Endoscopic sleeve gastroplasty (ESG) as a treatment option for obesity in ulcerative colitis patients undergoing colectomy with ileal pouch anal anastomosis (IPAA)

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Endoscopic sleeve gastroplasty (ESG) as a treatment option for obesity in ulcerative colitis patients undergoing colectomy with ileal pouch anal anastomosis (IPAA)

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Protocol Signature Page

Study Title: Endoscopic sleeve gastroplasty (ESG) as a treatment option for obesity in ulcerative colitis patients undergoing colectomy with ileal pouch anal anastomosis (IPAA)

Protocol Version Number: Version 6

Protocol Date: 20MAY2025

Sponsor: Mayo Clinic, Rochester, MN

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

_____ _____
Principal Investigator's Signature Date

_____ _____
Site Name Site Number

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CNS	Central Nervous System
CRF	Case Report Form
CRTU	Clinical Research and Trials Unit
DSMB	Data and Safety Monitoring Board
DVT	Deep Vein Thrombosis
EBT	Endoscopic Bariatric Therapy
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
EMR	Electronic Medical Record
ESG	Endoscopic Sleeve Gastroplasty
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GSRS	Gastrointestinal Symptom Rating Scale
HbA1c	Hemoglobin A1c
HCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form

ICU	Intensive Care Unit
IGB	Intragastric Balloon
IPAA	Ileal Pouch Anal Anastomosis
IRB	Institutional Review Board
IUD	Intrauterine Device
LFT	Liver Function Test
mPDAI	Modified Pouch Disease Activity Index
PE	Pulmonary Embolism
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event/Serious Adverse Experience
SD	Standard Deviation
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SOC	Standard of Care
SOP	Standard Operating Procedure
TBWL	Total Body Weight Loss
UADE	Unanticipated Adverse Device Effect
UC	Ulcerative Colitis
UPIRTSO	Unanticipated Problem Involving Risk to Subjects or Others

Study Summary

Title	Endoscopic sleeve gastroplasty (ESG) as a treatment option for obesity in ulcerative colitis (UC) patients undergoing colectomy with ileal pouch anal anastomosis (IPAA)
Running Title	ESG use for weight loss in obese UC patients undergoing colectomy with IPAA
IRB Protocol Number	22-007643
Methodology	Single-Arm Interventional Trial
Overall Study Duration	3 years
Subject Participation Duration	Approximately 2 years
Objectives	To evaluate the efficacy and safety of ESG for weight loss in a population of obese UC patients undergoing colectomy with eventual IPAA
Number of Subjects	12
Diagnosis and Main Inclusion Criteria	Ulcerative colitis, obesity (BMI 30-50 for at least 6 months), plans for or history of colectomy with eventual IPAA
Reference therapy	Endoscopic sleeve gastroplasty (ESG)

Statistical Methodology	Our primary aim of six month %TBWL will be described both as a continuous variable, as well as categorical variable to report on proportion of patients reaching pre-specified %TBWL endpoints. All continuous variables will be reported as either mean and SD or median and range. Categorical variables will be reported as number and percentage. Descriptive statistics of adverse events, their severity and relatedness to the procedure will be reported.

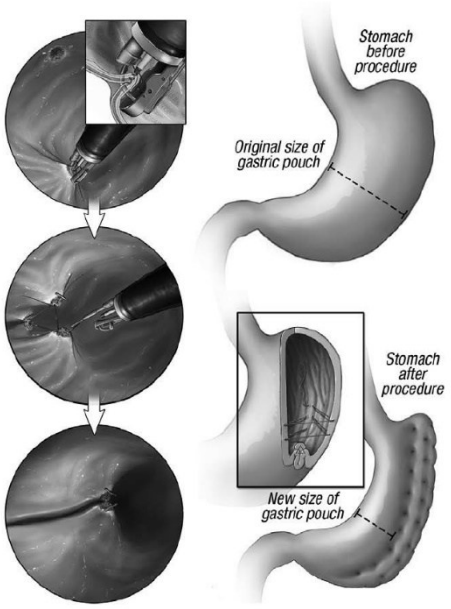
1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations and Mayo Clinic policies and procedures.

1.1 Background

The prevalence of obesity in the inflammatory bowel disease (**IBD**) population now mirrors that of the general population, with rates estimated between 15-40%.[1-4] Not only are the efficacy and safety of most weight loss interventions relatively unexplored in the IBD population, but a diagnosis of IBD is considered a relative contraindication to bariatric surgery. Outside of surgery, available strategies to treat obesity for the general population include diet and lifestyle modifications, pharmacotherapy, and recently endoscopic bariatric therapies (**EBTs**). Intensive lifestyle modifications and pharmacologic therapy are only modestly effective and fraught with limited durability.[5-6] Thus, EBT has emerged as an attractive weight loss modality, providing an effective, less invasive, organ-preserving, and potentially reversible means of filling a gap in the current obesity management paradigm. The application of EBT has not been prospectively studied in IBD patients. However, our group was able to describe a series of 7 IBD patients who underwent EBT, which appeared to be an effective weight loss strategy, with the majority of ESG patients losing weight on par with bariatric surgery. In these patients there were no device or procedure-related serious adverse events, outside of one case of aspiration pneumonia. IBD outcomes in these individuals also appeared favorable. Of the available EBTs, endoscopic sleeve gastroplasty (**ESG**) appears to have superior efficacy and tolerance as compared to intragastric balloon (**IGB**), and is also a more durable option given IGB is only placed for six months. ESG is performed via minimally invasive outpatient endoscopy where an FDA-approved full thickness endoscopic suturing device is utilized to reduce the volume of the stomach, promoting early satiation and resulting in a restrictive weight loss (*Figure 1*).

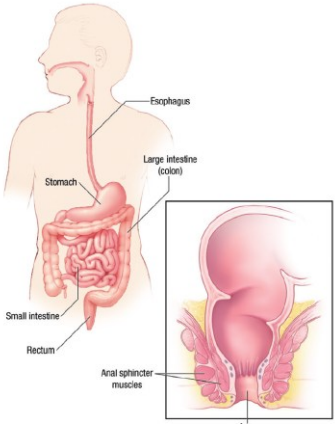
Figure 1. *Endoscopic sleeve gastroplasty*



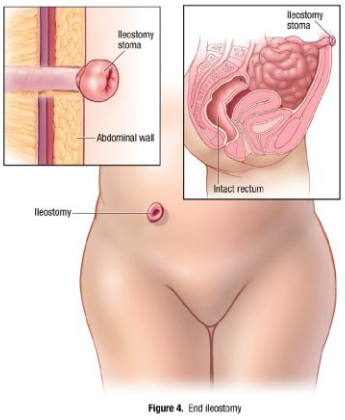
Because obesity is considered a low-grade inflammatory state, it has been postulated that it contributes to the inflammatory cascade and may be a negative prognostic factor in IBD, including ulcerative colitis (**UC**). Our group has demonstrated that rates of obesity have increased nearly 2-3 fold in recent decades, when comparing patients diagnosed with UC in the 1970s versus those diagnosed in the early 2000s.[1] We also found that the risk of future colectomy for patients diagnosed with UC between 1990-2010 rose by 5% with each incremental increase in body mass index (**BMI**) by 1 kg/m^2.[10] Irrespective of obesity, it is known that approximately 10-15% of UC patients will ultimately require colectomy during the first ten years following their diagnosis for either medically-refractory disease or the development of colorectal neoplasia.[11] In these settings, the most commonly performed procedure is a proctocolectomy with formation of ileal pouch anal anastomosis (**IPAA**) (*Figure 2*). Considering the fact that more than 1 million Americans are currently living with UC, IPAA is commonplace in the realm of IBD management. An IPAA is essentially a reservoir created from a loop of small bowel which allows full removal of the colon while maintaining bowel continuity, eliminating the need for a permanent ileostomy (*Figure 2)*. Obesity can prohibit the ability to create an IPAA due to inherent technical challenges, and thus patients are frequently advised to lose weight prior to IPAA.[7] In a 2016 study of 1175 UC patients who underwent proctocolectomy at our institution, the rates of unsuccessful IPAA rose significantly from 2% at a BMI of 30, to 5.7% and 15% when BMI rose to 35 and 40, respectively.[12] Weight loss not only improves technical feasibility, but has also been shown to improve pouch outcomes, given obesity has been associated with increased risk of post-operative complications and worse pouch function.[7-8,13-14]

For these reasons, the UC population with obesity would benefit from an expanded armamentarium of weight loss modalities that are more effective and durable than diet and lifestyle modification, without the irreversibility and risk of bariatric surgery[20]. Thus, **the goal of this proposal is to test the hypothesis that ESG is a safe and effective weight loss modality in obese UC patients undergoing total proctocolectomy with eventual IPAA.** We will also plan to evaluate short and long-term outcomes of IPAA. These hypotheses will be pursued though specific aims outlined later in this protocol.

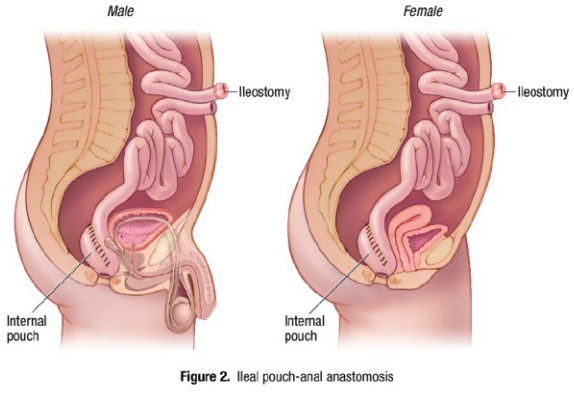
Figure 2. *Stages of total proctocolectomy with IPAA*[1]



Normal GI anatomy



Stage 1 (subtotal colectomy and end ileostomy)



Stage 2 (IPAA creation and loop ileostomy)
Stage 3 (loop ileostomy takedown)

[1] Performance of proctocolectomy with IPAA is performed in 2-3 stages over the course of several months.

1.2 Risk Analysis (Risks to Benefits Ratio)

1.2.1 Anticipated Risks

Study risks are anticipated to be similar to what is seen in the general population, as patients will be >4 weeks out from their colectomy at the time of ESG, which will have resulted in resection of their significant inflammatory burden and tapering off any corticosteroids they may have been taking pre-colectomy. The performance of ESG is now part of the standard of care (SOC) within the obesity management paradigm. The selection of UC patients (as opposed to those with Crohn's disease) means that these individuals should not have underlying luminal inflammation within the proximal gastrointestinal tract as UC only affects the colon. This reduces the chance that there are complications related to existing inflammation within the stomach. Precautions will be taken to limit the exposure of PHI including use of HIPAA compliant digital solutions such as EMR and eCRF.

1.2.2 Potential Benefits

Study participation may contribute to increasing the scientific knowledge of procedural options for managing obesity in UC patients. If successful weight loss is achieved, it is possible it may augment the likelihood of technical feasibility for IPAA formation.

1.3 Anticipated Duration of the Clinical Investigation

Subjects who are referred or identified by physicians or the study team will be screened by delegated personnel and confirmed for eligibility by the Principal Investigator (PI). Anticipated study duration includes 24 months of recruitment. Once a subject has been screened and enrolled, as defined by completed informed consent form (ICF) and completion of all tests and questionnaires, patients will be scheduled for a remote visit with the study dietician to review the post-op nutritional guidelines. This visit may occur remotely via video

or phone call. The study team will coordinate with clinical teams to schedule the ESG. The ESG will occur at least 4 weeks after colectomy (stage 1). Post-procedurally, subjects will have scheduled follow-up visits at weeks 4, 12, and 24, in addition to at the time of IPAA (stage 2), ileostomy takedown (stage 3), 12 months following ESG, and 12 months following ileostomy takedown and restoration of continuity. Weight loss will be assessed four weeks following ESG, six months following ESG prior to proceeding with IPAA formation (stage 2), 12 months following ESG, and 12 months following ileostomy takedown or time of last follow-up. Any post-ESG as well as post-IPAA complications will be recorded. Tolerance of ESG will be documented based on gastrointestinal symptom rating scale (GSRS). Pouch function and documentation of any pouch related complications will be assessed one year after restoration of continuity (ie. ileostomy takedown).

2 Study Objectives

The primary objective of this study is to assess the efficacy and safety of ESG use for weight loss in obese UC patients undergoing colectomy, prior to IPAA formation.

2.1 Primary Aims

***Aim 1*: Assess the proportion of individuals who achieve ≥5%, ≥10%, and ≥15% TBWL at 6 months following ESG.**
Hypothesis: UC patients will experience weight loss outcomes similar to that seen in the general population following performance of ESG.
***Aim 2*: Describe ESG safety by assessing device and procedural-related serious adverse events (SAEs)**

2.2 Secondary Aims

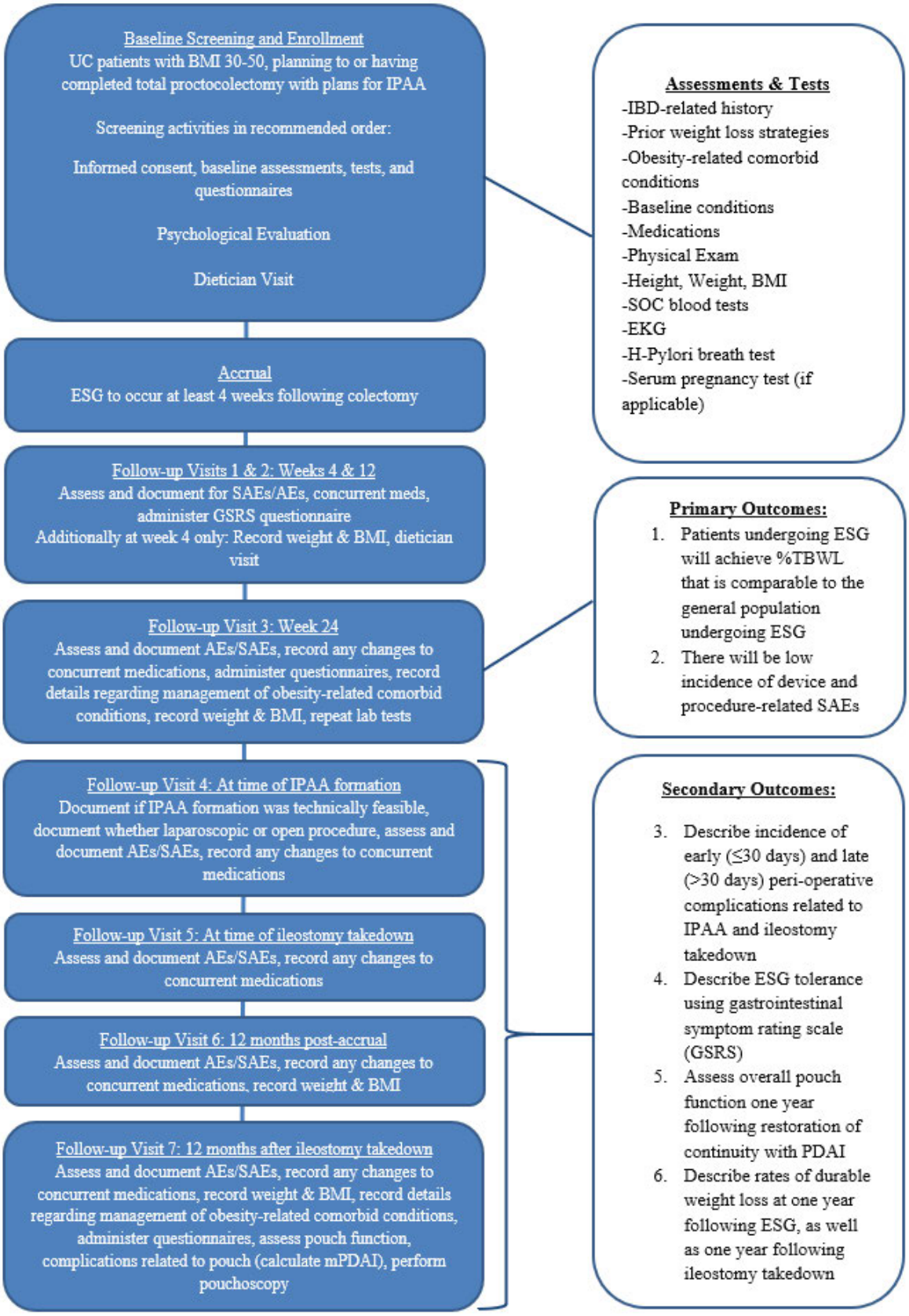
Aim 3: **Assess incidence of post-operative complications related to IPAA and ileostomy takedown**

A) Describe incidence of early (≤30 days) perioperative complications following IPAA formation
B) Assess long-term pouch outcomes by documenting presence of any late complications (>30 days, up to a year following takedown) following IPAA, such as pouchitis, Crohn's of the pouch, anastomotic leak, pelvic sepsis, pouch stricture, pouch fistula, and pouch excision

Aim 4: **Describe ESG tolerance using gastrointestinal symptom rating scale (GSRS)**
***Aim 5*: Assess overall pouch function one year following ileostomy takedown.** Pouch function will be measured by modified pouchitis disease activity index (m**PDAI**) score, which is based on reported symptoms as well as findings at time of follow-up pouchoscopy (which will be done as part of standard of care).
***Aim 6*: Describe rates of durable weight loss at 12 months following ESG, as well as one year following ileostomy takedown**
Hypothesis: Patients undergoing ESG will sustain durable weight loss

3 Study Design

3.1 General Design



3.2 Primary Study Outcome

A) Assess the proportion of individuals who achieve ≥5%, ≥10%, and ≥15% TBWL at 6 months.
B) Review rates of SAEs following ESG

3.3 Secondary Study Outcomes

A) Incidence of early (≤30 days) perioperative complications following IPAA formation
B) Incidence of late (≥30 days) IPAA-related complications following IPAA, including pouchitis, Crohn's of the pouch, anastomotic leak, pelvic sepsis, pouch stricture, pouch fistula, and pouch excision
C) Describe ESG tolerance using gastrointestinal symptom rating scale (GSRS)
D) Assess pouch function 1 year following restoration of continuity with mPDAI
E) Review technical feasibility of IPAA formation following ESG
F) Assess durable weight loss at 1 year following ESG and 1 year after restoration of continuity

Adverse event rates are defined in section 8.

4 Subject Selection, Enrollment and Withdrawal

4.1 Inclusion Criteria

1. BMI 30-50 kg/m^2 for at least 6 months prior to ESG
2. Ages 22-69
3. Diagnosis of UC with plans to undergo or who have already undergone colectomy as part of a plan to pursue eventual 3-stage ileal pouch anal anastomosis (IPAA)
4. Willing to adhere to the diet and behavior modifications required for ESG
5. Able to follow the visit schedule
6. Able to provide informed consent
7. If female, be either post-menopausal, surgically sterile, or agree to practice birth control for the duration of the study and have negative serum HCG at screening/baseline

4.2 Exclusion Criteria

1. Prior gastric or bariatric surgery or other alteration to upper gastrointestinal anatomy which would preclude safe or technical performance of ESG
2. Current or recent (last six months) gastric or duodenal ulceration
3. Esophageal or gastric varices
4. Significant motility disorder of the esophagus or stomach
5. Large hiatal hernia measuring >5 cm or ≤ 5 cm and associated with severe gastroesophageal reflux
6. Severe coagulopathy, hepatic insufficiency, or cirrhosis

7. Gastric mass
8. Presence of any other medical condition which precludes safe performance of elective endoscopy such as poor general health and/or history of severe hepatic, cardiac, or pulmonary disease
9. Serious or uncontrolled psychiatric illness which may compromise patient understanding of procedure or compliance with follow-up visits
10. Unwilling to participate in an established diet and behavior modification program, with routine follow-up
11. Anticipate needing ongoing corticosteroid use at a dose of >5 mg daily at the time of the ESG.
12. Daily use of anti-inflammatory agents such as non-steroidal medications, or anticoagulants without medical supervision
13. Alcohol or drug addiction
14. Females who are pregnant, nursing, or planning pregnancy within the next year
15. Concomitant use of or unwillingness to avoid any use of weight loss medications, weight loss supplements, or weight loss herbal preparations
16. Has a condition or is in a situation which in the investigator's opinion may put the subject at significant risk or may interfere significantly with the subject's participation in the study.

Female subjects of childbearing potential must agree to use one of the following birth control methods for the duration of the study: hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants, barrier methods used with a spermicide, intrauterine device (IUD), or abstinence.

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be recruited:

- From the Principal Investigator or Co-Investigator clinical practices
- Inflammatory Bowel Disease and Colorectal surgery clinical practices
- Referring physicians, advertisement, Mayo Clinic recruitment tools, etc.
- Information that is to be given to potential subjects (handouts, brochures, etc.)
- Screening requirements
- Evaluation and documentation of inclusion/exclusion criteria.
- If subjects have been enrolled and screen failed prior to accrual they will be screen failed and replaced.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Conditions or criteria under which a subject may be withdrawn from the study prior to that subject completing all of the study related procedures. Some reasons to address may include:

- Failure of subject to adhere to protocol requirements

- Subject decision to withdraw from the study (withdrawal of consent)

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Data will be collected and managed utilizing REDCap electronic data tools at Mayo Clinic Rochester, with data collection limited only to those approved as listed on the study protocol. If unavailable to conduct electronic source, physical CRF source worksheets will be available that can be added to the eCRF for investigator attestation. Data which is abstracted will be password-protected.

If a subject withdraws consent to participate in the study after procedure, for subject safety reasons, attempts should be made to obtain permission to collect follow up information whenever possible.

Subjects withdrawn may be replaced to meet accrual totals.

5 Study Methods

5.1 Subject Compliance Monitoring

Lead coordinating site, Mayo Clinic, will monitor subject compliance via REDCap submissions. Quarterly reviews are anticipated for queries as needed during the duration of the study.

5.2 Study Date Ranges

Months shall be accounted for in a 30-day period, years will be calculated at 365-day interval, and study visit day ranges are outlined in section 6.

6 Study Procedures

6.1 Baseline Screening & Enrollment

Patients will be recruited from the inpatient and outpatient setting in both our IBD and Colorectal surgery clinics. We will also utilize Mayo Clinic's Research Recruitment Services to develop marketing materials including a social media campaign leveraging Mayo Clinic's enterprise social media accounts for recruitment. We also plan to use Mayo Clinic repositories such as Advanced Text Explorer (ATE), Mayo Data Explorer (MDE), I2B2, Epic Reports, and/or Epic Slicer Dicer to identify and contact potentially eligible patients. Patients who meet inclusion criteria and are interested in participating will be enrolled.

Before any study activity, enrollment will be established via completion of an informed consent form obtained in a private setting with ample time for consideration. Informed consent may be obtained electronically through remote video or tele-consent according to local IRB policies and procedures. A history to include IBD-related history, prior weight loss strategies, obesity-related comorbid conditions, medications, baseline conditions, and physical exam (including height and weight) will be obtained. The weight that is recorded during screening is the weight that will be used as baseline from which to calculate %TBWL for the duration of the study. Subjects will also undergo baseline standard blood tests, electrocardiogram (EKG), Helicobacter pylori breath testing (while off any proton pump

inhibitor), and serum pregnancy test if female of childbearing potential. Laboratory tests will include complete blood count (CBC), chemistry panel, coagulation tests, liver function test (LFT), fasting insulin, fasting glucose, lipid panel, C-reactive protein, and HbA1c. Subjects will be asked to complete the GSRS and Short Inflammatory Bowel Disease Questionnaire (SIBDQ) questionnaires during the window for screening/enrollment. Subjects must also meet with and be cleared by Psychiatry to undergo ESG. Subjects who have met all inclusion and none of the exclusion criteria thus far will be verified by PI, and will conduct a video or phone visit with the research dietician, who will provide advisement on diet and lifestyle management and the post-op nutritional guidelines. Patients may also be offered co-enrollment into our SPARC registry, which is a biobank for IBD patients through which serum and stool samples will be collected.

6.2 Procedure & Accrual

Subjects will have to have verified by PI that they meet Psych eligibility. On this day, the subject may have their weight and BMI recorded clinically, however, this measure may not reflect the standards required for research measurements (screening weight will validate inclusion/exclusion criteria) necessary for primary outcomes, therefore it will not be recorded in study CRFs. On the day of endoscopic sleeve gastroplasty (noted as day 0), the subject will be taken to the outpatient endoscopy suite where they will undergo ESG by one of two expert bariatric endoscopists at our center who have extensive experience in endoscopic suturing. ESG is performed utilizing a U.S. Food and Drug Administration (FDA)-approved and commercially available endoscopic suturing device to place suture plications which result in a reduction of gastric volume by approximately 70-80%.

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. If the PI feels it is necessary to see a patient in clinic, an unscheduled visit will be scheduled appropriately.

All patients will be on a low-calorie healthy diet personalized by the dietician according to individual patients' needs and conducive to weight loss for the duration of the study. Subjects will start this diet immediately following a standard transitional diet after undergoing the ESG procedure. This transitional diet will consist of 2 days of clear liquids, 4 weeks of full liquid protein shakes, 2 weeks of blended foods, 4 weeks of soft foods, and finally progress to regular foods. It is designed to allow suture healing and incorporation within the plicated gastric wall. Physical activity will be encouraged and assessed for all subjects throughout 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.

Follow-up visits will be calculated as calendar days with weeks calculated in 7 day increments measured against the accrual day (procedure day).

6.3 Visits 1-2

For the week 4 (Range: Days 21-35) and week 12 (Range: weeks 10-14) visits, the study team will record details of any change in concurrent medications or adverse events on the

eCRFs (including management of these events or symptoms) including those related to colectomy and those related to ESG. The GSRS questionnaire will also be completed to document any GI-associated symptoms. At the week 4 visit, all subjects will also meet with the CRTU dietician for follow-up, and weight and body mass index will be recorded. The week 12 visit will be conducted remotely.

6.4 Visit 3

For the week 24 (Range: weeks 22-26) visit, the study team will record details of any adverse events related to ESG on the eCRFs (including management of these events or symptoms), weight and body mass index, complete the SIBDQ and GSRS questionnaires to document any GI-associated symptoms, as well as record medications and details regarding management of obesity-related comorbid conditions (if present at baseline on eCRFs). Subjects will undergo repeat laboratory tests for CBC, chemistry panel, LFTs, fasting insulin, fasting glucose, lipid panel, C-reactive protein, and HbA1c. There is an option to conduct this visit remotely, in which case the participant will self-report their weight to the study team. Labs may be drawn at a location local to the subject if they are unable to attend this visit in-person. If labs are drawn locally, results will be made available to the study team for review and the subject will be reimbursed for any incurred charges.

6.5 Visit 4

Visit 4 will occur at time of ileal pouch anal anastomosis (IPAA) formation (stage 2 operation), which may vary between patients depending on clinical factors which will determine most appropriate timing for IPAA formation, though this should not occur any earlier than 24 weeks following ESG. It is also possible that Visit 3 could serve as Visit 4 should IPAA formation take place at the six-month mark. IPAA will be performed in standard fashion based on discretion of Colorectal surgery team. Study team will document whether IPAA formation was ultimately technically feasible, and whether surgery was laparoscopic vs open. Any changes to concurrent medications or adverse events will be recorded. This visit, if not at the same time as visit 3, will be conducted remotely.

6.6 Visit 5

Visit 5 will take place at the time of planned ileostomy takedown (stage 3). This typically occurs 2-3 months following IPAA formation. The study team will record peri-operative adverse events and medications on eCRFs. This visit will be conducted remotely.

6.7 Visit 6

Visit 6 will take place 12 months post-ESG. The study team will record any changes to concurrent medications and details of any adverse events related to ESG on the eCRFs (including management of these events or symptoms), as well as weight and body mass index. There is an option to conduct this visit remotely, in which case the participant will self-report their weight to the study team.

6.8 Visit 7

Visit 7 will take place 12 months (Range: 11-13 months) following restoration of continuity (ileostomy takedown). The study team will record weight, BMI, details on management of any obesity-related complications if present at baseline, any changes in concurrent

medications, any adverse events or pouch-related complications that have occurred in the interim, SIBDQ and GSRS questionnaires, results of pouchoscopy, and mPDAI (following pouchoscopy) to assess pouch function. There is an option to conduct this visit remotely, in which case the participant will self-report their weight to the study team.

Note: If it is found to be ultimately technically unfeasible for a subject to undergo IPAA formation and takedown (stages 2 and 3), that participant will exit the study after completing visit 6. Visits 4, 5, and 7 will not be completed.

6.9 Table 1: Schedule of Events

Study Activity	**Screening/ Enrollment**	**Procedure/ Accrual** Day 0	**Visits 1-2**[4] Weeks 4,12[4]	**Visit 3**[5] 6 Month (week 24) May also serve as Visit 4	**Visit 4**[4] At time of IPAA formation	**Visit 5**[4] At time of ileostomy takedown	**Visit 6**[5] 12 month post-accrual	**Visit 7**[5] 12 months following ileostomy takedown	**Unscheduled Visit**
In-Window Range	Day -90 to 0	Day 0	Day 28 (+/-7); 84 (+/-14)	Day 168 (+/-14)	Clinically determined	Clinically determined	Day 365 (+/-14)	Clinically determinate triggered by Visit 5+365 Days (+/-30)	As needed
Consent	X								
History	X								
Physical Exam	X								X
Labs[3]	X[2]			X[6]					
EKG	X								
H-Pylori Breath	X								
Pregnancy Assessment (if female of childbearing potential)	X								
Psych Eval	X								
Weight (kg) & body mass index (BMI)	X		X (Week 4 only)	X			X	X	X
Concurrent Medications	X		X	X	X	X	X	X	X
Obesity-related comorbid conditions	X			X				X	
Dietician visit	X[1,4]		X						

			(Week 4 only)						
Endoscopic sleeve gastroplasty (ESG)		X							
AE / SAE			X	X	X	X	X	X	X
Case Report Forms	X	X	X	X			X	X	
GSRS	X		X	X				X	
SIBDQ	X			X				X	
Pouchoscopy (SOC)								X	
mPDAI score								X	
Remuneration			X (Week 4 only)	X			X	X	

[1]Scheduled once subjects have completed all other screening activities and are found to meet eligibility criteria
[2]SOC Tests
[3]Tests include: complete blood count (CBC), chemistry panel, liver function test (LFT), fasting insulin, fasting glucose, lipid panel, C-reactive protein, and HbA1c. Coagulation tests will also be included at baseline only.
[4]Visits to be conducted remotely via phone or video call
[5]Visits may be conducted either remotely or in-person (self-reported weight if remote)
[6]Reimbursement for local lab charges if drawn elsewhere

7 Statistical Plan

7.1 Sample Size Determination

We plan to recruit 12 patients over two years.

7.2 Statistical Methods

Our primary aim of six month %TBWL will be described both as a continuous variable, as well as categorical variable to report on proportion of patients reaching pre-specified %TBWL endpoints. All continuous variables will be reported as either mean and SD or median and range and compared using Wilcoxon Rank Sum tests. Categorical variables will be reported as number and percentage. Descriptive statistics of adverse events, their severity and relatedness to the procedure will be reported. Number and percentage of 30-day postoperative complications along with complications greater than 30 days will be reported. SIBDQ and GSRS questionnaire data along with the mPDAI score will be reported using mean and SD. Durable weight loss rates at 12 months will be reported as number and percentage. Those who withdraw from the study or are found to not meet inclusion criteria will be excluded.

Percent Total Body Weight Loss (%TBWL) will be defined as the equation below. Baseline measurement to be taken from CRTU calibrated scales (not procedure day weight) during screening to be used in %TBWL calculation for the duration of the study.

%TBWL = [(Baseline screening weight in kg - Follow-up weight in kg) / (Baseline screening weight in kg)]*100

Weights recorded in the CRTU are reported to the tenths place.

7.2.1 Handling of Missing Data

In the analysis of outcomes at 6 months, we expect little missing data. This will also be around the time when patients are expected to follow-up for the second stage of their IPAA surgery/formation. Efforts will be made by study coordinators to document reason for dropout when possible.

7.2.2 Primary Outcomes

Aim #1 Hypothesis: Patients with UC following colectomy who have undergone ESG will achieve comparable %TBWL after six months of follow-up as compared to what is described in the general population undergoing ESG.

Aim #2 Hypothesis: We hope to report on incidence of device and procedural-related SAEs following ESG to include: abdominal pain, nausea, or other GI symptoms requiring hospitalization, upper gastrointestinal bleeding, perigastric leak or collection, infection, deep vein thrombosis (DVT) or pulmonary embolism (PE), and pneumoperitoneum.

We will utilize descriptive statistics to report the proportion of patients who experienced the aforementioned SAEs presumed related to the ESG.

7.2.3 Interim Analysis

No interim analysis will be performed while the study is ongoing. The analysis of the primary outcome following completion of all 6-month follow-up, but prior to long-term follow up, is not considered an interim analysis.

7.2.4 Secondary Outcomes

Secondary outcomes are listed in Section 3.3 including:

A) Incidence of early (≤30 days) and late (>30 days) perioperative complications following IPAA formation
   - *Hypothesis: Patients undergoing ESG will experience low rates of post-operative complications (following IPAA)*

B) Assess tolerance of ESG through GSRS questionnaire
   - *Hypothesis: ESG will be well-tolerated*

C) Assess pouch function based on mPDAI 1 year following restoration of continuity

D) Assess durable weight loss at 1 year following restoration of continuity
   - *Hypothesis: Patients undergoing ESG will sustain durable weight loss*

The secondary outcomes of early (≤30 days) and late (>30 days) post-operative complications following IPAA will be assessed at visits 5 and 6, respectively.

8 Safety and Adverse Events

All complications during the study that are related to the clinical procedures will be recorded on the appropriate CRFs. All adverse events occurring during the study that are presumably related to the ESG procedure or device will be recorded. Records of these events will be maintained, and reports submitted to the FDA and IRB according to the regulatory requirements. Expected clinical adverse events and nonsignificant (not serious) clinical adverse events will not be reported. Serious adverse events are defined using the Clavien-Dindo classification for severity:

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

8.1 Definitions

Adverse Event: Any untoward medical occurrence in a subject involved in clinical study that is related or possibly related to the ESG procedure or associated procedural devices.

Life-threatening adverse effect: Any adverse effect that places the subject, in the view of either the investigator or the sponsor, at immediate risk of death from the effect **as it occurred**. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse effect: An adverse effect is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity

General Physical Examination Findings: At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery: Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as an unanticipated adverse device effect unless specifically instructed otherwise in this protocol.

Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.
Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstance:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful

Post-study Adverse Event: All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the local investigator should instruct each subject to report, to the local investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The local investigator should notify the study regulatory sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the local investigator should become aware of the development of problems, cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Pre-existing Condition: A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period and is presumably related to the ESG procedure or device itself.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets all of the following three criteria:

- Serious: Serious problems or events that result in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**

Related: A problem or event is "related" if it is possibly related to the research procedures.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Study subjects will be routinely questioned about adverse effects at study visits. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the CRF or in a separate adverse event worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded that are related to the ESG procedure. For all adverse effects sufficient information will be pursued and or obtained as to permit; an adequate determination of the outcome, an assessment of the casual relationship between the adverse effect and the procedure or device or, if applicable other study treatment. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

Causality and severity assessment

The sponsor-investigator will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the procedure, devices, or other study treatments; and 3) if the adverse effect meets the criteria for a serious adverse effect.

If the sponsor-investigator's final determination of causality is "unknown and of questionable relationship to the study treatments," the adverse effect will be classified as associated with the procedure or other study treatments for reporting purposes. If the sponsor-investigator's final determination of causality is "unknown but not related to the procedure or other study treatments," this determination and the rationale for the determination will be documented in the respective subject's case history.

8.2.1 Sponsor-Investigator Reporting, Notifying IRB

The sponsor-investigator will report to sites respective IRB requirements any UPIRTSOs and Non-UPIRTSOs according to their IRB Policy and Procedures.

Deviations from the investigational plan.

The sponsor-investigator shall notify IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor-investigator is required for changes in or deviations from a plan, and if these changes or deviations may

affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB notification also is required.

8.3 Stopping Rules

No stopping rules or data safety monitoring board will be required or applicable for this study as both interventions are considered standard of care.

8.4 Monitoring

Data will have periodic monitoring of REDCap database for quality and completeness of the data. Lack of compliance may result in in-person monitoring or removal from study.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

9.3 Case Report Forms

An electronic CRF will be completed for each subject enrolled into the clinical study. The investigator-sponsor will review, approve each completed eCRF; the investigator-sponsor's

signature serving as attestation of the investigator-sponsor's responsibility for ensuring that all clinical and laboratory data entered on the eCRF are complete, accurate and authentic. The eCRF is the primary data collection instrument for the study. All data requested on the eCRF must be recorded. All missing data must be explained. If a space on the eCRF is left blank because the procedure was not done or the question was not asked, record "N/D". If the item is not applicable to the individual case, write "N/A".

Data Management
REDCap will be utilized for recording the eCRF. Mayo Clinic will act as the coordinating site.

Data Processing
The eCRF will include required fields and formatting notes to guide individuals to the proper format, and ensure quality standards and minimize missing information.

Data Security and Confidentiality
Subject numbers will be recorded within Electronic Data Capture (EDC) to reduce risk of PHI transmission. Study records will be stored either in a secured area on-site at the institution, or digitally on a password protected server.

Data Quality Assurance
Quarterly monitoring checks of EDC to ensure data is complete and up to date. If site is not meeting quality checks, in-person site monitoring may be administered by either a Mayo Clinic delegate or appointed agent.

Data Clarification Process
Delegated coordinators will monitor data on a quarterly basis throughout subject participation, querying through REDCap. Notification to lead coordinators will be sent upon query. Site is responsible to complete query responses within a reasonable time.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports during the study and for the longer of the following;

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy"[redacted]

   OR

2. A period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as a sponsor-investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This investigator-initiated study is financed through the institutional funding by way of the Jerry A. Wenger Career Development Award in Gastroenterology Research.

12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a

Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

12.3 Subject Stipends or Payments

Subjects will be provided the ESG at no cost and will receive remuneration after the completion of visits 1, 3, 6 & 7 as outlined in the table below. The total possible remuneration will be $290.

Visit	Remuneration
Visit 1	$60
Visit 3	$100
Visit 6	$60
Visit 7	$70

In addition to the above outlined remuneration, participants who have laboratory tests conducted at a local facility will be reimbursed for the costs incurred for the local blood collection.

All other costs associated with the tests, colectomy, IPAA, ileostomy takedown, and procedures (pouchoscopy) will be billed to patient's insurance as SOC.

13 Publication Plan

National Meetings and Journals to be determined by principal investigator and study team.

14 References

1. Johnson AM, Harmsen WS, Aniwan S, et al. Prevalence and Impact of Obesity on Disease-Specific Outcomes in a Population-Based Cohort of Patients with Ulcerative Colitis. J Crohns Colitis. 2021 Jun;jjab097. doi: 10.1093/ecco-jcc/jjab097. Online ahead of print.
2. Flores A, Burstein E, Cipher DJ, et al. Obesity in Inflammatory Bowel Disease: A Marker of Less Severe Disease. *Dig Dis Sci*. 2015 Aug;60(8):2436-45.
3. Steed H, Walsh S, Reynolds N. A brief report of the epidemiology of obesity in the inflammatory bowel disease population of Tayside, Scotland. *Obes Facts*. 2009;2(6):370-372.
4. Seminerio JL, Koutroubakis IE, Ramos-Rivers C, et al. Impact of Obesity on the Management and Clinical Course of Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2015 Dec;21(12):2857-63.
5. Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood pressure: results of the trials of hypertension prevention, phase II. Ann Intern Med 2001;134:1-11.
6. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA, 2014. 311;74-86.
7. Kiran RP, Remzi FH, Fazio VW, et al. Complications and functional results after ileoanal pouch formation in obese patients. *J Gastrointest Surg.* 2008;12(4):668–674.

8. Klos CL, Safar B, Jamal N, et al. Obesity increases risk for pouch-related complications following restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) *J Gastrointest Surg.* 2014;18(3):573–579.
9. Dahlhamer JM, Zammitti EP, Ward BW, et al. Prevalence of inflammatory bowel disease among adults aged ≥18 years — United States, 2015. *MMWR Morb Mortal Wkly Rep.* 2016;65(42):1166–1169.
10. Lynn AM, Harmsen WS, Tremaine WJ, Bazerbachi F, Abu Dayyeh BK, Loftus EV. Impact of obesity on future IBD-related complications in a population-based cohort of Crohn's disease (CD) and ulcerative colitis (UC) patients. *Gastroenterology*. 2018;154(6 Suppl):S620-S621
11. Tsai L, Ma C, Dulai PS, et al. Contemporary Risk of Surgery in Patients With Ulcerative Colitis and Crohn's Disease: A Meta-Analysis of Population-Based Cohorts. Clin Gastroenterol Hepatol. 2021;19(10):2031-45.
12. Khasawneh MA, McKenna NP, Abdelsattar ZM, et al. Impact of BMI on Ability to Successfully Create an IPAA. Dis Col Rectum. 2016 Nov;59(11):1034-38.
13. Wu XR, Zhu H, Kiran RP. Excessive weight gain is associated with an increased risk for pouch failure in patients with restorative proctocolectomy. Inflamm Bowel Dis. 2013;19:2173-2181.
14. Liu G, Wu X, Li Y, et al. Postoperative excessive gain in visceral adipose tissue as well as body mass index are associated with adverse outcomes of an ileal pouch. Gastroenterol Rep (Oxf). 2017 Feb;5(1):29-35.
15. Sullivan S, Kumar N, Edmundowicz SA, et al. ASGE position statement on endoscopic bariatric therapies in clinical practice. Gastrointestinal Endosc. 2015;82(5):767-72.
16. ASGE Bariatric Endoscopy Task Force and ASGE Technology Committee, Abu Dayyeh BK, Kumar N, Edmundowicz SA, et al. ASGE Bariatric Endoscopy Task Force systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies. Gastrointest Endosc. 2015 Sep;82(3):425-38.e5.
17. Abu Dayyeh BK, Acosta A, Camilleri M. Endoscopic Sleeve Gastroplasty Alters Gastric Physiology and Induces Loss of Body Weight in Obese Individuals. Clin Gastroenterol Hepatol. 2017 Jan;15(1):37-43.
18. Abu Dayyeh BK, Rajan E, Gostout CJ. Endoscopic sleeve gastroplasty: a potential endoscopic alternative to surgical sleeve gastrectomy for treatment of obesity. Gastrointest Endosc. 2013 Sep;78(3):530-5.
19. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient: 2013 update – cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. Sur Obes Relat Dis. 2013;9:159-91.
20. Dayyeh, B.K.A., et al., Endoscopic sleeve gastroplasty for treatment of class 1 and 2 obesity (MERIT): a prospective, multicentre, randomised trial. 2022. 400(10350): p. 441-451.