A Pilot and Feasibility Trial of G-POEM for Gastroparesis to Assess Safety, Physiological Mechanisms and Efficacy

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TITLE: A pilot and feasibility trial of G-POEM for gastroparesis to assess safety, physiological mechanisms, and efficacy

(two-center study Mayo Clinic Rochester and Mayo Clinic Arizona)

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Contents

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the ICH E6, applicable Code of Federal Regulations, and the NIDDK Terms of Award. The Principal Investigators will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the SIRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and Good Clinical Practice (GCP) Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the single Institutional Review Board (sIRB) and local IRBs for review and approval. Approval of both the protocol and the consent form must be obtained from both the sIRB and local IRB before any participant is enrolled. Any amendment to the protocol will require review and approval by the sIRB before the changes are implemented to the study. In addition, all changes to the consent form will be sIRB-approved; a determination will be made regarding whether a new consent needs to be obtained from patients who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 Synopsis

Study Description: This is a sham-controlled, randomized trial (RCT) with blinded outcome assessment of G-POEM vs. sham surgery in 30 patients (15 in each group) with idiopathic or diabetic gastroparesis at two clinical sites. During the G-POEM or sham procedure sedated pre and post EndoFlip measurement of the pyloric distensibility will be taken. Participants will be observed for 2 weeks during baseline, in person within 2 weeks post-procedure, every 6 weeks thereafter (by phone) and final in-person encounter at 48 weeks which will also include a repeat gastric emptying, nutrient drink test and EndoFLIP measurement.

Objectives: To evaluate the 12-month treatment effect of peroral endoscopic pyloromyotomy (G-POEM) vs. sham surgery in patients with drug-refractory gastroparesis, as measured by change in 2-week recall Gastroparesis Cardinal Symptom Index (GCSI) from the PAGI-SYM, and to perform a pilot analysis of factors predictive of the outcome including demographics, etiology, vagal dysfunction, *in vivo* gastric physiology, (emptying of solids, postprandial antral motility, gastric dysrhythmia and pyloric motor functions) and pyloric pathology.

Outcomes:

Primary Outcome: 48-week change in GCSI-DD, relative to baseline GCSI-DD, based on an average of the last 2 weeks' daily GCSI; as well as 2-week recall GSCI from the PAGI-SYM at baseline, 6, 12, 24, 36 and 48 weeks

Secondary Outcomes: (we shall compare patients assigned to G-POEM vs sham procedure for differences in the following parameters):

- Gastric emptying for solids ($T_{1/2}$, 1-, 2- and 4-hour % retention)
- Average GCSI daily diary over 46-48 weeks
- GCSI subscales from PAGI-SYM: nausea/vomiting, postprandial fullness/satiety, bloating at 6, 12, 24, 36 and 48 weeks
- PAGI-QOL questionnaire
- Adequate relief question at 6, 12, 24, 36 and 48 weeks
- Adverse events including effects on other GI symptoms (e.g., dumping syndrome, change in bowel movements)
- Improvement in pyloric physiologic parameters (EndoFLIP) before and after completion of G-POEM during the G-POEM/sham procedure
- Nutritional assessment including change in weight, BMI, serum total protein, albumin at 48 weeks compared to baseline
- Volume to fullness, maximum tolerated volume, aggregate postprandial symptoms at

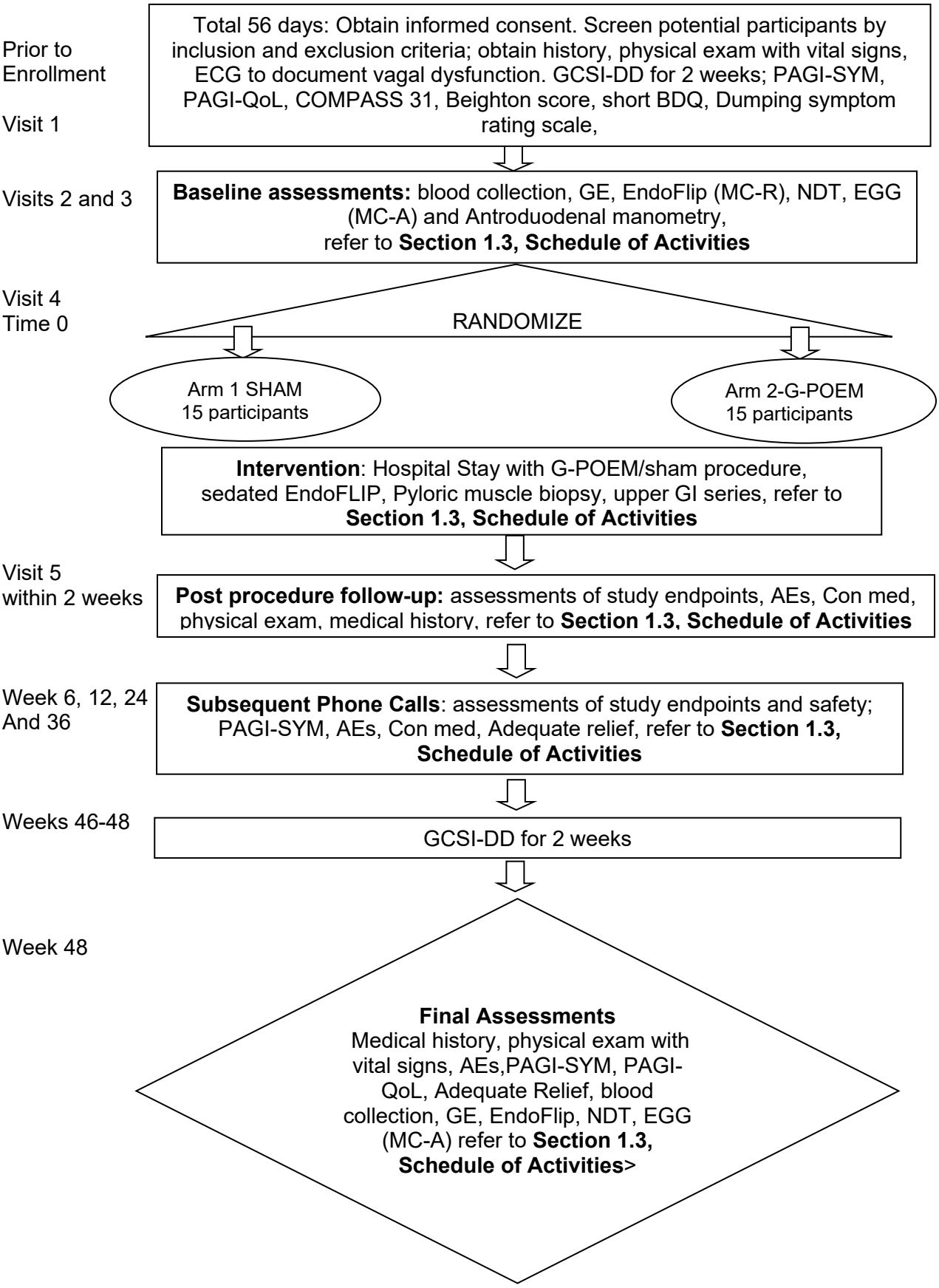
48 weeks compared to baseline
- Gastric electrical rhythm (fasting, pre-nutrient drink test [NDT], and post-NDT) at 48 weeks compared to baseline
- Frequency and quantity of rescue medication use throughout the 48 weeks

Exploratory outcomes. Demographic features and biomarkers obtained at baseline that will be explored as potential predictors of efficacy of G-POEM are:

- 1 hour postprandial antral motility index (normal vs. hypomotility), frequency of distal antral contractions during first postprandial hour (<1 vs. >1.1 distal antral contractions per minute),
- pylorospasm (divided into 2 cohorts based on median observed value),
- sex, etiology of gastroparesis (idiopathic vs. diabetic),
- volume to fullness and maximum tolerated volume based on nutrient drink test, aggregate symptom score 30 minutes after nutrient drink test,
- vagal neuropathy (dichotomized as present/absent based on EKG), and numerical counts of ICC and CD206 macrophages in the pyloric biopsies.

Study Population:	The study population will be 30 adult men and women aged 18-70 years, located in the United States, with symptoms of gastroparesis for one year.
Sites Enrolling Participants:	Mayo Clinic Rochester and Mayo Clinic Arizona
Description of Study	Participants will receive either peroral endoscopic pyloromyotomy (G-POEM) surgery or a sham surgery.
Intervention:	
Study Duration:	We estimate 48 months from when the study opens to enrollment until completion of data analyses.
Participant Duration:	Each individual participant will complete all participant visits in 12 months.

1.2 Schema


Prior to Enrollment
Visit 1
Total 56 days: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, physical exam with vital signs, ECG to document vagal dysfunction. GCSI-DD for 2 weeks; PAGI-SYM, PAGI-QoL, COMPASS 31, Beighton score, short BDQ, Dumping symptom rating scale,
Visits 2 and 3
Baseline assessments: blood collection, GE, EndoFlip (MC-R), NDT, EGG (MC-A) and Antroduodenal manometry, refer to Section 1.3, Schedule of Activities
Visit 4 Time 0
RANDOMIZE
Arm 1 SHAM 15 participants
Arm 2-G-POEM 15 participants
Intervention: Hospital Stay with G-POEM/sham procedure, sedated EndoFLIP, Pyloric muscle biopsy, upper GI series, refer to Section 1.3, Schedule of Activities
Visit 5 within 2 weeks
Post procedure follow-up: assessments of study endpoints, AEs, Con med, physical exam, medical history, refer to Section 1.3, Schedule of Activities
Week 6, 12, 24 And 36
Subsequent Phone Calls: assessments of study endpoints and safety; PAGI-SYM, AEs, Con med, Adequate relief, refer to Section 1.3, Schedule of Activities
Weeks 46-48
GCSI-DD for 2 weeks
Week 48
Final Assessments
Medical history, physical exam with vital signs, AEs,PAGI-SYM, PAGI-QoL, Adequate Relief, blood collection, GE, EndoFlip, NDT, EGG (MC-A) refer to Section 1.3, Schedule of Activities>

1.3 Schedule of Activities (SoA)

Procedures	Screening 56 Days	Baseline Study Visits 1-3	Randomization Visit 4 Intervention Days 0-2	Days 1-14 Study Visit Post-Procedure	Week 6 phone call	Week 12 phone call	Week 24 phone call	Week 36 phone call	Week 46-48	Week 48 Study Visits 6-7
Informed consent & Demographics	X									
Medical history	X			X						X
Physical exam (including height & weight)	X			X						X
Vital signs	X	X	X	X						X
Patient Questionnaire-PAGI-SYM	X				X	X	X	X		X
Patient Questionnaire-PAGI-QoL	X									X
Patient Questionnaire-Adequate Relief					X	X	X	X		X
Patient Questionnaire-GCSI-DD (2 wks)	X								X	
COMPASS-31 Questionnaire	X									
Dumping Syndrome	X				X	X	X	X		X
short Bowel Disease questionnaire	X				X	X	X	X		X
Beighton Score of Joint Hypermobility	X									
Gastric Emptying test		X								X
Electrocardiogram (ECG)	X									
Urine Pregnancy test, if needed	X	X	X							X
Concomitant medication review	X	X	X	X	X	X	X	X		X
Complete Metabolic Panel	X									X
Complete Blood Count	X									X
C Reactive Protein	X									X
Erythrocyte sedimentation rate (ESR)	X									X
HbA1c on all	X									X
Future Use serum	X									X
Fasting blood glucose (fingerstick) (diabeticsubjects only)	X	X	X							X
Nutrient Drink Test with Ensure®		X								X
Electrogastrogram (EGG) - MC-A only		MC-A								MC-A
Gastroduodenal Motility Test		X								
Randomization			X							
Sedated EndoFLIP Assessment			X							
Unsedated EndoFlip Assessment -Mayo		MC-R								MC-R
G-POEM/ sham procedure			X							
Pyloric muscle biopsies			X							
Hospitalization (1 day observation)			X							
Upper GI series			X							
Adverse event review and evaluation	X	X	X	X	X	X	X	X		X
Use of rescue medications evaluation				X	X	X	X	X		X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X

CMP: glucose, calcium, sodium, potassium, carbon dioxide, and chloride, albumin, total protein, ALP (alkaline phosphatase), ALT (alanine transaminase), and AST (aspartate aminotransferase), bilirubin, BUN (blood urea nitrogen), creatinine

*Approximately 35 mL of blood will be collected for the laboratory tests and future use serum; results in the last 30 days accepted

2 INTRODUCTION

2.1 Abstract

Gastroparesis is defined as a gastrointestinal motility disorder with objectively delayed gastric emptying of solids in the absence of mechanical obstruction, associated with upper gastrointestinal symptoms including early satiety, postprandial fullness, nausea, vomiting, bloating, and upper abdominal pain. The pathophysiology of gastroparesis includes postprandial antral hypomotility and pylorospasm, which may reflect extrinsic (vagal) denervation, enteric (intrinsic) neuropathy involving excitatory or inhibitory neurons or electrical syncytium (such as interstitial cells of Cajal) which may result from imbalance of CD206-positive macrophages that protect these intrinsic mechanisms. The introduction of G-POEM involving endoscopic pyloromyotomy has focused attention on pyloric dysfunction as a potentially important factor in the pathogenesis of this syndrome. However, many unknowns remain. First, the reported trials are uncontrolled with results that are short-term and inconsistent, so the true efficacy of this procedure is not clear. Second, given that it is unlikely that G-POEM is a panacea for all patients, it is important to determine which of several possible factors influence outcome e.g. etiology (specifically diabetic versus idiopathic gastroparesis); demographic factors (age, BMI, psychological factors, duration of illness), baseline severity of gastric retention; gastric dysrhythmia, pyloric distensibility or scarring (as measured by EndoFLIP), postprandial antral motility and “isolated” pylorospasm (tonic elevation of baseline pressure independent of antral contractions).
Our general hypothesis is that G-POEM is efficacious in relieving some or all symptoms of gastroparesis and that efficacy differs according to diagnosis, baseline retardation of gastric emptying, antropyloroduodenal motility and pyloric sphincter diameter and compliance. We will examine this hypothesis in a controlled short-term study that will inform future, more definitive trials on G-POEM on the optimal patient selection and outcome criteria.

The aims of this pilot and feasibility, hypothesis-generating study are:
Aim 1: To evaluate the 12-month treatment effect of peroral endoscopic pyloromyotomy (G-POEM) vs. sham surgery in patients with drug-refractory gastroparesis, as measured by validated questionnaires and to perform a pilot analysis of factors predictive of the outcome including demographics, etiology, vagal dysfunction, *in vivo* gastric physiology, (emptying of solids, postprandial antral motility, gastric dysrhythmia, and pyloric motor functions).

Aim 2. To compare the long-term (1 year or more) outcomes in patients randomized to G-POEM with matched patients prospectively followed in the national Gastroparesis registry run by the Gastroparesis Clinical Research Consortium (GpCRC).

2.2 Project Narrative / Relevance

Gastroparesis is a disorder of gastric function characterized by delay in gastric emptying, frequently associated with chronic nausea and vomiting, early satiety, postprandial fullness, abdominal pain, and malnutrition that may require nutritional support. There are few effective treatments available; more recently, a procedure called G-POEM (gastric peroral endoscopic myotomy) has been advocated to relieve symptoms by improving gastric emptying. However, it is not clear whether this is safe or effective. The primary aim of this pilot and feasibility, hypothesis-generating study therefore is to evaluate the effect of peroral endoscopic pyloromyotomy (G-POEM) vs. sham endoscopic surgery on symptoms in patients with diabetic or idiopathic gastroparesis.

3 SPECIFIC AIMS

Gastroparesis is defined as a gastrointestinal motility disorder with objectively delayed gastric emptying in the absence of mechanical obstruction that is associated with upper gastrointestinal symptoms including early satiety, postprandial fullness, nausea, vomiting, bloating, and upper abdominal pain. The most common etiologies of gastroparesis are diabetes mellitus and idiopathic; together, they constitute more than 90% of cases seen in practice.

The initial management of gastroparesis is based on dietary therapy, nutritional support, and optimizing treatment of the underlying etiology such as diabetes or opioid analgesics. Prokinetic agents to accelerate gastric emptying and improve gastroparesis symptoms are the first line of treatment but the only approved drug

is metoclopramide, a dopamine D_2 antagonist and 5-HT_4 agonist, which carries a black-box warning from FDA because of the potential for serious neurological adverse effects. Given the paucity of available efficacious treatments, many patients are considered refractory and undergo treatment with experimental devices (such as stents), electrical stimulation, surgery and gastric per-oral endoscopic myotomy of the pylorus (G-POEM) without proven benefit in sham-controlled trials.

In this context, there have been multiple uncontrolled studies on G-POEM with inconsistent results. For example, a study by the Emory University group showed dramatic improvements in outcome sustained for 12 months, whereas the larger study from the Cleveland Clinic, using the same metrics showed a much less robust improvement. Given these results, the uncontrolled clinical experience to date, and the potential for irreversible changes to gastrointestinal motility with unclear long-term consequences, this approach should currently be considered experimental, even though promising. Indeed, it is based on the same presumptions that prompted the use of botulinum toxin: early uncontrolled studies showing 90% improvement but later randomized controlled trials (RCTs) found no difference compared to placebo.

Equally importantly, even if G-POEM is proven to be efficacious, it is unlikely to be effective in all patients. It is therefore highly desirable to understand predictors of a favorable outcome if such is the case. As described in this proposal, perhaps the most important factor, and one that has not been considered to date, is the state of antral motility, given that the impact of pyloric resistance on gastric emptying is always relative to the propulsive forces. Obtaining an integrated view of antropyloric motility is therefore a key scientific aspect of this proposal. Other potential predictors that will also be studied include etiology (specifically diabetic versus idiopathic gastroparesis), demographic factors (age, BMI, psychological factors, duration of illness), baseline severity of symptoms and/or gastric retention. A third and novel (although exploratory) objective of this proposal is to develop and validate the tools to truly understand pyloric pathophysiology and pathology in gastroparesis.

Given the many uncertainties in this area and the invasive (and costly) procedures involved, it may be premature to launch a traditional, large, multi-center RCT without the benefit of more objective data on whether enough patients can accept randomization in such circumstances, more reliable estimates (based on sham-control) of expected outcomes and their durability, and potential predictors of the same. To this end, we therefore propose to perform a pilot and feasibility, hypothesis-generating trial with the following specific aims:

Aim 1: To evaluate the 12-month treatment effect of peroral endoscopic pyloromyotomy (G-POEM) vs. sham surgery in patients with drug-refractory gastroparesis, as measured by validated questionnaires and to perform a pilot analysis of factors predictive of the outcome including demographics, etiology, vagal dysfunction, *in vivo* gastric physiology (emptying of solids, postprandial antral motility, gastric dysrhythmia, and pyloric motor functions) and pyloric pathology.

Aim 2. To compare the long-term (1 year or more) outcomes in patients randomized to G-POEM with matched patients prospectively followed in the national Gastroparesis registry run by the Gastroparesis Clinical Research Consortium (GpCRC).

This study will provide us robust estimates of the effect size and duration of benefit from G-POEM and indicate the feasibility of detecting predictors of responsiveness for future hypothesis-testing studies.

3.1 Significance

The defining feature of gastroparesis is a delay in gastric emptying and efforts to improve gastric emptying is a central tenet of the current therapeutic approach, supported by studies that show this strategy may result in improved symptoms.[1, 2] However, this is not easy to achieve using currently available drugs. In the community, it is estimated that 15-25% of patients with gastroparesis are refractory to standard treatments[3,4] and this number is as high as 70% in tertiary medical practices[5]. Refractory gastroparesis is therefore a challenging disorder characterized by symptoms of nausea, vomiting, early satiety, postprandial fullness, and abdominal pain for which viable effective treatment options are scarce[6]. In part, this is because of inadequate

understanding of the pathophysiology of the gastroparesis. A delay in gastric emptying has traditionally been attributed to gastric (particularly antral) hypomotility. However, in recent years investigators have also begun focusing on outlet resistance by the pyloric sphincter with refractory patients often being offered intra-pyloric botulinum toxin injection, or increasingly in recent years, G-POEM.

Understanding and assessing pyloric dysfunction in gastroparesis and the significance of antral motility

This is a very important question as gastric motility and emptying is far more complex as compared with organs such as the esophagus, where POEM has been very successful. The esophagus can drain by gravity in the upright position; the stomach is constrained within a uniformly negative (- 4 mm Hg) intra-abdominal pressure. As reviewed recently by one of the investigators[7], there are *two requirements for gastric emptying to be enhanced by a wider distal (pyloric) opening:* (i) effective antral contractions and (ii) pyloric resistance relative to the height/hydrostatic pressure of the pool of distal gastric content (which determines how much "spillover" occurs into the duodenum). If antral hypomotility is a component of the pathophysiology in a patient undergoing G-POEM, then merely widening the pyloric diameter may not be sufficient therapy. A recent study reported G-POEM significantly increased the mean cross-sectional area from 176 to 206.9 mm^2.[8] Assuming the pyloric shape is circular, the change in radius is from 7.5 to 8.1 mm. It is unclear whether this anatomic change of just over 1 mm in diameter represents a physiologically relevant change, and it emphasizes the importance of antral trituration. It is also unclear whether the efficacy of G-POEM results from an increase in the distensibility or in the diameter of the pyloric lumen. Given the emptying of mostly liquid and triturated solids from the stomach, greater distensibility may have a greater impact than the average diameter change of 1 mm. On the other hand, the greater (albeit minimal) sphincter opening may conceivably require less antral "systolic" pressure and, therefore, facilitate emptying with mild antral hypomotility. At present, it is unclear how incomplete pyloric opening, or pyloro-spasm, contributes to delayed gastric emptying from causes as varied as diabetes, scleroderma, vagal injury, postsurgical, or post-infectious gastroparesis, and the contribution of pyloric dysfunction may be variable at best. These considerations reinforce the proposed detailed studies of antropyloroduodenal motility studies.

Until recently, this was not considered practical because of technical limitations with conventional manometry. Stationary manometry cannot quantify radial force nor distinguish between relaxed and contracted states; in addition, the older manometric probes with limited number of sensors may miss postprandial pyloric and antral motility because of movement of the distal stomach relative to the location of the sensors. Two newer technologies overcome these limitations: First, the development of water perfused catheters that have 14 closely spaced sensors to ensure continuous recordings of the entire antro-pyloro-duodenal region over the entire postprandial period, as shown in **Figure** 1.[22] The other promising tool in this context is the EndoFLIP and several centers have begun reporting the results of this balloon-based technique (**Figure 2**) to measure the distensibility/compliance and diameter of the pyloric sphincter in healthy subjects and patients with gastroparesis.[9-12]

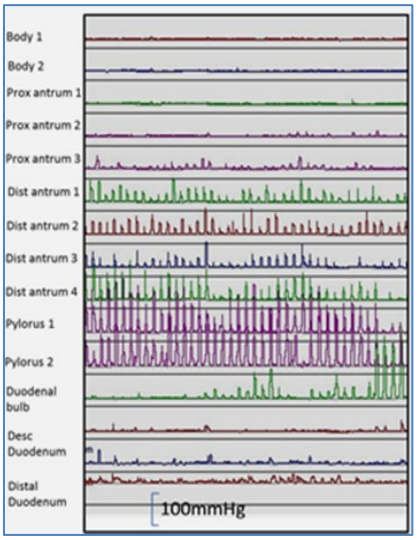


Figure 1. Post prandial gastroduodenal manometry in a healthy subject.

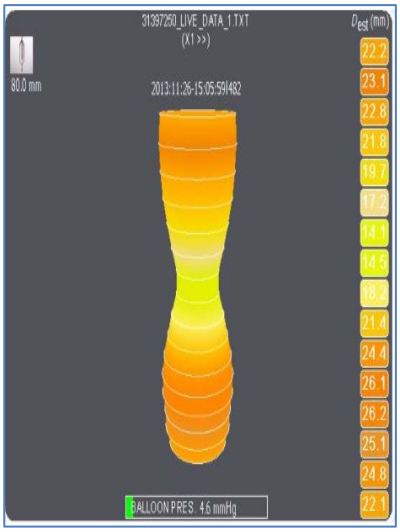


Figure 2. EndoFLIP of the pylorus at 40 ml distension.

In a study of both idiopathic and diabetic gastroparesis, there was an inverse correlation of diameter and cross-sectional area of the pylorus with early satiety and postprandial fullness.[11] Additionally, the basal pyloric pressure was observed to be elevated in almost half of the patients with nausea and vomiting and delayed gastric emptying. Interestingly, in contrast to the authors' hypothesis, no differences were found between those with idiopathic gastroparesis and those with diabetic gastroparesis. From these and other studies, we can conclude that pyloric dysfunction exists in a subset of patients with gastroparesis. However, the critical issue is that the functional significance of this phenomenon remains unknown: Although a relationship between baseline pyloric characteristics and clinical symptoms of gastroparesis was seen, there was no correlation with functional aspects of the pylorus such as distensibility.

With Balloon at 30mL inflation (Data mean ± SD)	Prior to G-POEM	Post-G-POEM
Average Pressure, mmHg	15.7 ± 8.4	9.6 ± 10.8
Cross-sectional area, mm^2	78.2 ± 34.8	83.6 ± 27.3
Distensibility, mm^2/mmHg	6.0 ± 3.3	6.6 ± 5.2
Compliance , mm^3/mmHg	196 ± 99	203 ± 178

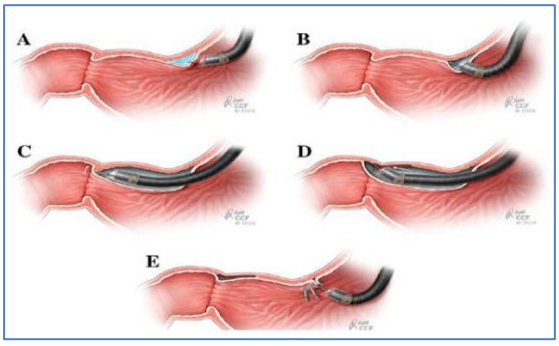
Table 1. Endoflip measurements pre- & post G-POEM[32]

Objective measurements with the EndoFLIP® device can be monitored immediately in response to G-POEM as shown by Malik et al in **Table 1**: there appeared to be a significant decline in pyloric pressure but not in other metrics such as distensibility. This may perhaps explain the fact that the clinical outcome was less robust than some other studies, although this study had too few patients to be confident about this conclusion.[11] A recent study showed the importance of pyloric distensibility on outcomes in response to pyloric intervention. Thus, gastric fullness (from 3.5 to 2.5; p=0.03) and bloating (from 3.0 to 2.0; p=0.01) improved with intra-pyloric botulinum toxin treatment in patients with altered pyloric distensibility; no symptoms improved in those with normal pyloric distensibility.[13] These and other studies support the use of this tool to assess pyloric dysfunction before and after G-POEM as testable predictive factors of the efficacy of G-POEM.

Rationale and experience with interventions directed at the pylorus

When Mearin, Camilleri and Malagelada first described pyloric dysfunction in diabetic gastroparesis in 1986, the pathophysiology of the disease was unclear[14]. However, these observations prompted the use of botulinum neurotoxin (BoNT) injections into the pylorus based on the hypothesis that dysfunction of this sphincter may be responsible for a functional obstruction. There have been multiple open-label trials attesting to the efficacy of this approach,[15-17] but only two randomized controlled trials,[18, 19] both of which failed to show any improvement in symptoms. Nevertheless, more robust interventions such as surgical pyloroplasty have been increasingly advocated with the goal of improving gastric emptying and symptoms. Small numbers of retrospective reports provide evidence that this is feasible, with meaningful short-term improvements in clinical outcomes[20,21,22]. These results set the stage for further technological advancements in the form of gastric peroral endoscopic myotomy, or G-POEM, first described by Khashab and colleagues in 2017.[23] The technique is graphically illustrated in **Figure 3**.

Figure 3. The G-POEM technique.
(A) Methylene blue injection creates the submucosal tunnel;
(B) development of the submucosal tunnel;
(C) extension of submucosal tunnel to first part of duodenum;
(D) pyloromyotomy, beginning ~ 2cm proximal to pylorus and ending in the first part of the duodenum;
(E) closure of the myotomy with endoscopic clips[5].



Since then, there have been multiple uncontrolled studies describing inconsistent results. The studies suggest that this technique has promise but that results are not homogenous and somewhat incongruous, as summarized in **Table 2**. However, nearly all studies have shown significant improvements in gastric emptying, as described in recent meta-analysis[24,11, 25-30-37]

Table 2. Published studies on G-POEM to date.

n	Types of patients	Changes in gastric emptying	Changes in symptoms	Duration follow up	Adverse events	Author, year
29	diabetic=7 idiopathic= 15 post-surgical=5 scleroderma=2	70% Normalized	79% at 3 months; 69% at 6 months. GCSI improved from 3.5 to 0.9 at 3 months	3 and 6 months	17% (2/12) Pneumoperito-neum requiring decompression	**Gonzalez et al 2017**[27]
16	diabetic = 9 idiopathic = 5 post-surgical = 1 post-infectious= 1	75% normalized, 25% improved	81% improvement. GCSI improved from baseline of 3.4 to 1.46 12 months later	12 months	None	**Dacha et al 2017**[24]
47	diabetic =12 idiopathic =27 post-surgical=8	4 h mean retention improved from 37.2 to 20.4%	GCSI improved from 4.6 to 3.3	3 months (available in 31/47 patients)	One death (unrelated)	**Rodriguez et al 2017**[25]
30	diabetic =11 idiopathic =7 post-surgical =12	47% Normalized	No validated outcome measure available	6 months	2/30 (6%)- one pre-pyloric ulcer and 1 capno-peritoneum	**Khashab et al 2017**[28]
13	diabetic =1 idiopathic = 4 post-surgical = 8	4/6 improved; % retention at 4h improved from 49 to 33%	11/13 responded: no GCSI data; 4 considerably better, 4 somewhat better, 1 unchanged, 2 worse	3 months	3 accidental mucosotomy closed with clips; 1 pulmonary embolism	**Malik et al 2018**[29]
16	diabetic =3 post-surgical =13	Mean % retention (radiolabeled bread) at 2h from 69.3% to 33.4%	Mean total symptom score from 24.25 to 6.37; 13/16 substantial improvement	3 months	1 pyloric stenosis at day 45	**Xu et al 2018**[31]
20	diabetic=10 Non-diabetic=10	% retention at 4h improved from 57.5 to 15%; and 30% normalized	GCSI improved from 3.5 to 1.3; QOL improved	3 months	3 mild hemorrhage, 3 gastric perforation, 1 moderate dyspepsia	**Jacques et al 2018**[30]
40	diabetic =15 nondiabetic =25 (of which 18 idiopathic)	% retention at 4h reduced by 41.7%	Improved GCSI, nausea/ vomiting, not bloating	median 15 months	1 tension capno-peritoneum, 1 exacerbation of COPD; 1 EDS disrupted mucosotomy + ulcer	**Mekaroon-Kamol et al 2019**[30]
22	diabetic =8, idiopathic=14, all with GES	7/11 with post-G-POEM GE were normal	GCSI improved (reduction 1.63 points); improved all sub-scores	1 and 3 months	1 laparoscopy for pain due to capnoperitoneum and adhesions	**Strong et al 2019**[32]
38	Post-surgical gastroparesis (76% fundoplication or hiatal hernia repair)	% retention at 4h improved from 46.4 to 17.9%; 50% normalized	GCSI improved (mean reduction 1.29 points); improved all sub-scores	1 month	2 readmissions: 1 melena; 1 dehydration	**Strong et al 2019**[33]

Given these results, the small clinical experience to date and the potential for irreversible changes to gastrointestinal motility, this approach, although promising, should currently be considered experimental as it is based on the same presumptions that prompted the use of botulinum toxin (with early uncontrolled studies showing 90% improvement).[19] However, G-POEM is increasingly being offered as a therapeutic choice to patients, which is a reflection of the large symptomatic burden of these patients, and the paucity of effective alternatives. It is therefore imperative to provide robust scientific evidence for the efficacy and safety of G-POEM for gastroparesis, as well as its pathophysiological rationale (pyloric dysfunction).

<u>Understanding the pathological basis of pyloric dysfunction in gastroparesis</u>

There is evidence that enteric or intrinsic mechanisms may play a role in the development of gastroparesis. These include interstitial cells of Cajal (ICC), platelet-derived growth factor receptor-α (PDGFRα)-positive

Cellular marker	Diabetic Gastro-paresis (n=11)	Idiopathic Gastro-paresis (n=6)	Controls (n=5)	ANOVA /KW test p value
c-Kit (CM)	2.28± 0.16	2.53± 0.47	6.05± 0.62	0.004
PDGFRα staining FLC (CM)	11.03±0.96 (n=10)	11.72±0.96 (n=10)	10.75±0.87	>0.05
CD45 (CM)	13.82± 1.09	11.38± 0.54	19.25±4.05	0.07
CD45 (MP)	14.72± 0.61	18.34± 2.24	22.90± 3.15	0.09
CD206 (CM)	3.87±0.32	4.16±0.52	6.59±1.09	0.04
CD206 (MP)	3.83±0.27	3.59±0.68	7.46±0.51	0.004
n NOS neurons (MP)	1.85± 0.12	2.00± 0.34	2.07±0.30	0.82
n NOS neurons (CM)	27.15± 2.95	35.43±4.75	26.57±3.90	0.27
Tyrosine hydroxylase (MP)	32.50± 4.01	41.57±4.69	38.32±4.67	0.30

CM= circular muscle; MP=myenteric plexus; Data show mean/HPF ± SEM; 1 *hpf* = 0.09 mm^2
KW =Kruskal-Wallis test; ANOVA= analysis of variance

Table 3: Morphological data from full thickness gastric biopsies in gastroparesis

fibroblast-like cells, nitrergic neurons and CD206 positive macrophages. Specifically, it has been demonstrated that quantifiable abnormalities in the enteric neural control including disorders of the pacemaker cells (ICC, PDGRFα cells) are associated with idiopathic or diabetic gastroparesis, manifesting as delayed gastric emptying (**Table 3**).[34-36] Further, ICC loss correlates with loss of the protective CD206 macrophage phenotype. This indicates the feasibility of obtaining useful pathological information from biopsies of the of the circular muscle performed as proposed in the G-POEM procedure.

Other pathophysiological processes that may be important include vagal neuropathy in the setting of autonomic dysfunction[37-41], with or without impaired fundic accommodation and pyloric dysfunction.[42]

Summary and Overall Significance of Application

This study is a preliminary, hypothesis-generating, pilot and feasibility study of safety and efficacy of G-POEM, for the first time, compared to SHAM procedure. Given the unmet need for efficacious treatments for gastroparesis with at least 25% being refractory to pharmacological therapy including prokinetics, there is the prospect of extensive use of G-POEM in the absence of SHAM-controlled data. This study may provide evidence of efficacy using scientifically valid methods for the first time. It is by design, powered on assumptions of very large differences in outcomes between the two arms in aim 1 (which is justified given the invasive nature of the procedure). Long-term efficacy is of critical importance in a chronic disorder such as gastroparesis and will be examined in Aim 2 by prospectively comparing outcomes with data from similar refractory patients but managed by non-invasive 'state-of-the-art" measures at 6 specialized centers in the NIH gastroparesis consortium. Even if the trial does not provide evidence of G-POEM efficacy in aim 1, a trend towards improvement will provide an estimate of the variance in the response, and hence inform the sample size required to test efficacy in a future, larger, hypothesis-testing trial. Alternatively, completely negative results will attest to the futility of further trials and discourage the use of G-POEM. Either of these outcomes are highly significant for society as a whole as they have the potential to impact patients, physicians, and other stakeholders (including funding agencies and third-party payors). Furthermore, this study will provide some indication of predictors of responsiveness, to enhance patient selection for this invasive procedure, and "enrichment" could be factored in a future larger trial.

3.2 Innovation

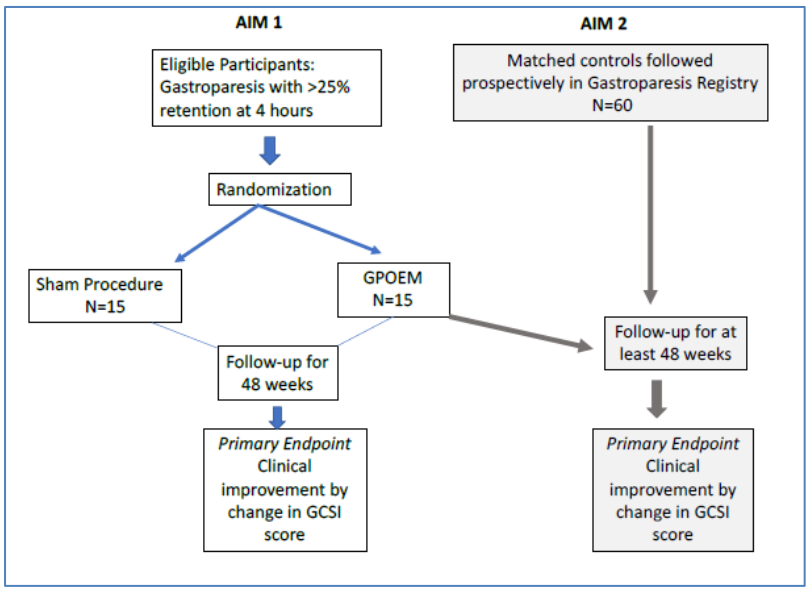
Aim 1 will be conducted at centers with expertise in mechanistic studies of gastric and pyloric motility, a track record for management of patients with gastroparesis and expert endoscopic therapeutic teams.

This proposal has several highly innovative aspects. There have been no new medications approved for patients with gastroparesis since 1979. The only currently approved medication, metoclopramide, is poorly efficacious, associated with an FDA black box warning because of the potential for adverse neurological effects, some of which, like tardive dyskinesia, can be permanent. Preliminary data suggests G-POEM may be efficacious for improving symptoms and gastric emptying; however, there are presently no known biomarkers or factors that predict positive response, and it is not clear that the response is durable. Before this procedure is accepted as clinical standard of care, it is therefore essential to establish safety and efficacy and estimate the likelihood of being able to identify predictors of response. The signals on these various parameters obtained in this study will be invaluable to inform the design of a larger, far more expensive study, should it be necessary.

Further, this study will for the first time, provide a comprehensive functional and pathological profile of the pyloric sphincter in gastroparesis and indicate which subset of patients, if any, are more likely to respond to pyloric interventions such as G-POEM. This has been suggested in previous studies but to date, we have no real evidence for the role of pyloric dysfunction in this syndrome. We will use state of the art techniques to obtain an integrated view of pyloric function as it relates to antroduodenal motility, as well as correlate this with sophisticated neuropathological analysis of biopsies obtained from this region. Thus, Aim 1 will further advance our knowledge of the pathogenesis of gastroparesis and by a sham-controlled trial, provide an estimate of how robust an effect we can expect with G-POEM, and inform the field of the possible predictors of efficacy.
In Aim 2, we will be able to determine the durability of the response and how it changes over time when compared to a carefully phenotyped and matched cohort of patients followed prospectively.

3.3 Approach

The overall approach of study and its two aims is summarized in **Figure 4.**



4 SPECIFIC AIM 1

To evaluate the 12-month treatment effect of peroral endoscopic pyloromyotomy (G-POEM) vs. sham surgery in patients with drug-refractory gastroparesis, as measured by change in Gastroparesis Cardinal Symptom Index (GCSI), and to perform a pilot analysis of factors predictive of the outcome including demographics, etiology, vagal dysfunction, *in vivo* gastric physiology, (emptying of solids, postprandial antral motility, gastric dysrhythmia, and pyloric motor functions) and pyloric pathology.
Hypothesis: *G-POEM relieves symptoms of gastroparesis.*

4.1 Study plan

This is a sham-controlled, randomized trial (RCT) with blinded outcome assessment of G-POEM vs. sham surgery in 30 patients (15 in each group) with idiopathic or diabetic gastroparesis at two clinical sites. During the G-POEM or sham procedure sedated pre and post EndoFlip measurement of the pyloric distensibility will be taken. Participants will be observed for 2 weeks during baseline, in person within 2 weeks post-procedure, over the phone at 6, 12, 24, and 36 weeks and final in-person encounter at 48 weeks which will also include a repeat gastric emptying, nutrient drink test and EndoFLIP measurement. At the Mayo Rochester site, Endoflip measurements of pyloric distensibility (Figure 5) will be unsedated at baseline and 48 weeks. At the Mayo Arizona site, the subject will have a 48-week upper endoscopy (sedated) with EndoFlip measurement of the pyloric distensibility.

4.2 Scientific Rationale for Study Design

The 12-month duration of follow-up) is appropriate in this pilot and feasibility study: As noted in table 2, symptoms improved markedly in 1 to 3 months in 7/10 G-POEM studies. Although longer duration may increase dropouts (in the “refractory” patients) compromising study goals, this study will give us an estimate of the feasibility of providing a longer duration of the blind period for future studies.

4.3 Study Design

Up to 8 weeks (56 days) following the informed consent process, patients diagnosed with gastroparesis will enter the two-week screening period to complete baseline diaries and tests. A medical history and review of body systems along with demographic data will be obtained for all patients during the screening period. Data that will be recorded in the source document/CRF include sex, race, date of birth, cigarette smoking history, alcohol use, drug use, marijuana use and concomitant medication use. Participants will then undergo baseline tests, which would include gastric emptying, antroduodenal manometry, nutrient drink test (with electrogastrography (EGG) at Mayo Clinic in Arizona only). Participants will undergo an unsedated pyloric measurement using Endoflip® at Mayo Clinic in Rochester. If the patient successfully undergoes all the tests during this period and meets the eligibility criteria, including a baseline delayed gastric emptying (defined as gastric emptying T half of greater than 174 minutes or gastric retention at 2 hours of greater than 75% or at 4 hours of greater than 25%), he or she will be randomized 1:1 to either G-POEM or sham. A blinded, local site coordinator will complete the informed consent, clinical assessment, and the follow-up visits. This individual will also facilitate the process of randomization but remain masked to the assignment.

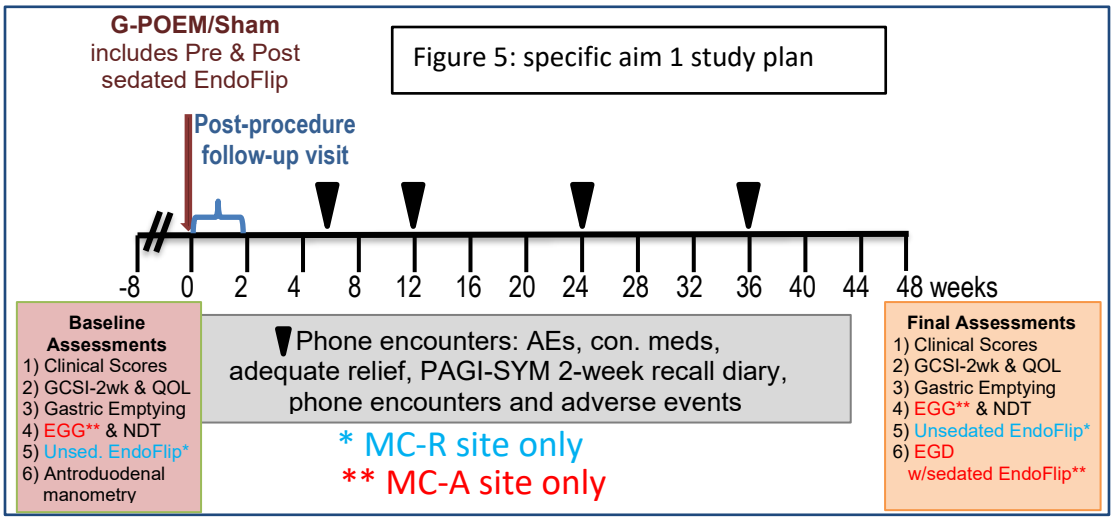


Figure 5: specific aim 1 study plan

4.4 Study Sites

There are two study sites: Mayo Clinic, Rochester (MC-R) and Arizona (MC-A) Each site PI is a nationally recognized expert in gastroparesis. Mayo Clinic Rochester, and Mayo Clinic Arizona Medical Centers will be the only sites where the sham-controlled study is performed. At some of these sites, facilities are available through NIH CTSA to facilitate the human studies. For example, studies at Mayo Clinic Rochester will be conducted in the CRTU (Clinical Research Trials Unit) of the Mayo Clinic CTSA.

4.5 Estimated Study Duration and Timeline

Given the invasive nature of the procedure and the possibility of undergoing a sham procedure, we expect that patient recruitment will take time. To achieve a targeted enrollment of approximately 30 randomized subjects during a 4 year period would require 7-8 patients/year at both sites. We estimate starting enrollment within 6 months of the grant start date and completing enrollment over the next 3.5 years. We will follow all randomized patients for 12 months including the patients undergoing the sham procedure.

5 STUDY POPULATION AND ELIGIBILITY CRITERIA

Subject Population:

Thirty patients with gastroparesis unresponsive to medical therapy and having persistent symptoms of gastroparesis will be recruited at the two participating centers, - Mayo-Rochester and Mayo Arizona Medical Centers. Prospective participants will be screened by means of a gastroparesis disease questionnaire to insure they have gastrointestinal symptoms and test results that are consistent with this diagnosis and further, that appropriate conventional treatment has been provided and symptoms have been deemed refractory. No subpopulations or special classes of subjects are involved in this trial. Participants will fulfill eligibility criteria and it is anticipated that there will be 4 females to 1 male, and 80% will be idiopathic and 20% diabetic gastroparesis, consistent with database collected in the gastroparesis consortium studies. A total of 30 patients will be enrolled and randomly assigned to either G-POEM or sham.

All patients with gastroparesis, ages 18-70 years, seen at the two clinical sites will be screened for eligibility.

5.1 Inclusion Criteria

1. Symptoms of chronic nausea or vomiting compatible with gastroparesis (idiopathic or diabetic) must be present for at least one year (does not have to be contiguous) prior to registration
2. Must have a mean total Gastroparesis Cardinal Symptom Index (GCSI) score of **≥ 2.3** at screening visit
3. Refractory gastroparesis, defined using our previously published data[5], as a failure to improve over the last 6 months, despite an adequate trial of one or more standard prokinetics (metoclopramide, erythromycin, prucalopride), antinauseants (5-HT_3 antagonists, promethazine, prochlorperazine, dronabinol), or neuromodulators (mirtazapine, buspirone)
4. Moderate to severe delay in gastric emptying, defined as > 25% solid retained at 4 hours or > 75% retained at 2 hours or gastric emptying T half greater than 174 minutes. For inclusion, the qualifying gastric emptying scintigraphy will be the baseline gastric emptying test
5. No evidence of mechanical obstruction based on upper GI endoscopy or upper GI series in their medical history

5.2 Exclusion Criteria

Note that the cessation of treatments refers to the time before "qualifying" gastric emptying study,

1. Another active disorder which could explain symptoms in the opinion of the investigator
2. Gastric retention of solids at 4 hours < 25% or < 75% at 2 hours
3. Use of GLP -1 analog or agonists in the last 7 days for daily-administered medication (e.g. liraglutide) and 30 days for weekly-administered medications (semaglutide, tirzepatide). In addition, these medications are prohibited throughout the 48 week study.
4. Use of prokinetics (metoclopramide, erythromycin, cisapride, domperidone, and prucalopride) in the last 7 days. In addition, these medications are prohibited throughout the 48 week study, except when used as rescue medications with documentation (see section 7.6 on rescue medications).
5. Use of narcotics in the last 15 days. In addition, these medications are prohibited throughout the 48 week study.
6. Use of cannabis (marijuana) and cannabinoid medications within 15 days. These medications are prohibited throughout the 48 week study.
7. Significant systemic illness such as chronic renal failure (adjusted for age) or liver disease as defined by Child-Pugh score of 10 or greater.
8. Poorly controlled diabetes with HbA1c of greater than 10% at time of screening
9. New medications for gastroparesis-related symptoms started within 1 month prior to registration
10. Botox injection into the pylorus within 3 months prior to registration
11. Pregnancy or nursing
12. Failure to give informed consent
13. Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study
14. Allergy to eggs and Ensure®.

5.2b: Special consideration for ESTABLISHED use of antidepressants in patients with gastroparesis

The NIH Gastroparesis Consortium studies documented that antidepressant use was one of the factors that significantly and independently reduced symptoms during 48 weeks of follow-up in patients with gastroparesis [42B].

Therefore, the medications listed below will be **permitted at the stable doses established at least 30 days prior to the qualification visit:**

1, Amitriptyline (Elavil)
2, Desipramine (Norpramin)
3, Imipramine (Tofranil)

4, Nortriptyline (Pamelor)
5, Citalopram (Celexa)
6, Escitalopram (Lexapro)
7, Fluoxetine (Prozac)
8, Paroxetine (Paxil)
9, Sertraline (Zoloft)
10, Duloxetine (Cymbalta)
11, Minacipran (Savella)
12, Venlafaxine (Effexor)
13, Buproprion (Wellbutrin)
14, Buspirone (Buspar)
15, Mirtazapine (Remeron)
16, Trazadone (Desyrel)
17, Aripiprazole (Abilify)
18, Brexipiprazole (Rexulti)
19, Lurasidone (Latuda)
20, Olanzapine (Zyprexa)
21, Quetiapine (Seroquel)
22, Ziprasidone (Geodon)

5.3 Screen Failures
Screen failures are defined as participants who consent to participate in the study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a GCSI score may be rescreened one time. Rescreened participants should be assigned the same participant number as for the initial screening.

6 PATIENT RECRUITMENT AND RETENTION
6.1 Patient Recruitment Methods
Both clinical sites have large practices specializing in gastroparesis. At Mayo Clinic Rochester and Arizona, we see over 500 patients a year with known or suspected gastroparesis. These are seen not only by the PI's but by several of their colleagues who are also experts in the field. Two of these are co-investigators on this proposal. In addition, all other clinicians (including gastroenterologists and diabetologists) who see patients with gastroparesis will be made aware of this protocol and the eligibility requirements. The process of access to the physicians and research coordinators has been streamlined and refined over the past several years by each of the PIs, whose published track record attests to their success in recruiting large numbers of patients with gastroparesis. In addition, if necessary, public advertisement may be made as follows:

> *Volunteers with gastroparesis and prior documentation of delayed gastric emptying, aged 18-70 years, are needed for a study to evaluate the effect of an endoscopic treatment that involves opening the sphincter at the lower end of the stomach, on movement of food through the stomach, and their symptoms over 12 months after treatment. This study requires non-invasive tests to measure stomach emptying and feelings of fullness after meals, as well as invasive tests of stomach functions such as endoscopy and placement of a tube through the nose into the stomach to measure the contractions of the stomach and intestine. Remuneration offered. For more information, call XXXXX or send email to YYYYYYYY*.
>
> The methods used for recruitment of participants in the study will be non-coercive and not involve any restrictions on sociodemographic factors including age, sex, or ethnic characteristics of the participant population beyond what is listed in the eligibility criteria. We expect to recruit approximately 4 females to one male patient for these studies. This is consistent with the observations for sex and age in the

NIH gastroparesis consortium as published in 2015: 47 (18%) males and 215 (82%) females, with an average age of 44 years. In advertisements for patients, we shall specifically solicit participation of minorities, but we anticipate that there will be a majority of Whites with representation of Blacks and Asians consistent with the ethnic constitution of communities where the participating centers are located. Participants will be recruited through the sites' existing referral networks and scheduling offices at their standard clinical evaluation. In addition, participants in recent trials will be eligible from 30 days after the end of their participation.

Consideration of sex as a biological variable

Cohorts of patients with gastroparesis show 70% or more were female. There is no *a priori* evidence that the pathophysiological mechanisms or the effect of G-POEM differs between sexes. The inclusion of males (1:4 female) will provide pilot data in males.

Screening Logs

Screening logs will be submitted monthly to The Data Coordination Center (DCC) listing all potential subjects from a Clinical Center with gastroparesis, documentation of ineligibility and reasons for non-enrollment of any otherwise eligible patient. Screening data will be reviewed to assure that full efforts are being made with respect to recruitment and enrollment and to identify any patterns with regard to ineligibility or reasons for non-enrollment.

Patient Consent

Informed consent will be obtained by either the Principal Investigator or by individuals approved by him and local IRB prior to the initiation of any screening procedures.

6.2 Retention of Subjects

The PI's acknowledge that adequate retention of enrolled subjects is a key requirement for the success of a trial. We will follow our established and proven policies to retain subjects including the following measures:

1. Retention begins by paying adequate attention to subject selection, taking into account their lifestyle, work-related issues, geographical distance, family and other constraints that could increase the risk of drop-out.
2. Taking the time and effort to make sure that the subject fully understands the "burden of the study" in terms of time, questionnaires, interventions and procedures
3. Ensuring a trusting patient-physician relationship is established and maintained between the subject and at least one physician member of the study team.
4. Research coordinators that are always accessible, knowledgeable and empathetic, as well as trained to detect early signs of dissatisfaction at each encounter.
5. Provision of incentives such as parking coupons, light refreshments during the visit (as per protocol) and other assistance, as allowed by the IRB and NIH guidelines.

7 STUDY PROCEDURES AND INTERVENTIONS

7.1 Study procedures

Physical examination

A physical examination will be performed during the screening period to confirm eligibility.

Concomitant medication review

A review of concomitant medications will be conducted during the screening period and at every study visit or call. Any medications taken by study patients or changes in dose regimens will be recorded on a Concomitant Medication CRF. Subjects will be offered the use of an optional paper log to record concomitant medication changes.

Vital signs and weight

Vital signs will be obtained in the sitting position. Body temperature (°C) and respiration rate (breaths/minute) will be recorded at each time point when vital signs are measured. Height (cm) and weight (kg) will be measured at the screening visit.

Pregnancy testing

Urine pregnancy testing will be done for women of childbearing potential prior to performance of the G-POEM procedure, as well as on Days prior to the studies involving radioisotope use or fluoroscopy.

A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea >12 consecutive months; or women with documented plasma follicle-stimulating hormone level >35IU/mL]. Women who are using oral, implanted or injectable contraceptive hormones, an intrauterine device, barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, practicing abstinence or where partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.

7.2 Screening and Baseline Data Collection

Consent for screening and HIPAA authorization to disclose protected health information for this G-POEM study will be obtained from the participant prior to initiating data collection for G-POEM This consent and HIPAA authorization must be obtained at the start of the initial screening visit. At the initial screening visit, the details of G-POEM participation will be discussed with the participant. All study procedures and all possible risks will be explained to the potential participants. The informed consent will be reviewed with the participant and after they sign the informed consent, they will be registered into the study to begin the screening process. Recording of screening data on G-POEM data collection forms may not start until the patient has signed the consent statement.

Screening will include both prospective and retrospective data collection. Prospective data collection will be carried out by completion of forms and questionnaires by participants and by performance of laboratory tests. Retrospective data collection will be carried out by review of the patient's medical chart and abstraction of various data elements. Abstracted data may include laboratory, radiologic test results including gastric emptying scintigraphy, and previous surgical, endoscopic, or scintigraphic findings and other illnesses and contraindications for participation. The ***baseline visits may occur on separate calendar days and may take place over several visits occurring over a period of up to 56 days after consent. The day of consent and baseline visit may also be separate.***

Screening and baseline data collection procedures will include questionnaires, a medical history, cigarette smoking history, alcohol use, drug use, marijuana use and medication use history, and physical examination including (body weight [kg], body height [cm], body mass index [BMI], vital signs, Beighton examination for joint hypermobility, and electrocardiogram to assess R-R interval as an indirect measure of cardiovagal function, complete Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) questionnaire which is a 2-week recall and calculate the GCSI, complete a COMPASS 31 questionnaire, complete the short Bowel Disease Questionnaire, complete a Dumping Symptom Rating scale questionnaire, complete a GCSI-Daily Diary for two weeks, as well as Patient Assessment of Upper Gastrointestinal Disorders Quality of Life questionnaire (PAGI-QOL). Have 35 mL blood drawn for complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), HbA1c. and obtain a serum sample for possible future use will be collected and frozen at -80 C. Prior and current therapy for gastroparesis will be reviewed as outlined in the inclusion and criteria.

The purpose of the screening visits is to collect data needed to determine eligibility and establish baseline values. Activities at screening visits include:

- Reviewing and signing the G-POEM informed consent and HIPAA authorization form
- Clinical center coordinator to register patient in study data system
- Assignment of G-POEM patient identification number
- Patient to provide location/contact information to clinic staff
- Obtain retrospective health history information/materials relevant to study eligibility
- If needed, clinical center coordinator to request prior reports from health care provider
- If needed, patient to sign medical records release to obtain prior reports
- Detailed medical/medication history, including race and ethnic background, presence of diabetes, use of pain medications

Review results of prior gastrointestinal tests including endoscopy

7.2.1 Baseline gastric emptying scintigraphy test documentation

The prokinetic agent(s) will need to be stopped once the patient starts the pre-randomization measurements of gastric motor function such as emptying, pyloric measurements, and antropyloro-duodenal manometry typically during the week prior to randomization to sham versus active G POEM procedure.

Eligibility for participants with symptoms of gastroparesis requires gastric emptying scintigraphy test documentation prior to proceeding with the G-POEM study. The baseline gastric emptying scintigraphy test is performed as a procedure in this study and is considered the qualifying gastric emptying test. Participants must discontinue use of GLP -1 analog or agonists in the last 7 days for daily-administered medication (e.g. liraglutide) and 30 days for weekly-administered medications (semaglutide, tirzepatide). Participants must discontinue marijuana, cannabis containing medications, narcotics or opioids (e.g., oxycodone, morphine, fentanyl, Dilaudid) 15 days prior to the gastric emptying test Participants must discontinue prokinetic medications (metoclopramide, erythromycin, cisapride, domperidone, and prucalopride) at least 7 days before the gastric emptying test.

Participants will remain off these medications until completion of the study.

7.3 Baseline Assessments

Prior to randomization, patients will undergo

7.3.1 Gastric Emptying Scintigraphy test

Radio-labeled solid food will be ingested and movement of food out of the stomach will be captured by external gamma cameras to form two-dimensional images. 99mTc-sulfur colloid (0.5 mCi) will be added to two real eggs during the scrambling and cooking process. The eggs will be served on 1 slice of whole wheat bread and with 240 mL of skim milk (320 kcal, 32% protein, 35% fat, 33% carbohydrate). Scans will be taken at 30 minutes (optional), 1, 2, 3, 4 (± 5 minutes) hours post meal will provide an assessment of the stomach's ability to empty. Geometric means of decay-corrected counts in anterior and posterior gastric regions of interest will be used to figure the proportion of 99mTc retained at each time point. The secondary endpoints of $T_{1/2}$, 1-, 2- and 4-hour % retention will be documented.

7.3.2 Unsedated EndoFLIP measurement of the pylorus function

This will be performed at the Mayo Clinic Rochester (MC-R) site only. Under local anesthesia using 20% benzocaine spray of the throat, we shall advance the EndoFlip catheter transorally, checking its position using fluoroscopy and identifying the pyloric high pressure. The FLIP probe will be positioned with the distal 2-3 impedance sensors beyond the pylorus. After 5 minutes of rest, the balloon inflations of 40, 50 and 60 ml will be administered and recorded for analysis. The following measurements will be obtained: average pressure, cross-sectional area, and distensibility.

7.3.3 Gastric Sensation (Nutrient drink test)

The nutrient drink test (NDT) will be used to measure gastric sensation using volume to fullness (VTF) and maximum tolerated volume (MTV) of Ensure® ingested at a rate of 30mL/min.[48] Sensations of nausea, fullness, bloating and pain will be measured and recorded 30 minutes after reaching maximum tolerated volume. Prior studies have shown that up to 750 mL, the MTV is also well correlated with gastric accommodation.[49]

7.3.4 Electrogastrography (EGG)

This will be performed at the Mayo Clinic Arizona site only. Electrogastrogram (EGG) signals [49B] will be recorded for 15 minutes before and for 30 minutes after the Ensure® NDT and analyzed by custom software to provide a frequency analysis (by running spectral analysis) of the gastric rhythm (GR) before and after the NDT. Normal gastric rhythm is ~ 3 cpm (2.5–3.75 cpm); dysrhythmias are tachygastria (3.75–10 cpm) or bradygastria (<2.5 cpm).

7.3.5 Antropyloroduodenal manometry

All the antropyloroduodenal motility recordings will be recorded electronically and analyzed using computer-based software at a single center (Mayo Clinic Rochester) (see common methods section). This procedure involves a custom water-perfused catheter that is advanced transnasal into the stomach to measure the pressure changes which occur within the stomach and upper intestine during digestion.

In this test, manometry ports are placed in the gastric antrum, duodenum, and proximal jejunum. Pressure is monitored in both fasting (one hour) and fed (2 hours) states. Placement of the GDM catheter is assisted and confirmed with the use of fluoroscopy.
After an overnight fast, tube placement will be performed as described[45] The total time of study is approximately 3.0 hours: 1 hours fasting and 2 hours post prandial (from start of meal). Antral and duodenal motility will be measured and motility indices calculated.
After one hour the participant receives the chicken/potato/pudding meal with glass of water which is approximately 500 calories. Participant may salt and pepper to taste. They have 15 minutes to finish the meal if possible.
Participant is required to eat a minimum of ¾ of the meal (the more the better).For identifying pylorospasms, the area under the pyloric tone is measured as the average tonic elevation of baseline pressure multiplied by duration. Each episode during the postprandial hour is cumulated for a total pylorospasm score. Pyloric activity that is well coordinated with antral phasic pressure activity is not regarded as evidence of pylorospasm.

The following will be documented from the APD manometry tracings:

		First 30 min		Second 30 min			1 hr postprandial a			2nd hour post prandial		
	Freq	Amplitude	MI	Freq	Amplitude	MI	Freq	Amplitude	MI	Freq	Amplitude	MI
Distal antrum												
Pylorus												
Tonic elevation												

7.4 Randomization

Once all screening procedures are complete and the patient has met all eligibility criteria, patients will be asked to re-affirm their consent for participation for the scheduled surgery. On the day of the surgery, an unblinded staff member will enter the randomization form and receive the treatment assignment for the endoscopist. The date of randomization is when all screening procedures are completed and eligibility is confirmed by entry of the Randomization Form into the data system, and will be the date from which the follow-up visits are timed (i.e., time zero)

7.5 Treatment Procedures

Participants will be assigned by a central randomization procedure to one of the treatment groups at the time of the endoscopic procedure and communicated to the operator in the room. Treatment assignment of each subject will only be disclosed to the endoscopist and the assisting team.

7.5.1 G-POEM

Under propofol anesthesia, EndoFLIP will be used to assess pyloric diameter and distensibility, prior to and after G-POEM, performed by an endoscopist skilled in this technique. This procedure involves placement of clips to ensure hemostasis. After the procedure, the patient will be observed in the hospital for 1 day. Patients will undergo an upper GI series to rule out perforation. If the patient develops a complication from the procedure, he or she will be managed per standard clinical practice by the treating (unblinded) endoscopist. (Figure 3)

7.5.2 Sham Procedure

Patients assigned to the sham procedure will be treated identically as above, except for the performance of the G-POEM. Endoscopy and EndoFLIP will be performed, and sedation will be stopped when the upper endoscopy is completed. During this procedure, clips will also be placed in the distal antrum of the stomach to ensure blinding of the procedure when the patient undergoes the post-procedure radiographic examination. Since sham endoscopy is expected to take less time than G-POEM, the patient should remain in the endoscopy procedure room for a minimum of 30 minutes (including the time required to complete the upper endoscopy). After the procedure, the patient will be

observed in the hospital for 1-day. All patients will undergo an upper GI series radiographic examination to rule out perforation in order to maintain study blind.

7.5.3 Sedated EndoFLIP measurement of pyloric function

This will be performed immediately before and after the G-POEM/sham procedure, and following measurements will be obtained: average pressure, cross-sectional area, and distensibility. This will take place under sedation (also see Figure 4)

Balloon volume		40mL distension		50mL distension			60mL distension		
	diameter	pressure	DI	diameter	pressure	DI	diameter	pressure	DI
Pylorus									

7.6 Follow-up Procedures

7.6.1 2-week follow-up

Appropriate compliance strategies will be in place to support protocol adherence by patients. A blinded, research coordinator will complete the required within 2-week follow-up encounter during which the dumping and bowel symptoms will be reviewed, data collected and entered. In addition, the blinded study coordinator will assess for adverse events that may have occurred since randomization, as well medications used. During this visit, the patient will also be seen and examined by the clinical investigator(s) and/or the endoscopist and a brief medical history will be performed.

7.6.2 Subsequent phone calls

Periodic phone calls call by research coordinators will be made at 6, 12, 24, and 36 weeks during which the 2-week recall PAGI-SYM GCSI -questionnaires will be reviewed, , In addition, the blinded study coordinator will assess for adverse events that may have occurred since randomization using the dumping symptom, bowel disease questionnaire , as well as medications used. The patients will also answer the Adequate relief question.

7.6.3 46 to 48-weeks

At week 46, patients will receive the GCSI daily diary to complete every day for 2 weeks

7.6.4 48-week follow-up

All patients will complete a follow-up study encounter at the end of the first phase of this trial (i.e., at 48 weeks). The 2-week recall PAGI-SYM GCSI, the GCSI-Daily diary data, adverse event assessment using the dumping symptom, and bowel disease questionnaires will be collected. The patients will also complete the Adequate Relief question, concomitant. medication review, and the Quality of Life questionnaire. The patients will have a physical exam and their medical history reviewed by a study physician. Patients will undergo another gastric emptying test, nutrient drink test with EGG (EGG only at Mayo Clinic - Arizona site), and unsedated EndoFLIP (only at MC-R site). In addition, blood will be drawn for tests as per baseline.

All relevant data collected will be entered in REDCap.

7.7 Rescue Medication

Allowable rescue medications include anti-nausea medications such as 5-HT3 antagonists (e.g., ondansetron), promethazine or prochlorperazine or prokinetics such as metoclopramide, domperidone, erythromycin or prucalopride. Antidepressants used chronically with stable doses for at least 30 days prior to the qualification visit will be permissible as detailed in **section 5.2B.**

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Any rescue medication use or change in neuromodulators will be documented by the patient in the case record form

8 OUTCOMES

8.1 Primary outcome

48-week change in GCSI-DD, relative to baseline GCSI-DD, based on an average of the last 2 weeks'

daily GCSI; as well as the 2-week recall GCSI from the PAGI-SYM at baseline, 6, 12, 24, 36 and 48 weeks

8.2 Secondary outcomes

We shall compare patients assigned to G-POEM vs sham procedure for differences in the following parameters:

- Gastric emptying for solids (T1/2, 2- and 4-hour % retention)
- Average GCSI daily diary over 46-48 weeks
- GCSI subscales from PAGI-SYM: nausea/vomiting, postprandial fullness/satiety, bloating for at 6, 12, 24, 36 and 48 weeks and averaged
- PAGI-QOL questionnaire
- Adequate Relief question at 6, 12, 24, 36 and 48 weeks
- Adverse events including effects on other GI symptoms (e.g., dumping syndrome, change in bowel movements)
- Improvement in pyloric physiologic parameters (EndoFLIP) before and after completion of G-POEM -during the G-POEM/sham procedure
- Nutritional assessment including change in weight, BMI, serum total protein, albumin at 48 weeks compared to baseline
- Volume to fullness, maximum tolerated volume, aggregate postprandial symptoms at 48 weeks compared to baseline
- Gastric electrical rhythm (fasting, pre-nutrient drink test [NDT], and post-NDT) at 48 weeks compared to baseline
- Frequency and quantity of rescue medication use throughout the 48 weeks

8.3 Exploratory outcomes

Demographic features and biomarkers obtained at baseline that will be explored as potential predictors of efficacy of G-POEM are:

- 1 hour postprandial antral motility index (normal vs. hypomotility), frequency of distal antral contractions during first postprandial hour (<1 vs. >1.1 distal antral contractions per minute) based on the high resolution antropyloroduodenal manometry measurements,
- pylorospasm (divided into 2 cohorts based on median observed value) based on the high resolution antropyloroduodenal manometry measurements,
- sex, etiology of gastroparesis (idiopathic vs. diabetic),
- volume to fullness and maximum tolerated volume based on nutrient drink (Ensure® ingested at 30mL/min) test, and aggregate symptom score 30 minutes after reaching maximum tolerated volume on the nutrient drink test,
- vagal neuropathy (dichotomized as present/absent based on EKG), and
- numerical counts of ICC and CD206 macrophages in the pyloric biopsies.

These analyses are considered exploratory: given the small sample size, we are looking for signals that may provide the basis for detecting predictive factors in larger studies in the future (if the efficacy and safety data from this trial is positive).

9 SAMPLE SIZE AND STATISTICAL ANALYSIS

The primary outcome is the change in 48-week mean GCSI 2-week recall score compared to baseline. The primary analysis is intention-to-treat comparison of the treatment group difference in change in the baseline outcome measure vs. the 48-week post-treatment outcome measurement. The statistical model for change in the primary outcome will be an ANCOVA model with an indicator variable for treatment group adjusted for primary outcome at baseline. If the percentage of patients with missing follow-up data on the primary outcome is greater than 10%, multiple imputation using chained equations method with 50 imputations modeling will be used to impute missing values; otherwise, complete-case analysis will be used.

The trial has 90% power to detect a very large treatment effect of 1.2 SDs given a sample size of 30 patients (15 in both the G-POEM and sham surgery groups), a 2-sided Type I error of 5%, 10% missing data, ANCOVA method of analysis, SD of 48-week change = 0.93 and correlation between baseline and follow-up of 0.39. This

translates into a 48-week mean change of -1.55 in G-POEM group vs. -0.43 in the sham surgery group (estimated from natural history data[36]). We believe this estimate may be conservative given a larger estimate of the G-POEM treatment effect of 3 to 12 month mean change in GCSI of -1.92 was seen in a meta-analysis of 3 pilot studies[22, 25, 43]. Although the estimate of improvement has deliberately been set very high because of the pilot nature of this study, estimates of a large (as opposed to very large) treatment effect of 1.0 SDs show the trial still has 79% power to detect a significant treatment effect of -0.93 (-1.35 vs -0.42) GCSI total score given similar estimates as above. Sensitivity analyses include use of robust regression for ANCOVA.

10 METHODOLGY FOR PHYSIOLOGICAL PROCEDURES

10.1 Patient Reported Outcomes (PROs)

10.1.1 PAGI-SYM Questionnaire

Participants will fill in the validated 2-week recall GCSI PAGI-SYM Questionnaire[44](which covers the relevant symptoms from the patient's perspective. It contains the GCSI which appraises 9 symptom severity items, which cover the following domains: nausea/vomiting (three items); fullness/early satiety (four items); and bloating (two items). Symptoms are rated by the patients from none (0) to very severe (5). Patients will complete this at baseline, 6, 12, 24, 36 and 48-week timepoints.

10.1.2 PAGI-QOL

Quality of life will be measured using the PAGI-QOL,[45] a validated 30 item questionnaire to assess quality of life in patients with dyspepsia, GERD, or gastroparesis at baseline and at 12 months after treatment in sham and G-POEM groups.

10.1.3 GCSI – Daily Diary

Participants will fill in the validated Daily Diary GCSI Questionnaire[44](which covers the relevant symptoms from the patient's perspective. It contains the GCSI which appraises 9 symptom severity items, in the following domains: nausea/vomiting (three items); fullness/early satiety (four items); and bloating (two items). Symptoms are rated by the patients from none (0) to very severe (5). Patients will complete this after consenting during the baseline period and between weeks 46–48.

10.1.4 Adequate Relief

The adequate relief questionnaire is a single question asking if during the past 7 days did the patient experience relief of their upper abdominal pain or discomfort. Patients will complete this at 6, 12, 24, 36 and 48-week timepoints.

10.1.5 Dumping Symptom Rating Scale

The Dumping Symptom Rating scale is questionnaire intended to assess if patients experience dumping symptoms at baseline, 6, 12, 24, 36 and 48 weeks

10.1.6 Bowel Disease Questionnaire

The abridged Bowel Disease questionnaire is intended to assess what bowel symptoms patients experience at baseline, 6, 12, 24, 36 and 48 weeks

10.1.7 COMPASS 31

The COMPASS 31 questionnaire is a refined, internally consistent questionnaire providing a quantitative measure of autonomic symptoms that provides clinically relevant scores of autonomic symptoms.

10.2 Physiological Measures

10.2.1 Gastric Emptying (GE)

Gastric emptying (GE) will be measured by radioscintigraphy after overnight fast using a standardized meal.[46] Glucose monitoring and control in relation to measurement of GE will be performed in patients with diabetic gastroparesis ensuring the fasting blood glucose is not greater than 200 mg/dL, and measuring blood glucose during the gastric emptying study in accordance with clinical practice that is if the patient develops symptoms suggestive of either hyperglycemia or hypoglycemia.

10.2.2 Gastric Sensation

Measurement of Gastric Sensation by nutrient tolerance and postprandial symptoms: After a six hour fast, the nutrient drink test (NDT) will be used to measure volume to fullness (VTF) and maximum tolerated volume (MTV) of Ensure® ingested at a rate of 30mL/min.[48] Sensation of nausea, fullness, bloating and pain will be measured 30 minutes after reaching maximum tolerated volume. Prior studies

have shown that up to 750 mL, the MTV is also well correlated with gastric accommodation.[49]

10.2.3 Electrogastrogram (EGG)

Measurement of Gastric Electrical Rhythm (GER): Electrogastrogram (EGG) signals [49B] will be recorded for 15 minutes before and after the Ensure® NDT and analyzed by custom software to provide a frequency analysis (by running spectral analysis) of the GER before and after the NDT. Normal gastric rhythm is ~ 3 cpm (2.5–3.75 cpm); dysrhythmias are tachygastria (3.75–10 cpm) or bradygastria (<2.5 cpm). Three silver-silver chloride electrodes will be placed on the skin in the epigastrium using the standard positions. The electrodes will be connected to the recording device (3 CPM Company). This test will only be performed at the Mayo Clinic Arizona site.

10.2.4 Antropyloroduodenal Motility

Measurement of Antropyloroduodenal Motility[50]: After an overnight fast, tube placement will be performed as previously described[45]. Fasting motility is recorded for 60 minutes, participants ingest a 511kcal solid-liquid meal (chicken, potato, butter, pudding, and 190mL of water); and motility is then monitored for 120 minutes after the meal. Antral and duodenal motility will be measured, and motility indices calculated. For identifying pylorospasms, the area under the pyloric tone is measured as the average tonic elevation of baseline pressure multiplied by duration (Figure 6). In this example, this would be (10mmHg *5minutes) or 50mmHg.min. Each episode during the postprandial hours is cumulated for a total pylorospasm score. Pyloric activity that is well coordinated with antral phasic pressure activity is not regarded as evidence of pylorospasm.

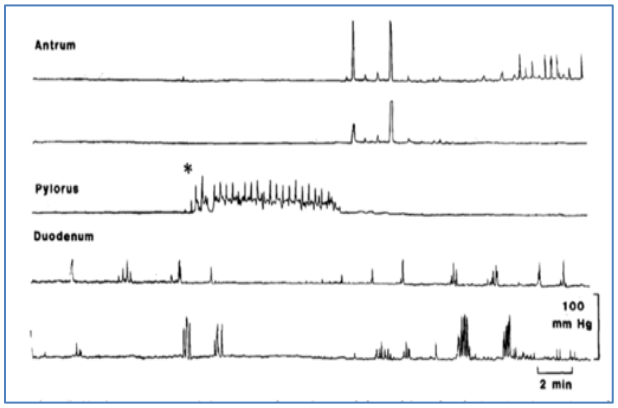

Figure 6: Postprandial pylorospasm with paucity of distal antral contractions in diabetic patient (17)

10.2.5 Sedated EndoFLIP measurement

Sedated EndoFLIP measurements of pyloric function This will be performed immediately before and after the G-POEM/sham procedure, and following measurements will be obtained: average pressure, cross-sectional area, distensibility, compliance. This will take place under sedation.(also see Figure 4)

10.2.6 Unsedated EndoFlip measurement

Unsedated EndoFlip measurement of the pyloric function will be performed at baseline and 48 weeks at the Mayo Clinic Rochester site.

10.2.7 Vagal Dysfunction

In order to assess vagal function, all patients will undergo a 12-lead electrocardiogram in order to check for the presence of sinus arrhythmia and sympathetic/parasympathetic balance as described by us.[51] The main parameter that will be collected is the R-R interval variability with sinus arrhythmia defining normal vagal function and sinus arrhythmia based on R-R interval greater than 0.1200 milliseconds Data from the motility, EndoFLIP, EGG, and vagal recordings will be submitted electronically to the Data Research Center at Johns Hopkins. After a quality control check, these will then be transmitted to the Mayo Clinic Rochester GI Motility Laboratory, under the direction of co-PI Michael Camilleri MD, which will serve as the single center for analysis. Quality control of all of these physiological data will be conducted by the Mayo Clinic investigator site.

10.2.8 Morphological Studies of Pyloric Circular muscle

This pilot study also provides a first opportunity to investigate the feasibility and utility of pyloric muscle biopsies. At Mayo Clinic Rochester and Arizona, tissue collection will be done in standardized fashion with established protocols by the participating sites (already established for the GpCRC). Patients will have consented to undergo this biopsy prior to the performance of the endoscopic procedure as part of the general consent to participate in the study. Two biopsies with jumbo forceps (3-4mm) will be obtained from the circular muscle after entering the submucosal tunnel, one will be fixed in 4% formaldehyde and the other cryopreserved. Specimens will be shipped to the Enteric Neuroscience Program at the Mayo Clinic, where all previous histopathological analyses of gastric tissue have been performed for the GpCRC. This lab has standardized the methodology and published normative data

on quantification of cellular changes in gastroparesis. [34-36, 47] We will re-assess sample size and yield after the first five cases, and if feasible, will perform additional assays including Western blots (using the Wes system, which is available at that lab) and RT-PCR for targeted gene expression, using the information in our previous publications on proteomic and RNA-seq studies.[52, 53] We appreciate the size of the biopsies will be limited and control tissue from the SHAM treated group will be unavailable, since biopsies on patients in the SHAM group might compromise assessment of safety and efficacy, the primary objectives of the trial. Therefore, we shall assess ***association*** between physiological measurements of pylorus by manometry and EndoFLIP with a limited morphological assessment as part of the pilot and feasibility study. In addition, we will explore the hypothesis that pyloric neuropathology may be a predictor of response to G-POEM.

11 POTENTIAL PITFALLS, PRECAUTIONS TAKEN, AND ALTERNATIVE STRATEGIES

11.1 Patient recruitment.

According to our previous study, about 70% of patients in the GpCRC registries (and by implication, at similar tertiary medical centers) meet the definition of "refractory gastroparesis"[5]. Given the prior GpR3 registry with 406 participants and current GpR4 registry target of 250 patients, this translates into 280 patients. The Mayo group recently completed a prospective study of 30 patients with intractable gastroparesis in 18 months (NCT03281577) and is currently enrolling gastroparesis patients for another prospective clinical trial (NCT03941288).

11.2 Participant Discontinuation/Withdrawal

We plan to include in the informed consent forms clear information to differentiate treatment discontinuation from study withdrawal, as well as a statement educating patients about the continued scientific importance of their data, even if they discontinue study participation early (before 48 weeks). The power calculation has factored in a 10% dropout rate.

Lost to Follow-up

Patients will be reminded about each visit at the visit prior. Patients will be called a week prior to the study visit to remind patients. If patients do not show up, they will be called and rescheduled. If no response, the PI will attempt to contact the patient for follow up.

Participants are considered lost to follow-up when they stop reporting to scheduled study visits and cannot be reached to complete all protocol-required study procedures.

The following actions will be taken if a participant fails to return to clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

11.3 Continuation of Masking and maintenance of blind

The endoscopy report and medical record will not state whether a G-POEM was performed but instead state the following: "This patient was enrolled in a study protocol in which he/she was randomized to undergo upper endoscopy with G-POEM or no G-POEM". The endoscopist will document the actual procedure in a separate note that will be secured in his or her records for the study. After the sham or G-POEM procedure all patients will be admitted to the hospital for one/two days and follow the same protocol. Their care will be provided by members of the GI team who will be unaware of the assignment of the patient. If medical events necessitate knowledge of the nature of the intervention by care providers, a mechanism will be provided for urgent unmasking of the providers caring for the patient through the SDRC. All facility and professional charges associated with the randomization procedure and interventions will be billed to the research study. To test the

effectiveness of blinding procedures, subjects and blinded study personnel will be asked to which group they believe the subject has been assigned at the 8- and 24-week follow-up. If a subject becomes knowledgeable of their treatment assignment at any point during study participation, this will be documented in the study database. The subject will remain in the study and be part of the analysis population. If participants require breaking of the study blind for clinical reasons either during (e.g., for complication) or after completing the one year follow-up period, the caring physician who is *not an investigator* will apply to the chair of the DSMB for this information and henceforth the *care of the patient will not involve any member of the investigator teams.*

12 MORPHOLOGY STUDIES

Morphological studies of pyloric myenteric plexus: Since the major morphological changes in gastroparesis are in the tunica muscularis and the myenteric plexus, this would require full thickness biopsies with potential risks. It has not yet been demonstrated that this can be conducted safely at the time of the G-POEM. It is also conceivable that the addition of full thickness biopsy would add an unstandardized variable that may impact the interpretation of the clinical (patient response) outcomes. Therefore, in this study, we will substitute a full thickness biopsy with a biopsy of the circular muscle layer at the time of pyloric muscle exposure that occurs prior to the myotomy.

13 DATA COORDINATION AND SAFETY MONITORING

The Johns Hopkins Bloomberg School of Public Health Scientific and Data Research Center (SDRC) for the GpCRC will serve as data coordinating center (DCC) for the G-POEM trial (see supplemental materials) Specifically, the center will collect and quality control the data acquired from each center through the quarterly collection of GCSI 2-week recall; the center will collect safety data from the endoscopic and other procedures for annual submission to the IRBs and data safety monitoring board.

Data Safety Monitoring Board: We will appoint an independent DSMB which will be charged with annual review of safety and recruitment data and decision to continue the study based on the safety reported. A full plan is included in the Human Safety section.

14 SPECIFIC RISKS

G-POEM is an invasive procedure, although it does not involve incision of the skin such as with laparoscopic pyloromyotomy. Nevertheless, reports so far suggest it is relatively safe with few serious complications reported. The major risks theoretically are capnoperitoneum (with the possibility of respiratory and cardiovascular compromise) and perforation with peritonitis (reported at a rate of 1-10%). As compared with laparoscopic pyloroplasty, G-POEM offers the advantages of a shorter procedure time (mean of about 50 minutes compared with 110-175 minutes with laparoscopic techniques) and a comparable length of hospital stay. As a precaution, all participants (regardless of the intervention) will stay in hospital for 24 hours after the G-POEM procedure and will undergo upper GI series post-procedure with the stated intent to exclude perforation.

• Potential Risks:

The potential risks associated with the study are:

a. Radiation exposure from scintigraphy at baseline and at the end of 48 weeks' observation post-G-POEM

b. Radiation fluoroscopy during placement of the antropyloroduodenal manometry catheters and EndoFLIP procedures

c. Risk from venipuncture

d. Risk from endoscopic procedures

14.1 Safety/risk issues

14.2 Radiation exposure

Radiation exposure results from 99mTc sulfur colloid used to measure gastric transit and fluoroscopy. These exposures conform to previously approved levels of radiation exposure approved by the Radiation Control Committee at Mayo Clinic.

H_e or the radiation effective dose to the body summarizes the risk to the whole body as the individual doses to each of the organs; effective dose is used to compare risks among various types of x-ray and radionuclide studies:
For ^{99m}Tc sulfur colloid (0.5 mCi) the He is 45 mrem
The radiation dosimetry and organ exposures (in mrad) from the gastric emptying are listed below:

Region	Body	Gonads	Breast	Red Marrow	Lung	Thyroid	Bone	ULI	Colon	Stomach	Bladder	Liver	Esophagus
Exposure (mrad)	10	45	0	10	0	0	0	210	150	65	10	50	110

During the proposed study, participants will undergo two studies of gastric emptying of solids Radiation exposure from fluoroscopy for insertion of the antroduodenal manometry catheter are as follows:

Average time <1minute; no more than 2 minutes will ever be used.
Estimated radiation exposure is 1Rad.

In view of the radiation exposure, all females of childbearing age will be required to have a negative blood/urine pregnancy test within 48 hours of the radioisotope studies.

14.3 Risk from venipuncture

The venipuncture associated risks are mild and occur in <5% of participants

14.4 Risks from endoscopic procedures

1. The risk of a simple upper endoscopy under conscious or deep sedation are common to both the sham and G-POEM procedure are rare, usually mild. Large series report adverse event rates (cardiopulmonary, infection, perforation and bleeding) of 1 in 200 to 1 in 10,000 and mortality rates ranging from none to 1 in 2000.
2. The risks of G-POEM specifically are relatively higher but reportedly in an acceptable range for an invasive procedure. Post-procedural hemorrhage, pyloric ulcer, and tension capnoperitoneum or perforation have been reported as serious adverse events of per-oral pyloroplasty (G-POEM) with complication rate ranging from 0-6.7%. Only expert endoscopists, Drs. Law, and Wong Kee Song will perform these procedures at Mayo Clinic.

14.5 Medical complications

All procedures will be performed by highly trained personnel. Patients will be monitored in the hospital for 48 hours after the endoscopic procedure. If a complication develops, the patient will be treated appropriately using the full resources of the hospital.

14.6 Protections against risk

All participating institutions have established a formal program for Investigator Training Program designed to provide all personnel involved in human subject research with training about human subject protection. All personnel engaged in human subject research are required to complete the course. The primary objectives of the course are to provide the historical framework for current human subject protection regulations and to explore the evolving issues related to human subject research.
The courses are divided into four sections:

* Course introduction and general overview
* History section with examples of unethical behavior in human subject research
* Review of major human subject protection issues
* Discussion of the various roles and responsibilities of individuals involved in human subject research
* At the conclusion of the instruction, individuals are required to complete a multiple question assessment.

Research material will be the medical records (of those who authorize review of the records for research purposes), prospectively acquired measurements of gastroparesis symptoms, as well as gastrointestinal functions (e.g., gastric emptying, pyloric distensibility and compliance via EndoFLIP and antroduodenal manometry) and pyloric biopsies.

Results of studies will be accessed by a secure password available only to study personnel. Data will be merged for studies of associations or predictors of responsiveness by the study biostatisticians. All of the information collected in this study will be for research purposes only.

14.7 Potential Benefits of the Proposed Research to the Subjects and Others
The proposed research has the potential to develop a new approach to the treatment of gastroparesis and understanding the factors that predict best outcomes to facilitate future selection of patients for the procedure and avoid the procedure in those less likely to benefit. The benefits to participants may include recommendations on the treatment of their symptoms with gastroparesis.

14.8 Importance of the knowledge to be gained
The proposed research has the potential to develop a new approach to the treatment of gastroparesis, a significant clinical problem with unmet needs. The data obtained in this study will include the measurements by scintigraphy, blood and EKG as routine laboratory safety tests. Measurement of gastric, pyloric physiology and morphological analysis of pyloric muscle. Given the anticipated mechanistic insights to the participants in this research proposal, and to others who suffer from gastroparesis, including identifying biomarkers that predict outcomes, and the track record of the investigators in the conduct of such research, the benefits outweigh the risks in the studies proposed.

15 PROTECTION OF HUMAN SUBJECTS
ADVERSE EVENTS
Each patient must be evaluated for the development of any adverse events. This information will be obtained in the form of non-leading questions (e.g., “How are you feeling?”), from signs and symptoms detected during each examination, from laboratory evaluation, observations of study personnel, and spontaneous reports from patients. Monitoring of adverse events will be conducted throughout the study. Adverse events will be recorded in the CRFs. Serious adverse events will be recorded through Day 30 post-G-POEM procedure. All adverse events should be monitored until they are resolved or are clearly determined to be due to a patient’s stable or chronic condition or intercurrent illness(es).

15.1 Definitions, Documentation, and Reporting
An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered procedure-related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the intervention, without any judgment about causality. An adverse event or suspected adverse reaction is considered serious if, in the view of either the investigator or the study sponsor, it results in any of the following outcomes:

- Death
- Life-threatening - Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- In-patient hospitalization or prolongation of existing hospitalization – Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry, are not considered adverse events if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.

• Important medical event - An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but may be considered a serious adverse event when, based upon appropriate medical judgment, it may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for serious adverse events. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

15.2 Procedures for Adverse Event and Serious Adverse Event Reporting

Each patient will be carefully monitored for the development of any adverse events. All adverse events (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate page of the CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an adverse event and must be recorded on the appropriate pages of the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. The investigator will promptly notify the Institutional Review Board (IRB) of all unexpected serious adverse drug reactions involving risk to human subjects For both serious and non-serious adverse events, the investigator will determine both the intensity of the event and the relationship of the event to study intervention. Only those injection site reactions considered clinically significant by the investigator will be recorded as adverse events.

The intensity of all adverse events, including clinically significant treatment-emergent laboratory abnormalities, injection site reactions and potential systemic reactions, will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The CTCAE grade refers to the severity of the adverse event and ranges from Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) and Grade 4 (life-threatening or disabling) to Grade 5 (death related to adverse event).

Adverse events not listed by the CTCAE (e.g., physical signs or symptoms) will be classified as follows:

- Mild: discomfort noticed but no disruption of normal daily activity.
- Moderate: discomfort sufficient to reduce or affect daily activity.
- Severe: inability to work or perform normal daily activity.
- Life threatening: represents an immediate threat to life.

Relationship of the adverse event to study intervention will be determined by the investigator according to this attribution scale:

☐	The PI will determine the relationship of AEs to the test procedure/device/agent as definitely related, probably related, possibly related, unrelated, or unknown.
☒	The PI will use an alternative attribution scale (specify): • **None:** No relationship between the event and the administration of study intervention. The event is related to other etiologies, such as concomitant medications or subject's clinical state. • **Unlikely:** The current state of knowledge indicates that a relationship to study intervention is unlikely or the temporal relationship is such that study intervention would not have had any reasonable association with the observed event. • **Possible:** A reaction that follows a plausible temporal sequence from administration of the study intervention and follows a known response pattern to the suspected study intervention. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject. • **Probable:** A reaction that follows a plausible temporal sequence from administration of the study intervention and follows a known response pattern to the suspected study intervention. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject. For the purpose of safety analyses, all AEs that are classified as possible or probable will be considered treatment-related events.

For the purpose of safety analyses, all AEs that are classified as possible or probable will be considered treatment-related events. For the purpose of safety analyses, all adverse events that are classified as possible or probable will be considered treatment-related events.

Safety Assessments - Risks and Adverse Events - these will be included in the risks and AEs in the consent form, emphasizing those greater than minimal risk.

Risks and/or Anticipated Adverse Events	Assessment measures	Individual doing assessment	Assessment intervals or frequency	Interventions to decrease or respond to risks
Venipuncture or IV injection Bruising and pain	Subject observation and communication	Physician, study coordinator, RN, research technician	At time of event	Expected, decreased with pressure and ice
Radiation exposure	Documentation of radiation dose in each participant			No associated risks expected as radiation use is closely monitored by Radiation Control at Mayo Clinic and Johns Hopkins
Diarrhea	symptom	Subject with report to study coordinator and PI	Subject assesses daily stool/bowel function and reports to study team daily during the treatment period	no action taken unless clinically significant, e.g., dehydration requiring i.v. fluids, or presenting with postural hypotension secondary to dehydration
Post-POEM abdominal pain or distension	Subject observation and communi-cation	Physician, study coordinator, RN, in endoscopy suite or hospital	As per standard observation following significant endoscopic procedures such as ERCP including regular monitoring of vital signs and signs of peritonism	Main risks are perforation and pneumo- or capno-peritoneum during first 24hours after G-POEM. Patients will routinely undergo plain abdominal radiograph post-G-POEM procedure
Questionnaires	Standard and validated documents	Investigative team	As scheduled per protocol	Responses to questionnaires will be reviewed by study team. For any unanticipated responses that raise concern, the subject will be referred to appropriate follow-up with the subject's primary physician.

Note: Assessment findings are monitored by Physician, study coordinator, RN, research Technician

16 DATA AND SAFETY MONITORING PLAN (DSMP)

The Data Safety Monitoring Plan (DSMP) for this study will be led by an independent monitor, Lawrence A. Szarka, MD, Consultant in Internal Medicine and Gastroenterology and Hepatology at Mayo Clinic, Rochester, MN

Adherence Statement – The Data Safety Monitoring Plan (DSMP) outlined below for this application will adhere to the protocol approved by the Mayo Clinic IRB and Johns Hopkins Bloomberg School of Public Health IRB.

16.1 Confidentiality

A. Protection of Subject Privacy

During this study, medical history and physical examination will be performed, and questionnaires will be administered including validated questionnaires to appraise the symptoms of gastroparesis and functional dyspepsia. Additional research material will be review of medical records (of those who authorize review of the records for research purposes), quantitation of gastric motor functions with an external gamma camera, satiation testing by drinking an approved standard nutrient drink (Ensure®).
Data will be kept in strict confidence. No information will be given to anyone without permission from the subject. This statement guarantees confidentiality. Confidentiality is assured by use of identification codes. All data, whether generated in the laboratory or at the bedside, will be identified with a randomly generated identification code unique to the subject.

B. Database Protection

The database is secured with password protection. It is important to note that samples will be collected and

analyzed for DNA analysis using a laboratory number (identification code) to anonymize the sample. An independent data log will be set up to eventually link the laboratory number with the other biological, imaging and symptom data. Electronic communication with outside collaborators (not anticipated in the current study, but conceivably required in accordance with NIH rules on sharing of data) will involve only unidentifiable information.

C. Confidentiality during AE Reporting
Adverse Event reports and annual summaries will not include subject-identifiable material. Each will include the identification code only.

16.2 Adverse Event Information

Definition
An adverse event (AE) is any untoward medical occurrence in a subject temporally associated with participation in the clinical study. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.) or any combination of these.

A Serious Adverse Event (SAE) is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- Important medical event based upon appropriate medical judgment

Classification of AE Severity
AEs will be labeled according to severity which is based on their impact on the patient.
An AE will be termed:

- ‘mild’ if it does not have a major impact on the patient,
- ‘moderate’ if it causes the patient some minor inconvenience and
- ‘severe’ if it causes a substantial disruption to the patient’s wellbeing.

AE Attribution Scale
AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled either definitely, probably, possibly or unrelated to the study intervention.

The Data Coordinating Center (DCC), PIs at each site, and independent members of the Data Safety Monitoring Plan will review adverse event rates quarterly. Any adverse event rate over 10% in 12 months will be reported to both the IRBs and the NIH; a dropout rate of >30% will be carefully studied to understand the causes and plan for enhancing retention in the future study. Unexpected, serious, and/or intervention-related SAEs will be reported to the Independent Monitor, IRB, CRTU, NIDDK and other oversight organizations as appropriate. Anticipated or unrelated SAEs will be reported to the Independent Monitor, IRB, CRTU, and NIDDK. In the annual SAE summary, the Independent Monitor shall state that he has reviewed all adverse reports.

SAE Reporting
SAEs that are unanticipated, serious, and/or possibly related to the study intervention will be reported to the Independent Monitor, IRB, Clinical Research Trials Unit and NIDDK in accordance with requirements. Anticipated SAEs or those unrelated to the study intervention will be reported to the same individuals/entities in accordance with requirements.” The study team will address abnormal lab values discovered during the study and correct as early as possible.

Anxiety and Depression Assessment Safety Plan
Subjects are assessed for anxiety and depression at the Screening visit and at the end of 12 months after treatment. The PI and/or Co-Investigators on the study are informed of the results of these assessments. If a

subject indicates severe anxiety and/or depression as identified by a combined score of >8 on questions 23, 24, and 25 on the quality of life questionnaire (PAGI-QOL), it will be documented in the medical record that the subject was talked to about their score and encouraged to reach out to their regular care provider for further appraisal and follow-up.

16.3 Data Quality and Safety Review Plan and Monitoring

A. Data Quality and Management

Description of Plan for Data Quality and Management–The PI will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. A statement reflecting the results of the review will be sent to the NIDDK in the annual report (non-competing continuation). Although there are additional reports to be produced by the study coordinator as a result of this DSMP, there are no anticipated substantive changes to the study protocol that might require review by the NIDDK. The data safety monitoring plan will be reviewed by the DCC and independent monitors.

B. Frequency of Review

Data type	Frequency of review	Reviewer
Subject accrual (adherence to protocol regarding demographics, inclusion/exclusion)	Bi-annually	Principal Investigator, Independent Monitor
Adverse event rates (injuries)	Quarterly	Principal Investigator, Independent Monitor
Stopping rules report regarding statistical power implications of drop outs and missing data	Yearly	Principal Investigator, Independent Monitor

C. Subject Accrual and Compliance

Review of the rate of subject accrual, adherence to inclusion/exclusion criteria will occur quarterly during the 48-month recruitment phase of the study proposed. Review will occur at the end of each recruitment wave to assure that participants meet eligibility criteria and ethnic diversity goals outlined in the grant proposal.

D. Stopping Rules – This study will be stopped prior to its completion if adverse effects leading to voluntary withdrawal of participants occurs in >40% of the recruited cohort or if other developments significantly impact the risk-benefit ratio

E. Designation of an Independent Monitor – Lawrence Szarka, M.D. (Mayo Clinic) will serve as independent monitor- to perform an independent review of ongoing safety.

F. Safety Review Plan – Study progress and safety will be reviewed monthly (and more frequently, if needed). Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Independent Monitor every year. An annual report will be compiled and will include a list and summarization of adverse events.

In addition, the annual report will address:

(1) whether adverse event rates are consistent with pre-study assumptions;
(2) reason for dropouts from the study;
(3) whether all participants met entry criteria;
(4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and
(5) conditions whereby the study might be terminated prematurely (e.g. voluntary dropout of >40% of cohort).

The annual report will be reviewed by the Independent Monitor and will be forwarded to the IRB and NIDDK and the CRTU on an annual basis.

16.4 Informed Consent

Written informed consent will be obtained from each subject at entry into the study.
Informed consent is obtained by the following process:

- The subject will be asked to review the study consent form;
- The PI or Co-Investigator (Co-I) approved as such by the IRB will meet with the subject to review the form, to confirm the subject's understanding of the study, and to answer any questions that the subject might have. This can be an optional research e-consult or phone call. and
- Once the subject demonstrates understanding of the study and agrees to participate in the study, the consent will be signed in the presence of the PI (or Co-I as approved by the IRB) or electronically signed remote using the IRB's approved Remote Electronic Consent technology.

Dissemination Plan

Both participating sites have rigorous procedures for compliance with NIH policy on dissemination of information on clinical trials. As with all other studies that the PIs are conducting, this clinical trial will be registered in ClinicalTrials.gov and as they become available, results will be posted. Our informed consent documents will clearly state this. Our institutions have an office that monitors and assures compliance with policy requirements. In addition, the Gastroparesis consortium (GpCRC) will also list this trial on their website.

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