposing a randomized controlled trial to evaluate the long-term safety and efficacy of ESG in meeting efficacy endpoints set forth in a consensus statement by relevant societies (American Society or Gastrointestinal Endoscopy [ASGE] and American Society of Metabolic and Bariatric Surgery [ASMBS]) and its impact on obesity related co-morbidities in patients with obesity and body mass index (BMI) between 30-40 kg/m².

3 STUDY OBJECTIVES

1. Assess if ESG achieves safety and efficacy threshold as defined by joint societal consensus statement by ASGE and ASMBS
2. Assess the impact of ESG on obesity related co-morbidities (Hypertension and Diabetes)
3. Assess the mid-term durability of weight loss achieved by ESG at 24 months.
4. Assess the impact of re-tightening the ESG on weight loss trajectory.

4 STUDY DESIGN

4.1 General Description

This study is a multi-center, randomized, open-label clinical trial evaluating the efficacy and safety of ESG as an adjunct to life-style intervention for weight loss and improvement in obesity-related co-morbidities compared to lifestyle intervention alone in participants with a BMI ≥ 30 and ≤40 kg/m² who have failed to achieve and maintain weight loss with a non-surgical program.

Participants will be recruited from outpatient clinical weight loss clinics and from study-related institutional review board (IRB) approved advertisements. The cohort will include nor more than 50 patients without at least one of a) hypertension (HTN) on one or more anti-hypertensive medications or b) type II diabetes mellitus (DM) on oral agents only with HbA1c ≤ 9. Enrollment will be tracked continuously and enrollment closed to non-DM, non-HTN patients after meeting the target for that group.

Two hundred eligible participants will be stratified into three groups (obesity, obesity-hypertension, and obesity-diabetes) and then block-randomized 1 to 1.5 to treatment (80 participants) and control (120 participants) groups alone as depicted in the diagram on page 16. All treatment group participants will undergo endoscopy and those without endoscopic contraindications will undergo the ESG. All control subjects will follow a low-calorie, healthy lifestyle intervention only for 12 months. After 12 months of lifestyle intervention, eligible control participants will crossover to receive the ESG. Those who had the ESG will undergo a repeat upper endoscopy at 52 weeks +- 4 weeks to evaluate the durability of the plications and re-tighten the ESG if needed with continued follow-up for 12 additional months.

The study will have two levels:

1. Level 1: the randomized study phase with primary outcomes for both groups evaluated at 12 months
2. Level 2: the crossover, non-randomized study phase with outcomes for a) the initial treatment group at 24 months post ESG (12 months after the re-tightening procedure) b) for the controlled cross-over group evaluated at 12 months after ESG

4.2 Endpoints

4.2.1 Effectiveness

Primary:

- % EWL at 12 months from randomization by randomized arm measured at the week 52 visit. The null hypothesis is no difference in mean %EWL between randomized arms.

Secondary:

- Proportion with ≥25% EWL at 12 months by randomized arm
- Change in hypertension in the ESG group compared to LS only

  - Proportion of patients off or with reduction in their antihypertensive medications in the randomized control arm compared to lifestyle control at 12 months
  - Change in systolic and diastolic blood pressure in the randomized arm compared to lifestyle control at 12 months
  - Comparing diastolic and systolic blood pressures as continuous variables 12 months after ESG (compared to baseline) in the entire cohort that received ESG both in the randomized and cross-over segments of the trial
- Change in type II diabetes in the ESG groups compared to LS only
  - Proportion of patients off or with reduction in their diabetes medications in the randomized arm compared to lifestyle control at 12 months
  - Change in HgbA1c in the randomized arm compared to lifestyle control at 12 months
  - Comparing HgbA1c as a continues variable 12 months after ESG (compared to before) in the entire cohort that received ESG both in the randomized and cross-over segments of the trial.
- %TBWL in the ESG group compared to LS only
- % of patients in the ESG group achieving > 5% TBWL compared to LS only
- % of patients in the ESG group achieving > 10% TBWL compared to LS only
- Durability of the plication evaluated by endoscopy at 12 months (level 1) and effectiveness of re-tightening procedure performed at 12 months (level 1) in maintaining and / or enhancing weight loss at 24 months. Durability of the plication and procedure is defined as greater than 70% of the cohort undergoing repeat endoscopy achieving a score of ≥ 1 out of 3 prior to re-tightening (Grading system and evaluation in appendix). Efficacy of re-tightening is defined as ≥ 50% of the cohort undergoing the re-tightening maintaining or losing weight compared to the re-tightening weight at 12 months after the re-tightening procedure.
- Incidence of esophagitis at repeat endoscopy at 12 months (level 1). (LA grading system in form in appendix)
- Changes in quality of life assessed using standard validated questionnaires (IWQOL-lite and SF-36)
- Changes in depression assessed using PHQ-9 questionnaire
- Improvement/reduction of hunger and desire to eat evaluated using validated self-reported ratings of appetite based on a 100-mm visual-analogue scale
- Improvement in eating behaviors evaluated using the Three Factor Eating Questionnaire (TFEQ)
- Among LS randomized group with ESG at 12 months – outcome of 24 month %EWL

4.2.2 Safety

- The incidence, frequency, and severity of adverse events related to treatment with the device will be reported.
- <5% rate of serious adverse events related to the device or procedure (as determined by the site PI). Serious adverse events are classified in the Adverse Events table (page 25)

4.3 Study Setting

The study will be conducted at 9 US centers. The maximum enrollment at each individual site will be limited to 50 participants.

4.4 Subjects

Participants will be adult patients (21 years of age or above) with a BMI ≥ 30 and ≤40 kg/m^2 that meet the eligibility criteria below. All eligibility criteria must be met at the time of randomization.

4.5 Inclusion Criteria

1. Age 21-65
2. BMI ≥ 30 and ≤40 kg/m²
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, and completing diet counseling
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
9. ***There will be a quota for at least a) 50 patients with hypertension on one or more anti-hypertensive medication, b) 50 patients with type II diabetes mellitus on oral agents only with HgA1c ≤ 9, and thus the cohort of 200 patients will be stratified into three groups (Obesity, Obesity HTH, Obesity DM) and block randomized. No more than 50 participants without comorbidities will be enrolled in the trial.

4.6 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 severe (LA Grade C or D) 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. Gastrointestinal stromal tumors, history of premalignant gastric lesions (intestinal metaplasia), history of familial and nan-familial adenomatous syndromes.
8. A gastric mass or gastric polyps > 1 cm in size.
9. A hiatal hernia > 4cm of axial displacement of the z-line above the diaphragm or severe or intractable gastro-esophageal reflux symptoms.
10. A structural abnormality in the esophagus or pharynx such as a stricture or diverticulum that could impede passage of the endoscope.
11. Achalasia or any other severe esophageal motility disorder
12. Severe coagulopathy.
13. 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.
14. Subjects with any serious health condition unrelated to their weight that would increase the risk of endoscopy
15. Chronic abdominal pain
16. Motility disorders of the GI tract such as gross esophageal motility disorders, gastroparesis or intractable constipation
17. Hepatic insufficiency or cirrhosis
18. Use of an intragastric device prior to this study due to the increased thickness of the stomach wall preventing effective suturing.
19. Active psychological issues preventing participation in a life-style modification program as determined by a psychologist
20. Patients unwilling to participate in an established medically-supervised diet and behavior modification program, with routine medical follow-up.

21. Patients receiving daily prescribed treatment with high dose aspirin (> 80mg daily), anti-inflammatory agents, anticoagulants or other gastric irritants.
22. Patients who are unable or unwilling to take prescribed proton pump inhibitor medication
23. Patients who are pregnant or breast-feeding.
24. 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
25. Subjects taking medications on specified hourly intervals that may be affected by changes to gastric emptying, such as anti-seizure or anti-arrhythmic medications
26. Subjects who are taking corticosteroids, immunosuppressants, and narcotics
27. Subjects who are taking diet pills
28. Symptomatic congestive heart failure, cardiac arrhythmia or unstable coronary artery disease.
29. Pre-existing respiratory disease such as moderate or severe chronic obstructive pulmonary disease (COPD) requiring steroids, pneumonia or cancer.
30. Diagnosis of autoimmune connective tissue disorder (e.g. lupus, erythematous, scleroderma) or immunocompromised.
31. Specific diagnosed genetic disorder such as Prader Willi syndrome.
32. Eating disorders including night eating syndrome (NES), bulimia, binge eating disorder, or compulsive overeating
33. Known history of endocrine disorders affecting weight such as uncontrolled hypothyroidism.

5 TRIAL PROCEDURES

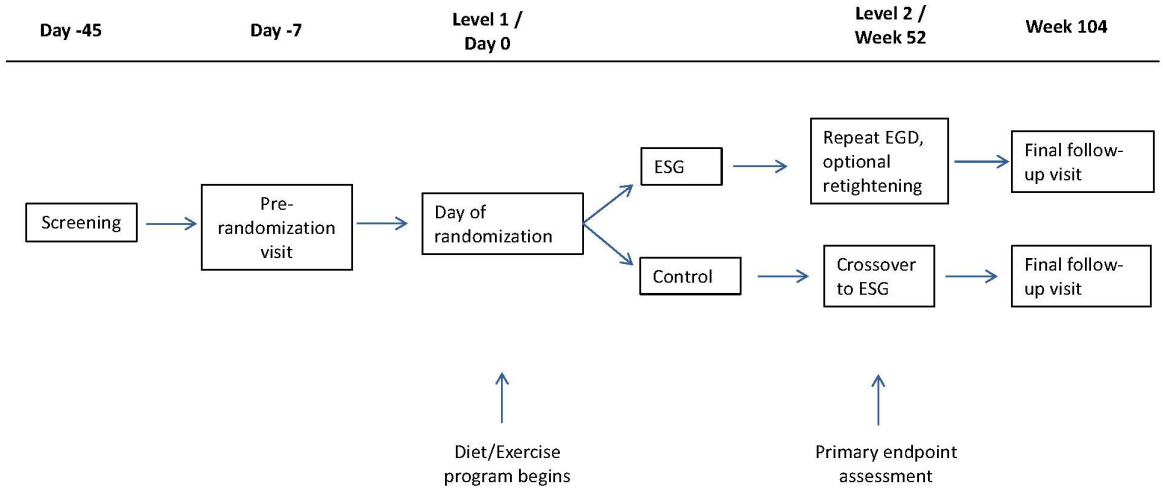
5.1 Informed consent

Prior to being enrolled in the trial, study participants must consent to participate after the nature, scope, and possible risks of the trial have been explained and outlined in an understandable form to them per the requirements of the IRB. The written informed consent document is provided in Appendix X. Participants are free to withdraw consent at any time.

After reading the informed consent document, the participant must sign and date the latest approved version of the informed consent form before any study procedures are performed. A copy of the signed consent document will be given to the participant, and the original signed consent form will be retained by the investigator.

5.2 Study Timeline

The study timeline is depicted in the figure below:



5.3 Screening and Eligibility Assessment

Screening will be conducted by the investigator or the co-investigator and documented on the Investigator delegated/medically qualified team member intake form (conventionally known as PI Intake Form) (Appendix A) and Screening Labs form (Appendix B). Screening must occur no more than 45 days prior to randomization.

Screening will include the following:

1. Sign informed consent form
2. Screening exam and intake by the investigator or co-investigator
3. Height, weight and BMI; waist and hip circumference; vital signs (blood pressure and pulse)
4. Dietary screening intake and approval
5. Laboratory tests (after 8 hours fasting)

- **CBC**: Hgb, Hct, WBC, MCV, platelets
- **Chemistry panel**: sodium, potassium, chloride, CO2, BUN, creatinine, fasting glucose, insulin, SGOT/AST, SGPT/ALT, alkaline phosphatase, total bilirubin, direct bilirubin, total protein, albumin, fasting lipids profile (total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol) Fe/TIBC, iron, B12, 25-Hydroxy Vitamin D, TSH, total Ghrelin level (only if available at participating institution), C-reactive protein.
- **Coag**: Pro Time or INR, PTT
- **PYY-1**, **GLP-1, Total Ghrelin** pending sites' availability to analyze
- **Urinalysis**
- **HgbA1C**
- **H. Pylori Breath Test**. **Patients with a positive h-pylori breath test will be treated and eradication must be confirmed with a stool antigen after treatment and prior to randomization**
- **EKG** for patients 50 years old or older
- **Urine pregnancy test** for women of child bearing potential

6. Questionnaires
7. Psychological evaluation and approval: Study psychologists will use their standard clinical evaluations for bariatric interventions.

Within one week of completion of the screening tests, the PI will review the results and determine the participant's eligibility. The center will inform the participant of their screening results within 10 days of completing testing. Any abnormal lab results will be communicated to the participant and they will be required to notify their primary care provider for any further action that may be necessary. All potential participants who qualify for randomization based on the initial screening assessments will return for a randomization visit where participants will have the chance to review any questions with the study staff, as well as a recap of the follow-up schedule, and they will then receive their randomization assignment.

5.4 Randomization

Participants will be stratified to three groups (Obesity, Obesity HTN, and Obesity DM) and will be randomly assigned to treatment or control group with a 1:1.5 allocation per a computer generated randomization using variable block randomization.

Participants will be notified of their randomization assignment on the day of the randomization visit. Participants randomized to the control group will proceed to an appointment with the dietician for their Week 1 visit on the day of randomization. Participants randomized to the treatment group will proceed to a brief visit with the dietician to review the post-op liquid diet, and the ESG will be scheduled within 30 days of randomization. Participants of child-bearing potential will be required to have a pregnancy test within 7 days of the scheduled ESG.

5.5 Trial Intervention

5.5.1.1.1 Control group

Participants randomized to the control group (lifestyle intervention only) in Level 1 will undergo a standard moderate intensity life-style intervention during the first 12 months of Level 1. The first dietary visit will be scheduled on the day of randomization. A low-calorie diet plan will be reviewed with each participant and will be adjusted according to each participant's needs. Participants in the control group will not undergo the liquid transitional diet as it is difficult to achieve compliance without intervention. Physical activity, including 150 minutes of aerobic exercise per week, will be encouraged and assessed for compliance during the study. Participants will have 12 follow-up visits in the 12 months of Level 1 as described in the schedule of events. Participants will receive $100 for every 4 visits they attend consecutively in Level 1 with the ability to earn a maximum of $300 at the end of the first 12 months of Level 1.

Control group participants who were compliant with at least 75% of visits in the first 12 months of Level 1, have not achieved ≥25% EWL measured at the week 52 visit, or still have a BMI ≥30 and ≤40, and have no new psychosocial contraindications as deemed by the treatment team to the procedure will cross over to receive ESG in Level 2, in addition to the standard moderate intensity lifestyle intervention program for 12 months. After crossing over into Level 2, participants will be able to earn the same remuneration as in Level 1 ($100 for every 4 consecutive visits attended). Those who were compliant with attending 75% of the visits in Level 2 (second 12 months) will receive a bonus of $300 at the final study visit, for a potential total of $900 earned in the two years.

5.5.1.1.2 Treatment Group

ESG is an endoluminal procedure similar to sleeve gastrectomy targeting the shape of the stomach. The targeted shape is tubular gastric body with a small pouch in the fundus. A step-by-step video circulated to all sites and a mandate to have the proctor present for the first case were done to ensure conformity to the technique. The same expert endoscopist will proctor all sites. In general, the technique involves 7-9 bites in a running O shaped pattern that is repeated 4-5 times in the stomach to achieve the desired shape. Proximally, it might be difficult to do the O sequence; thus, the operator can do triangular 3-4 bites interrupted suturing sequence. Each O sequence can be enforced by a layer of triangular interrupted suture. All bites are intended to be full thickness with the aid of tissue helix. The re-enforcing bites can be submucosal. The sequence is staggered to avoid gaps. In general, sutures used is limited to 10. ESG narrows the stomach axially and reduce its length longitudinally.

Participants assigned to the treatment group will report to the procedure suite within 30 days of randomization. Participants of child-bearing potential will be required to have a pregnancy test within 7 days of the scheduled ESG. Participants taking medications for hypertension and/or type II diabetes will be instructed to notify their prescribing physician of their procedure and to discuss any necessary medication changes for the post-op period.

The ESG is done in the outpatient setting. Within two hours prior to ESG, IV access will be obtained, IV hydration initiated, and a transdermal scopolamine patch placed for patients 50 years of age or younger (this will be removed in 24 to 48 hours after the procedure).

Prior to ESG, a standard upper endoscopy is performed to rule out any contraindicating findings. All ESG procedures will be done under general anesthesia with endotracheal intubation and utilizing CO2 insufflation. During the procedure, IV hydration will be continued and patients will be given the following: one dose of IV antibiotics (Zosyn, Ceftriaxone, or Ciprofloxacin), 8mg of IV Zofran, and 8mg of Decadron. A minimum of two liters of IV hydration (either normal saline or lactate ringers) should be administered in the perioperative recovery period before discharge. Sequential compression devices (SCDs) will be used perioperatively to decrease the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Patients will be prescribed the following medications after the procedure to manage expected post-procedural symptoms:

- Zofran 4mg rapid dissolving pills taken every 6 hours as needed for nausea for 7 days
- Phenergan 25mg suppositories taken twice daily as needed for nausea for 7 days
- Low dose liquid narcotic taken every 6 hours as needed for pain for 5 days
- Omeprazole 40mg capsule to be opened in apple sauce for the first 7 days after ESG, then taken as whole capsule daily for 12 months from date of ESG
- Ativan 0.5 mg taken orally once daily for up to 3 days as needed for intractable nausea or anxiety.

Admission for a 23 hours observation for symptom management is optional but permissible. All ESG patients will be given instructions prior to being discharged from the facility to help manage post-procedural symptoms, including nausea, vomiting and/or abdominal pain. Study staff will call patients once between 18-36 hours after the procedure to assess symptoms and to relay any issues to the PI. If the PI feels it is necessary to see a patient in clinic, an unscheduled visit will be scheduled appropriately.

All patients undergoing ESG will go on a 6 weeks transitional diet consisting of 4 weeks of full liquid protein shakes and 2 weeks of soft pureed diet (Appendix G). The transitional diet is designed to allow suture healing and incorporation within the plicated gastric wall. After the transitional diet period, all patients will be on a low-calorie healthy diet personalized by the dietician according to individual patients' needs and conducive to weight loss. Physical activity, including 150 minutes of aerobic exercise per week, will be encouraged and assessed for compliance during the study. It may be recommended for patients to take two chewable multivitamins and one calcium plus vitamin D supplement daily starting within 1 week of the ESG.

ESG patients will undergo a standard moderate intensity life-style intervention administered over 12 visits in the first year after ESG. Participants will be required to follow up with their prescribing physician to make any necessary changes to their hypertension and/or type II diabetes medications at 3, 6, 9 and 12 months. Completion of patient follow-up with providers for medication adjustment will be captured with completion of the appropriate CRF at the corresponding visits. In the event that participants are unable to contact their physician or participants are experiencing symptoms related to the medication dosing requiring urgent action, the study team will make any necessary

changes in their medication dosing and document these changes appropriately in the relevant CRFs. Any medication changes will be monitored and recorded by the study team.

All ESG patients in Level 1 (80) will be evaluated for %EWL at the end of Level 1 (measurement of primary endpoint). Those ESG patients who have achieved >25% EWL at the end of Level 1 will not undergo a repeat endoscopy and will continue to follow-up with a lifestyle intervention in Level 2. Those ESG patients who have not achieved >25% EWL at the end of Level 1 will undergo a repeat upper endoscopy at 52 to 60 weeks to assess the durability of the plications (see Plication Durability form), and perform a retightening of the ESG if needed. The need for re-tightening will be determined by the PI after evaluating the sutures based on a grading system presented in the retightening CRF. The retightening procedure will be performed if at least one of the three portions (proximal, mid, and distal) of the endoscopic sleeve is non-tubular in shape. For each tubular third of the sleeve, 1 point will be given. A score of 3/3 means the entire (proximal, mid, and distal) sleeve is tubular in shape. A score of 2/3 means that one-third of the sleeve is no longer tubular. A score of 1/3 means that two-thirds of the sleeve are no longer tubular. Finally a score of 0/3 means the entire sleeve is no longer tubular. Re-tightening will occur for patients with a score of 0, 1 or 2.

The retightening procedure will be performed in a similar fashion as the initial ESG with similar technique, peri-procedural care, transitional diet, and aftercare. However, the retightening procedure will only target open (non-restrictive) portions of the ESG; it should thus be an abbreviated procedure. The number of sutures used in the retightening procedure will be determined by the PI with the goal of re-capturing the tubular configuration of the sleeve.

All patients will continue follow-up with a modified lifestyle intervention program administered over 6 visits in the second year. Laboratory testing will be obtained as detailed in the study schedule of events (Appendix F).

Participants randomized to the ESG group will follow the same follow-up schedule as control participants in Level 1. Participants will receive $100 for every 4 visits they attend consecutively in Level 1 with the ability to earn a maximum of $300 at the end of the first 12 months of Level 1. In Level 2, participants will report for 6 visits, with the potential to earn $100 for every 2 consecutive visits they attend. If they attend all 6 visits, they will receive a bonus of $300 at the final visit, for a potential total earned of $900 for all visits across two years.

Participants will return for follow-up visits per the schedules of events below (Appendix F). An in-window visit will be considered as reporting for follow-up visits within a two-week window of the visit date.

5.6 Schedule of Events

5.6.1.1.1 Schedule of Events for Treatment Group, Year 1, Level 1

TABLE 1. MERIT SCHEDULE OF EVENTS (Year 1, Level 1, Treatment Group, 80 patients)											
	Enrollment; Screening/ Baseline	Randomization	ESG Procedure	Post-Op Phone Call	Weeks 1, 4, 8	Week 12	Weeks 16, 20	Week 24 (6 month)	Weeks 30, 36, 42, 48	Week 52 (Final Year 1 visit)	Unscheduled Visit
Visit Number	-1		0	-	1,2,3	4	5,6	7	8,9,10,11	12	
Informed consent	X										
Complete Physical Exam (CPE) by Investigator or Investigator delegated / medically qualified team member	X					X		X	X	X	X
Investigator or Investigator delegated/medically qualified team member exam					X	X	X	X	X	X	X
EKG if (> 50 yo)	X										
Formal nutritional assessment	X										
Formal psychology evaluation	X										
Pregnancy test (females of childbearing potential only)	X										
Laboratory tests, H-pylori breath testing (baseline only)**	X							X		X	
Questionnaires#	X					X		X		X	
Inclusion/exclusion criteria	X										
Endoscopy / Procedure			X								
Procedure Assessment Form			X								
GERD Questionnaire + Activity Assessment Form	X				X	X	X	X	X	X	
Weight, BMI/height, Waist and Hip Circumference Form	X		X		X	X	X	X	X	X	X
Vital Signs Form	X		X		X	X	X	X	X	X	X
Adverse Events Form			X	X	X	X	X	X	X	X	X
Medications Form##	X		X	X	X	X	X	X	X	X	X
Post-enrollment Nutrition / Exercise / satiety counseling and assessment		X++			X	X	X	X	X	X	
Randomization to ESG+	X	X									
Subject Satisfaction Questionnaire (treatment phase)										X	

** Electrolytes, Creatinine, CBC, Iron, TIBC, B12, 25-hydroxy Vitamin D, TSH, HgA1c, fasting blood sugar and insulin, PTT, fasting lipids profile (total cholesterol, LDL, HDL, and Triglyceride), ALT, AST, ALK-P, total bilirubin, direct bilirubin, BUN, total protein, albumin, CRP, urinalysis; also include PYY-1, GLP-1 and total Ghrelin pending sites' availability to analyze

Eating disorder questionnaire + hospital anxiety and depression questionnaires (only at base-line), IWQOL-Lite, SF36, PHQ9, Pittsburg Sleep Quality Index (PSQI), Three factor eating questionnaire (TFEQ)

Record all medications including dose and frequency; especially diabetes and blood pressure medication.

+ To occur after all screening assessments are complete; within 45 days of screening evaluations

++ Nutritional visit to discuss upcoming post-op liquid diet

5.6.1.1.2 Schedule of Events for Treatment Group, Year 2, Level 2

TABLE 2. MERIT SCHEDULE OF EVENTS (Year 2, Level 2, Treatment Group, 80 Patients)							
	ESG retightening+	**Post-Op Clinical Eval++**	**Follow-up after ESG retightening OR Week 60+**	**Week 72-76***	**Weeks 80, 88, 96**	**Week 104 (Final Year 2 visit)**	**Unscheduled Visit**
Visit Number	17	-	18	19	20, 21, 22	23	
Informed consent							
Complete Physical Exam (CPE) by Investigator or Investigator delegated / medically qualified team member				X		X	X
Investigator or Investigator delegated/medically qualified team member exam			X	X	X	X	X
EKG if (> 50 yo)							
Formal nutritional assessment							
Formal psychology evaluation							
Pregnancy test (females of childbearing potential only)							
Laboratory tests**				X		X	
Questionnaires#				X		X	
Inclusion/exclusion criteria							
Endoscopy / Procedure	X						
Procedure Assessment Form	X						
GERD Questionnaire + Activity Assessment Form			X	X	X	X	
Weight, BMI/height, Waist and Hip Circumference Form	X		X	X	X	X	X
Vital Signs Form	X		X	X	X	X	X
Adverse Events Form		X	X	X	X	X	X
Medications Form##			X	X	X	X	X
Post-enrollment Nutrition / Exercise / satiety counseling and assessment			X	X	X	X	
Subject Satisfaction Questionnaire (study termination)						X	

** Electrolytes, Creatinine, CBC, Iron, TIBC, B12, 25-hydroxy Vitamin D, TSH, HgA1c, fasting blood sugar and insulin, PTT, fasting lipids profile (total cholesterol, LDL, HDL, and Triglyceride), ALT, AST, ALK-P, total bilirubin, direct bilirubin, BUN, total protein, albumin, CRP, urinalysis; also include PYY-1, GLP-1 and total Ghrelin pending sites' availability to analyze

IWQOL-Lite, SF36, PHQ9, Pittsburg Sleep Quality Index (PSQI), Three factor eating questionnaire (TFEQ)

Record all medications including dose and frequency; especially diabetes and blood pressure medication.

++ Post-op phone call, no clinic visit, to occur between 18-36 hours post-op

+ ESG retightening to occur between Weeks 52-60 for those who qualify with in-clinic follow-up visit to occur 4 weeks post retightening, or subjects to continue to Week 60 for those who do not qualify for ESG retightening

*Lab draw to occur between Week 72-76

5.6.1.1.3 Schedule of Events for Control Group, Crossover in Year 1, Level 1

TABLE 3. MERIT SCHEDULE OF EVENTS (Year 1, Level 1, Control Group, 120 patients)									
	Enrollment; Screening/ Baseline	**Randomization / Week 1 visit**	**Weeks 4, 8**	**Week 12**	**Weeks 16, 20**	**Week 24 (6 month)**	**Weeks 30, 36, 42, 48**	**Week 52 (Final Year 1 visit), re-screen for crossover to ESG**	**Unscheduled Visit**
Visit Number	-1	1	2,3	4	5,6	7	8,9,10, 11,	12	
Informed consent	X								
Complete Physical Exam (CPE) by Investigator or Investigator delegated / medically qualified team member	X			X		X	X	X	X
Investigator or Investigator delegated/medically qualified team member exam		X++	X	X	X	X	X	X	X
EKG if (> 50 yo)	X							X	
Formal nutritional assessment	X								
Formal psychology evaluation	X								
Pregnancy test (females of childbearing potential only)	X								
Laboratory tests, H-pylori breath testing (baseline only)* *	X							X	
Questionnaires#	X			X		X		X	
Inclusion/exclusion criteria	X							X	
Endoscopy / Procedure									
Procedure Assessment Form									
GERD Questionnaire + Activity Assessment Form	X	X	X	X	X	X	X	X	
Weight, BMI/height, Waist and Hip Circumference Form	X	X	X	X	X	X	X	X	X
Vital Signs Form	X	X	X	X	X	X	X	X	X
Adverse Events Form		X	X	X	X	X	X	X	X
Medications Form##	X	X	X	X	X	X	X	X	X
Post-enrollment Nutrition / Exercise / satiety counseling and assessment		X	X	X	X	X	X	X	
Randomization to ESG vs. LS+		X							
Subject Satisfaction Questionnaire (control phase)								X	

** Electrolytes, Creatinine, CBC, Iron, TIBC, B12, 25-hydroxy Vitamin D, TSH, HgA1c, fasting blood sugar and insulin, PTT, fasting lipids profile (total cholesterol, LDL, HDL, and Triglyceride), ALT, AST, ALK-P, total bilirubin, direct bilirubin, BUN, total protein, albumin, CRP, urinalysis; also include PYY-1, GLP-1 and total Ghrelin pending sites' availability to analyze

Eating disorder questionnaire + hospital anxiety and depression questionnaires (only at base-line), IWQOL-Lite, SF36, PHQ9, Pittsburg Sleep Quality Index (PSQI), Three factor eating questionnaire (TFEQ)

Record all medications including dose and frequency; especially diabetes and blood pressure medication.

+ LS start with the week 1 visit with no transitional diet.

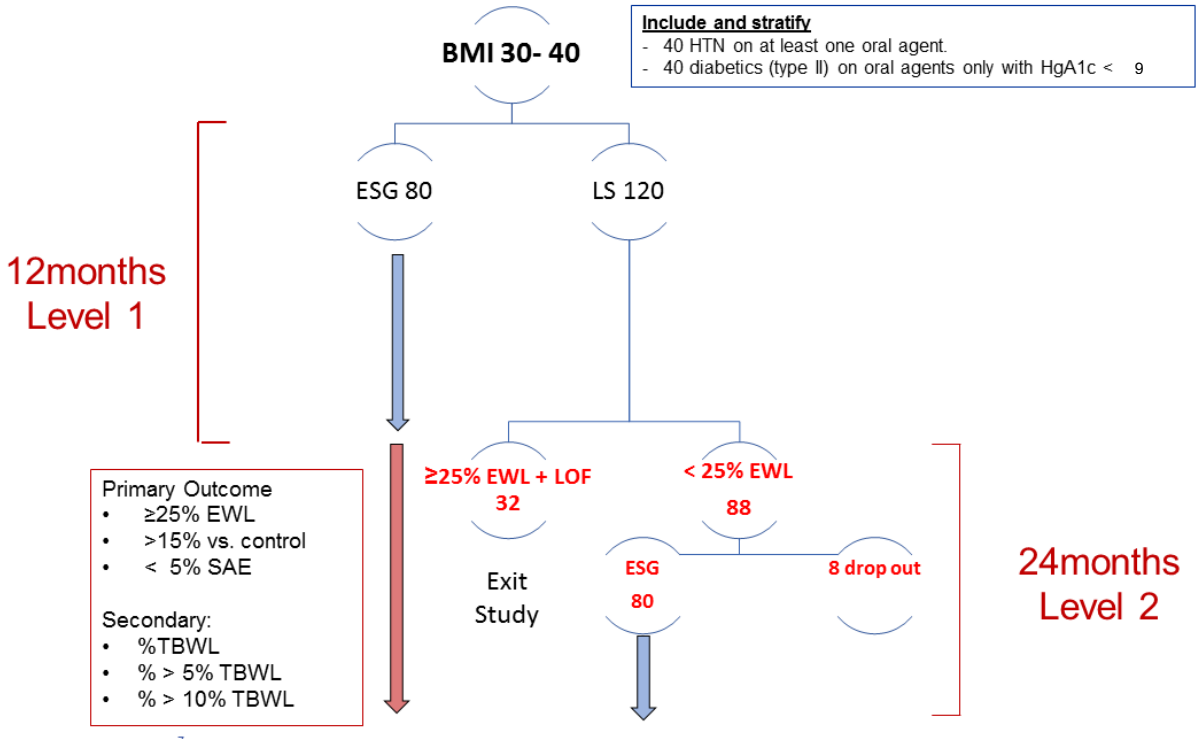
++ Required only for Week 1 visit

5.6.1.1.4 Schedule of Events for Control Group, Crossover in Year 2, Level 2

TABLE 3. MERIT SCHEDULE OF EVENTS (Year 2, Level 2, Control Group, cross-over 120 patients)									
	ESG Procedure	Post-Op Phone Call	Weeks 1, 4, 8	Week 12	Weeks 16, 20	Week 24 (6 month)	Weeks 30, 36, 42, 48	Week 52 (Final Year 1 visit)	Unscheduled Visit
Visit Number	0	-	1,2,3	4	5,6	7	8,9,10,11	12	
Informed consent for cross-over procedure									
Complete Physical Exam (CPE) by Investigator or Investigator delegated / medically qualified team member				X		X	X	X	X
Investigator or Investigator delegated/medically qualified team member exam			X	X	X	X	X	X	X
EKG if (> 50 yo)									
Pregnancy test (females of childbearing potential only)									
Laboratory tests **						X		X	
Questionnaires#				X		X		X	
Endoscopy / Procedure	X								
Procedure Assessment Form	X								
GERD Questionnaire + Activity Assessment Form			X	X	X	X	X	X	
Weight, BMI/height, Waist and Hip Circumference Form	X		X	X	X	X	X	X	X
Vital Signs Form	X		X	X	X	X	X	X	X
Adverse Events Form	X	X	X	X	X	X	X	X	X
Medications Form##	X	X	X	X	X	X	X	X	X
Post-enrollment Nutrition / Exercise / satiety counseling and assessment			X	X	X	X	X	X	
Subject Satisfaction Questionnaire (treatment phase)								X	

** Electrolytes, Creatinine, CBC, Iron, TIBC, B12, 25-hydroxy Vitamin D, TSH, HgA1c, fasting blood sugar and insulin, PTT, fasting lipids profile (total cholesterol, LDL, HDL, and Triglyceride), ALT, AST, ALK-P, total bilirubin, direct bilirubin, BUN, total protein, albumin, CRP, urinalysis; also include PYY-1, GLP-1 and total Ghrelin pending sites' availability to analyze
# Eating disorder questionnaire + hospital anxiety and depression questionnaires (only at baseline), IWQOL-Lite, SF36, PHQ9, Pittsburg Sleep Quality Index (PSQI), Three factor eating questionnaire (TFEQ)
Record all medications including dose and frequency; especially diabetes and blood pressure medication.

5.6.1.1.5 Study Flow 50htn 50dm 30-40 BMI



5.7 Participant Retention

All patients will be encouraged to complete study follow-up, and all reasonable efforts will be made to ensure completeness of follow-up.

It is understood that study participants may withdraw consent for study participation at any time irrespective of their reasons. The investigators may also withdraw a participant from the study in order to protect their safety or adverse device effects, and/or if they are unwilling or unable to comply with the required study procedures.

In the event of a patient withdrawing from the trial, the reason for withdrawal must be documented on the CRF.

5.8 Replacement of withdrawn subjects

Patients withdrawn prior to ESG or LS will not count towards the target enrollment. New patients will be randomized to target enrollment of 200 total patients receiving ESG or LS. The power and sample size calculation includes additional patients to improve power assuming some post-intervention dropout.

5.9 Source Documentation

Study case report forms will be used as source documentation for the trial for all participant follow-up visits. Source documentation from the electronic medical record will be required for the ESG procedure(s), medications, and any serious adverse medical events. Any additional pertinent documentation regarding the patient's trial participation will be also be required to be filed in the subject binder.

6 DATA MONITORING AND SAFETY REPORTING

6.1 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will serve as an autonomous advisory group for the trial. The DMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, adjudication of Adverse Events, and for monitoring the overall conduct of the clinical trial. The DMC may also provide recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMC members appointed for this trial consist of individuals who collectively have experience and expertise in the management of patients with obesity, experience in randomized clinical trials with endoscopic devices, experience in safety monitoring and absence of significant conflicts of interest or participation in the trial.

The first DMC meeting will occur once 25 participants have undergone the ESG. Subsequent DMC meetings will be scheduled every four months while the trial is actively going.

The DMC will be led by Dr. Natan Zundel, a world leader in bariatric and metabolic surgery at Florida International Univestity and past president of the International Federation of Bariatric Surgery.

6.1.1 Stopping rules

The study will be stopped if a) one death attributed to the procedure or the device, b) >1% of Grade IV AEs has occurred, and c) if > 5% Grade III or more AEs occur.

6.2 Adverse Events

6.2.1 Definitions

The following definitions will be used:

6.2.1.2 Adverse Event:

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) whether or not related to the study intervention. Each subject will be followed closely to ensure safety.

Adverse events will be classified using the Clavien-Dindo classification.

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

6.2.1.2.1 Treatment Criteria

6.2.1.2.1.1 Thiamine Replacement

Criteria for thiamine replacement for suspected or established vitamin B_1 deficiency on subjects with uncontrolled nausea and/or vomiting:

- Vomiting post ESG continues 7 days or more after EGS, in ability to take down adequate levels of hydration. Defined as vomiting >2 x a day.
- Nausea post ESG continues 7 days, daily with the inability to drink due to nausea, unrelieved by nausea medication, and continuing 7 days or more.

Thiamine replacement[26]:

- Hospitalization: 500 mg per day thiamine IV push for 3-5 day followed by 250 mg per day IV push + multivitamin in 1 L NS q day while in the hospital.
- Outpatient: Thiamine 100 mg TID daily for 3 months.

6.2.1.3 Serious Adverse Event (SAE):

An adverse event that meets one of the following criteria

- Led to death
- Resulted in serious deterioration in the health of the subject that results in:
  - Life-threatening illness or injury
  - Permanent impairment of a body structure or a body function

  - The need for in-patient care or prolongation of hospitalization (this does not include the optional 23 hours observation admission after ESG or re-tightening procedure).
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- **Planned hospitalization for a pre-existing condition, or a procedure required by the trial protocol, without serious deterioration in health, is not considered a serious adverse event**

Unanticipated problems, SAEs and AEs will be reported to governing IRBs per local guidelines.

6.2.1.4 Device-Related Adverse Event (DRAE):
An adverse event related to the use of the medical device. This definition includes any events resulting from incorrect delivery and operation of the device and/or of its approved accessories, or any malfunction of the device or its components. This definition also includes any event resulting from user error or from intentional misuse of the device.

6.2.1.5 Serious Device-Related Adverse Event (SDRAE):
Any untoward medical occurrence that can be attributed wholly or partly to the device, which resulted in any of the characteristics of a serious adverse event as described above.

6.2.1.6 Unanticipated Adverse Device Effects (UADE):
Any adverse device effect which by its nature, incidence, severity or outcome, has not been identified under the SAE section 6.2.

6.3 Protocol Deviations

All protocol deviations will be documented with the subject number and date of the protocol deviation. The following information will be documented for each protocol deviation:

- Inclusion/Exclusion exceptions or violations, including subject did not sign informed consent prior to study admission
- Follow-up visit not performed or Follow-up outside of window
- Required testing or questionnaire not performed
- Other (Describe)

Protocol deviations should be reported to the lead institutions within 72 hours of noting the deviation.

7 STATISTICAL ANALYSIS

7.1 Power and Sample Size

The primary endpoint for power and sample size is %EWL at 12 months. The null hypothesis is no difference in mean %EWL between ESG and LS randomized arms (Ho: $\mu t = \mu c$ where μt is the average %EWL in the ESG group and μc is average %EWL in the LS group). We will perform a two-sided hypothesis test at alpha level 0.05 (alternative hypothesis Ha: $\mu t \neq \mu c$) Based on the published literature with the ESG technique a conservative presumption is 25% EWL in the ESG arm with a standard deviation (SD) of 30% at 12 months compared to 10% EWL on LS alone with SD of 5%. We plan a 1:1.5 randomization scheme that allocates 3 patients to LS for every 2 to ESG at the time of randomization. Based on a two-sample t-test with unequal variances and two-sided alpha=0.05, we would have 80% power to detect a difference of 15% in average %EWL between groups with 34 patients allocated to ESG and 51 randomized to LS. 90% power would require group sizes of 45 and 68, respectively. To allow for dropout, and more importantly, to power exploratory aims for obesity comorbidity subgroups, we propose the initial randomization of 200 patients – 80 to ESG and 120 to LS.

120 subjects are initially randomized to LS in level 1. Of these, we anticipate up to 20% will achieve a successful decrease of ≥25% in %EWL through LS alone at 12 months. Further, we anticipate up to 20% may be lost to follow up or drop out prior to 12 month follow up. Thus, we anticipate at least 77 (120*0.8*0.8) subjects to continue to level 2 and be offered ESG. We will test the one-sample hypothesis (non-randomized) that of those offered ESG at 12 months, average change in %EWL will be at least 10%. Based on a one-sample t-test with two-sided alpha=0.05 and standard deviation at 24 months of 30%, 70 subjects completing ESG would have 98% power to detect an effect of 25% reduction in %EWL.

7.2 Statistical Analysis

Statistical analyses of randomized groups at 12 months will be performed based on a modified intent-to-treat (mITT) principle for efficacy analyses. Patients randomized but subsequently withdrawn or identified as meeting exclusion criteria prior to intervention (as applied to both the treatment and control arms) will be excluded from the analysis if the reason for exclusion is documented and unrelated to the randomized arm.

7.2.1 Primary Aim

The primary outcome is %EWL at 12 months assessed in the two randomized arms. A hierarchical linear regression model will be fitted to post-randomization %EWL measurements, planned for 11 post-randomization timepoints through 12 months. Post-randomization outcomes will be modeled as a function of discrete visit (instead of assuming a linear or other functional form of time since randomization) and treatment indicator variables. Models will also adjust for age, sex, baseline BMI, HTN, and DM status to reduce residual variation and improve power. The primary outcome comparison at 12 months is estimated from a linear combination of treatment and time indicators. A spatial autocorrelation covariance structure will be used.

Assumptions for normality of residuals and homoscedastic variance will be assessed; hierarchical median regression (Geraci and Bottai, 2014) will be considered under significant violations.

7.2.2 Secondary Aims

Continuous secondary outcomes, including change in systolic and diastolic blood pressure and change in HbA1c, QOL questionnaires such as the SF-36, PHQ-9, and eating behavior scores will be compared between treatment arms using ANCOVA with adjustment for the same variables specified in the primary analysis.

Binary outcomes, including proportion with ≥25% reduction in %EWL and incidence of esophogitis will be compared between treatment arms by Pearson Chi-square test.
Among patients randomized to the treatment ESG group, the association between the durability of plication at repeat endoscopy (score ≥1 on EGD grading system) and number of sutures required for re-tightening with change in EWL from 12 months to 24 months will be assessed using linear regression with adjustment for BMI, %EWL between randomization and 12 month follow up, HTN status, and DM status. This is an observational comparison.

Among patients randomized to the control LS arm, the percent EWL from the 12 month assessment to the 24 month assessment will be measured. This percentage will be compared to percent EWL in the same group with lifestyle intervention only in the first 12 months using a one sample t-test.

Among all subjects, %EWL will be compared at 24 months between initial and delayed ESG. However, this is not considered a comparison of randomized arms as follow up is not continued for patients with ≥25% EWL from LS at 12 months.

7.2.3 Secondary Analyses

A per-protocol analysis will compare ESG to LS randomized groups among protocol adherent patients – here, defined among ESG randomized patients as those actually receiving the procedure and making ≥ 80% follow-up visit in both treatment and control groups. Modified ITT will be considered the primary approach for all efficacy analyses, and will include patients who actually receive the ESG or started the life-style program regardless of adherence to follow-up visits. Safety endpoints and adverse events may be evaluated based on treated group (per-protocol).

Additional analyses may assess the moderating effect of HTN and DM on the effect of ESG vs LS at 12 months. Linear regression will include an interaction between HTN (or DM) and randomized group to determine the effect of ESG in subgroups and whether the effect is different between HTN and non-HTN (also, separately, DM and non-DM) patients.

Additional outcomes and analyses not specified here are considered exploratory and post-hoc and will be clearly identified as such in any publications.

7.3 Missing Data

The primary analysis uses a hierarchical regression model, assuming post-randomization dropout is missing at random (MAR) among subjects completing at least 1 of the 11 planned follow up visits.
Patients excluded after randomization and before ESG/LS on the basis of identified exclusion criteria will be excluded from analyses; reasons for meeting exclusion criteria will be documented. Patients that withdraw/dropout between randomization and ESG/LS are assumed to be missing completely at random. However, a sensitivity analysis will compare withdrawn subjects to participating subjects and perform analyses under MAR (including multiple imputation) assumptions if these subjects appear different or if dropout occurs at substantially different rate in one arm compared to the other. Participating patients who dropout prior to the first follow up visit will be analyzed similarly.

7.4 Randomization and Data Collection

Stratified block randomization schedules will be uploaded to REDCap, with strata defined by HTN and DM status. Data will be collected in REDCap data collection forms.

7.5 Interim Analysis

No interim analysis will be performed for efficacy endpoints. Adverse events will be monitored throughout and discussed with the data monitoring committee.

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