

Cover Page

Study Protocol and Statistical Analysis Plan

Official Title: EUS-guided Gastroenterostomy Versus Enteral Stenting for Palliation of Malignant Gastric Outlet Obstruction: A Randomized Clinical Trial

NCT Number: NCT03259763

Date: November 17, 2025

JHM IRB - eForm A – Protocol

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1. Abstract

- a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Gastric outlet obstruction (GOO) is a common complication of luminal malignancies which is associated with substantial morbidity. Palliation of GOO has traditionally been through surgical bypass of the obstructed lumen by creation of a gastroenterostomy.¹⁻³ In recent years, a less invasive approach with endoscopic enteral stenting has gained wide acceptance and is now commonly used as first line management of unresectable malignant gastric outlet obstruction. Data comparing surgical gastroenterostomy with enteral stenting suggest that the endoscopic method is associated with fewer complications and shorter length of hospitalization⁴.

Unfortunately, enteral stenting is limited by the greater need for reintervention (often due to stent occlusion due to tumor ingrowth/overgrowth) when compared to surgical gastroenterostomy.

Endoscopic ultrasonography-guided gastroenterostomy (EUS-GE) is the most recently described technique for palliation of malignant GOO and has the theoretical potential to minimize the risk for stent occlusion while maintaining the less invasive endoscopic approach. This novel endoscopic treatment entails creating a gastroenterostomy under EUS-guidance thereby bypassing the occluded lumen. Our institution published the first US experience with EUS-guided gastroenterostomy in gastric outlet obstruction and showed excellent results with 90% technical and clinical success with no procedure related adverse events⁵. We have performed EUS-GE to treat patients with GOO since 2014. Recently, we retrospectively showed that EUS-GE was comparable to enteral stenting (ES) in terms of efficacy and safety; however, EUS-GE was associated with a significantly decreased risk of recurrent GOO and reinterventions⁶.

Based on our clinical experience for the last three years and the abovementioned study results, the goal of this study is to prospectively compare EUS-GE with ES in the management of unresectable malignant gastric outlet obstruction. We hypothesize that EUS-GE is associated with comparable technical and clinical success and safety profile while requiring fewer re-interventions.

2. Objectives (include all primary and secondary objectives)

Primary Objective
To compare the rate of GOO recurrence as evidenced clinically by recurrence of nausea, vomiting, and/or inability to tolerate PO intake up to 3 months post procedure and documented endoscopically and/or radiographically following EUS-GE and ES procedures.
Secondary Objectives
To compare the safety (rate and severity of adverse events) of EUS-guided GE to the standard of care procedure, ES, for the treatment of adults with GOO due to unresectable malignancy.
To compare the rates of technical success between EUS-GE and ES.
To compare the clinical success of EUS-guided GE to the standard of care procedure, ES, for the treatment of adults with GOO due to unresectable malignancy.
To compare the rates of re-intervention for recurrent GOO between EUS-GE and ES including endoscopic, radiologic or surgical treatments for recurrence of GOO and management of adverse events
To compare the gastric outlet obstruction score over time between EUS-GE and ES during each follow up calls/visits.
To compare the time for GOO recurrence post procedure between EUS-GE and ES.
To compare the severity of adverse events between the EUS-GE and ES.
To compare the post-procedure length of hospital-stay between EUS-GE and ES.
To compare the change in the quality of life change (pre-intervention vs 1-month post-intervention) between EUS-GE and ES.
To compare the overall survival between EUS-GE and ES.
To compare the length of procedure between EUS-GE and ES.
To compare type of tolerated diet after procedure between EUS-GE and ES

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To compare time to tolerate full liquid diet after procedure between EUS-GE and ES
To compare time to tolerate any oral diet after procedure between EUS-GE and ES
To compare GOO score after procedure between EUS-GE and ES
To compare change in weight between EUS-GE and ES
To compare median time to start chemotherapy between EUS-GE and ES
To compare stent dysfunction rate between EUS-GE and ES
To compare duration of stent patency between EUS-GE and ES

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

3.a. Background and prior treatments

Gastric outlet obstruction (GOO) is a serious complication that could be due to various malignant and benign conditions, and is associated with substantial morbidity. In general, malignancies which lead to GOO are caused by unresectable tumors which requires chemotherapy. Therefore, one of the aims of treating malignant GOO is to also improve patient's quality of life by relieving symptoms such as nausea and vomiting, and also maintaining the capability of oral nutritional intake.

Palliation of GOO has traditionally been through surgical bypass of the obstructed lumen by creation of gastroenterostomy. Surgical gastroenterostomy, although provides a sustained patency of the gastric outlet, is associated with short term complications and a longer hospital stay¹⁻³.

In recent years, a less invasive approach with endoscopic enteral stenting (ES) has gained wide acceptance and is now commonly used as first line management of unresectable malignant GOO. Data comparing surgical gastroenterostomy with ES suggest that the endoscopic method is associated with fewer complications and shorter length of hospitalization⁴.

Unfortunately, enteral stenting is still far from being the ideal solution as it is limited by the greater need for re-intervention, often due to stent occlusion due to tumor ingrowth/overgrowth as compared to surgical^{4,8-11}.

3.b. EUS-GE with LAMS

Endoscopic ultrasonography-guided gastroenterostomy (EUS-GE) with lumen apposing metal stent (LAMS) is the most recently described technique for palliation of malignant GOO and has the theoretical potential to minimize the risk for stent occlusion while maintaining the less invasive endoscopic approach. This novel endoscopic treatment

entails creating a gastroenterostomy and fixing a LAMS under EUS-guidance, thereby bypassing the occluded lumen (Figure 1, 2).

EUS-GE with LAMS was developed for the first time in a series of five porcine models using AXIOS LAMS stent (Xlumena, Inc., Mountain View, CA) in 2011¹². Boston Scientific acquired Xlumena in April, 2015, and since then Boston Scientific corporation produce AXIOS LAMS. Following this experiment, Itoi et al. performed EUS-GE with assistance of a novel double-balloon occlusion catheter and a non-AXIOS LAMS (SPAXUS stent; Taewoong-Medical Co Ltd Seoul, Korea) in a series of five pigs¹³. The only adverse event in these two animal studies combined was an episode of early pneumoperitoneum which successfully resolved with no further complications.

According to a systematic search we performed, six case series have evaluated EUS-GE on human subjects till now. We published the first US experience on EUS-guided gastroenterostomy with LAMS (AXIOS-ECTM stent, Boston Scientific, Marlborough, MA, USA) on ten patients with GOO (three malignant and seven benign GOO). Our findings showed excellent results with 90% technical success and 100% clinical success among the patients with technical success. No procedure-related adverse events as well as symptom of GOO recurrence were detected during a mean follow-up period of 150 days (range 96-227 days)⁵.

In the largest case series, Chen et al. evaluated EUS-GE with AXIOS LAMS on 74 patients with GOO (49 malignant, and 25 benign obstructions). They reported technical and clinical success in 69 and 68 patients, respectively. Serious adverse events were occurred in 5 (6.7%) patients (4 moderate and 1 serious adverse events). All adverse events were because of stent misdeployment⁶.

Itoi et al. conducted a prospective study performing EUS-GE with AXIOS LAMS in a series of 20 patients with malignant GOO. They reported 90% technical and clinical success rate and one adverse event (5.5%), pneumoperitoneum. During the follow-up period (median 100 days; range 44-233 days), no stent occlusion was observed¹⁴.

The other case series of EUS-GE with AXIOS LAMS was reported by Tyberg et al on 26 patients with GOO (17 malignant, 9 benign). Technical and clinical success were achieved in 92% and 85% of the patients respectively. Adverse events were observed in 3 patients (1 pain, 1 bleeding, and 1 peritonitis leading to death). Follow-up period was 7.9

weeks (range 0-32), and no recurrent occlusion was observed in any of the clinically successful cases¹⁵.

Chin et al, in another multicenter retrospective study, compared EUS-GE using AXIOS LAMS with ES. Among the 30 patients who underwent EUS-GE, the technical and clinical success rate were 87% and 83%, respectively. They followed EUS-GE patients for a median of 103 days (IQR 54-187), and detected only one recurrent GOO, which was due to food impaction¹⁶.

Finally, in a small case series performing EUS-GE with AXIOS LAMS on 3 mixed benign and malignant patients, Barthet et al. achieved technical and clinical success in all the cases, and they had only one minor adverse events which was addressed endoscopically¹⁷.

3.c. EUS-GE vs prior methods

We have been performing EUS-GE using AXIOS LAMS to treat patients with GOO since 2014 at Johns Hopkins Hospital. Recently, we retrospectively showed that EUS-GE was comparable to enteral stenting (ES) in terms of efficacy and safety in malignant GOO. According to our results, technical and clinical success was not significantly different: 87% EUS-GE versus 94% ES ($p = 0.2$) and 83% EUS-GE versus 67% ES ($p = 0.12$), respectively. Likewise, the rates of overall adverse events and serious adverse events were not significantly different: 16.7% in EUS-GE versus 11.5% ES ($p = 0.5$) and 10% in EUS-GE versus 9.6% in ES ($p = 0.95$). However, the EUS-GE was associated with a significantly decreased risk of recurrent GOO and the need for re-intervention. The rate of GOO recurrence and re-intervention was 4.3% in EUS-GE group and 28.6% in ES group ($p = 0.015$). In the multivariate analysis the use of ES (instead of EUS-GE) was an independent predictor for recurrent GOO with OR of 12.8 (95% CI 1.3–123.8, $p = 0.027$)¹⁶.

EUS-GE with AXIOS LAMS has also been compared with surgical gastroenterostomy in two retrospective studies. Both studies showed that success rate were not significantly different between the two methods. In the Perez-Miranda et al's study, technical success rate was 100% in the Laparoscopic gastrojejunostomy group and 88% in

the EUS-GE group ($p = 0.11$)¹⁸. In our multicenter study, although the technical success was higher in the surgical gastrojejunostomy (SGJ) (100% vs 87%, $P = 0.009$), clinical success was not different between the two groups (90% in the SGJ group vs 87% in the EUS-GE group, $P = 0.18$). In terms of recurrence of GOO symptoms, EUS-GE tends to show lower recurrence rate. Perez-Miranda et al reported that adverse event was significantly lower in the group treated with EUS-GE with AXIOS LAMS (12% vs 41%, $p = 0.038$). In the experience of our institution, AEs were lower in the EUS-GE group; however, the difference was not statistically significant (16% vs 25%, $p = 0.3$)¹⁹.

3.d. Rationale and the purpose of this study

Based on our clinical experience for the last three years along with the above-mentioned study results, the goal of this study is to prospectively compare EUS-GE with ES in the management of unresectable malignant gastric outlet obstruction. We hypothesize that EUS-GE is associated with comparable technical and clinical success and safety profile while requiring fewer re-interventions.

The purpose of this study is to use lumen apposing stent (LAMS) (AXIOS™ stent, Boston Scientific, Marlborough, MA, USA) and electrocautery-enhanced LAMS (AXIOS-EC™ stent, Boston Scientific, Marlborough, MA, USA) in order to perform EUS-GE for palliation of malignant GOO and compare its safety and efficacy with endoscopic ES in a two-year study.

Figures adapted from Itoi et al. manuscript²⁰.

4. Study Procedures

- a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

4.a.i. Study population

Target population is patients ≥ 18 and ≤ 80 years with unresectable malignancies which resulted in gastric outlet obstruction. We expect to have at least 112 patients (56 in each treatment arm), enrolled from U.S. and international recruitment sites. We anticipate enrolling 70 patients at Johns Hopkins. We expect approximately 50% of the patients to be women. There is no limitation regarding racial/ethnic identity of the participants.

4.a.ii. Study design

This will be a randomized, active control, parallel group, multi-site, clinical trial to evaluate the efficacy and safety of EUS-GE for palliation of malignant GOO and compare it with those who receive ES. This study is to be conducted in compliance with Good Clinical Practice.

This study will be conducted in eight U.S. centers and four international centers. All sites have received local IRB approval. The French sites are under one IRB.

U.S.

1. Johns Hopkins University
2. New York University, New York
3. Wake Forest Baptist University, North Carolina
4. Sharp Healthcare, California
5. University of North Carolina
6. Yale University, Connecticut
7. Columbia University, New York
8. Brigham and Women's Hospital, Harvard University Medical School, Massachusetts

International:

1. The Research Institute at McGill Health Centre, Canada
2. IECED Ecuadorian Institute of Digestive Diseases, Ecuador

3. Asian Institute of Gastroenterology, India
4. Hospital Prive des Peupliers, France and Limoges University Hospital, France

Participants are patients with unresectable malignancy that results in GOO. At least 112 patients will be randomly allocated approximately equally into one of the two treatment groups: 1) Standard of care enteral stenting with self-expandable metal stent (SEMS) or 2) EUS-guided gastroenterostomy with LAMS.

Patients will be evaluated and assessed by an increase in their baseline GOO score by at least 1 point, and if that was attained within 1 week they will be labeled as having clinical success post-procedure. Change in the quality of life will be also assessed using a previously validated questionnaire that will be filled before, 1-month post procedure, and 3-months post procedure. In regards to safety assessment, it will be carried throughout the study by the following methods; Adverse events, symptoms indicating the severity of GOO or GOO recurrence will be evaluated by a phone-call meeting with one of the investigators at 1-week, 2-weeks, 3-weeks, 1-month, 3-months, 6-months and 12-months following the procedure. In addition to the above mentioned, during routine clinical visits with the endoscopist, patients will be evaluated for clinical improvements and possible adverse events. Nevertheless, patients are instructed to directly inform the endoscopist for any unusual symptoms or alarming signs.

The study design is described briefly in the randomization (Figure 3) and schedule diagrams (Figure 4)

Figure 3. Randomization flow diagram of the study

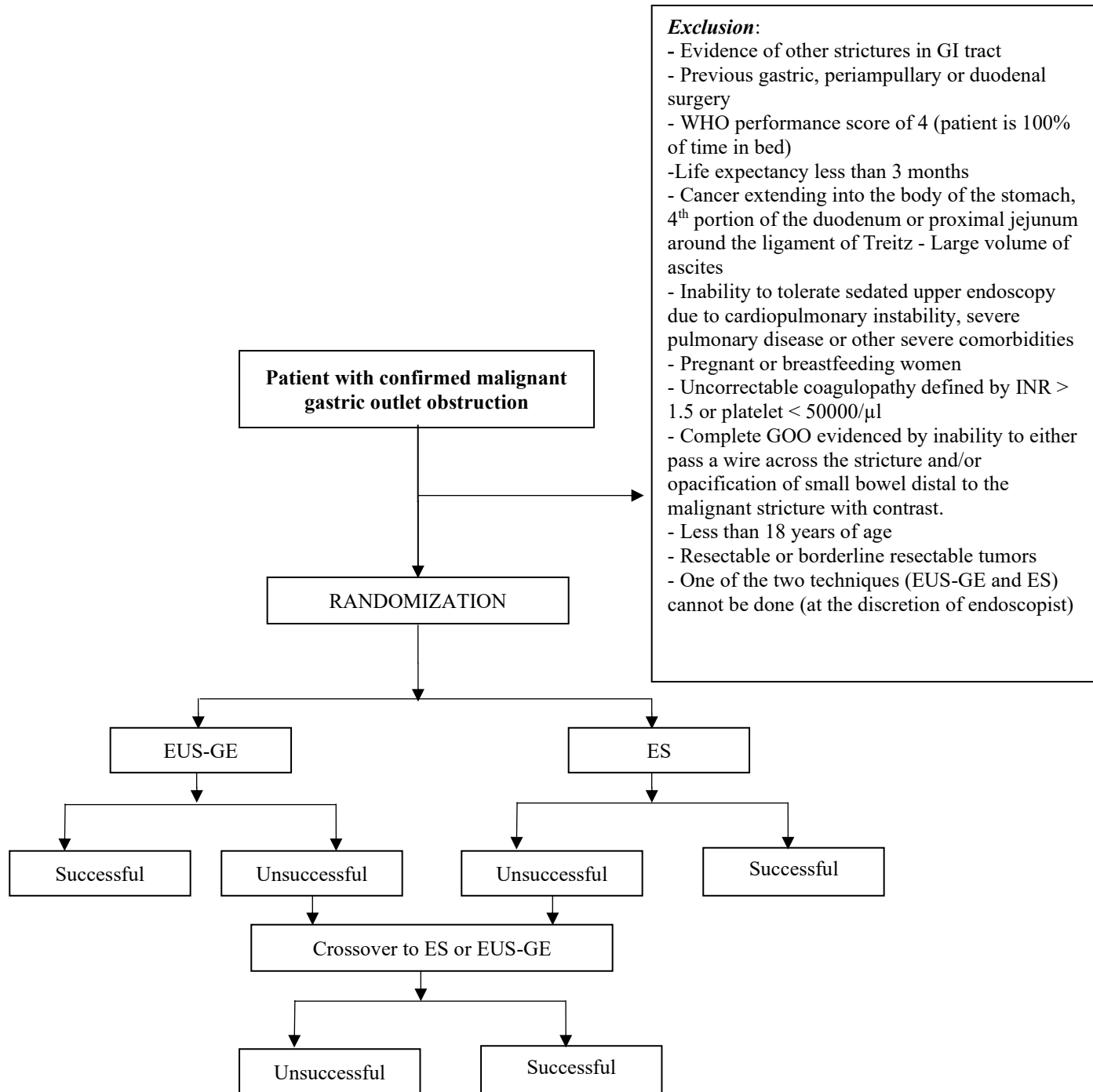


Figure 4. Study plan and schedule

	Pre-procedure	Day 0	1-day	2-days	1-week	2-weeks	3-weeks	1 month	3 months	6 months	12 months
Adverse events		X	X	X	X	X	X	X	X	X	X
Clinical Success					X						
Technical Success		X									
GOO Screening	X		X	X	X	X	X	X	X	X	X

4.a.iii. Randomization procedure

Randomization Schedule will be prepared by an unblinded statistician in the Coordinating-Center at Johns Hopkins Hospital. Participants will be randomly allocated, with a 1:1 ratio, to either EUS-GE or ES group. Randomization blocks will be generated in different sizes, ranging from 2 to 6, by STATA statistical software Version 13.1. Randomization numbers with their corresponding procedures will be fed to web-based central randomization system, research electronic data capture. All the investigators, except the statistician responsible to randomization schedule, will be blinded to the size of the blocks.

Patients who signed the informed consent will be included in the study. The assigned randomization will be reported as it appears on the research electronic data capture before the procedure and the participant will be randomized to one of the two endoscopic treatments according to the randomization number.

If before the randomization process, the endoscopist believed that either of the two techniques are not possible in a particular case, then the patient will be excluded. If after randomization, the assigned treatment cannot be carried out, the participant will be crossed to the alternative parallel treatment arm.

Participants who are not able to remain in the assigned study arm will be addressed by performing intention-to-treat vs per-protocol analysis at the end of the study.

Figure 3 has summarized the randomization process.

4.a.iv. Investigational device and delivery system

Lumen apposing metal stent (LAMS) is a flexible saddle-shaped cylindrical device covered with silicone which is produced in different diameters and lengths. The stent has two large end flanges which creates tissue apposition in the stent saddle allowing for creation of a conduit between two luminal structures into which the stent is deployed. The anchor flanges distribute pressure evenly on the luminal wall and securely anchor the stent and hold the jejunal or duodenal wall to the gastric wall, preventing detachment or migration. The Axios stent (Boston Scientific, Natick, Massachusetts, USA) is a fully covered LAMS, which is commercially available in 10 mm, 15mm, and more recently 20 mm internal diameters with the same saddle length of 10mm.

The stent is deployed using a catheter delivery system under the fluoroscopic, endoscopic or sonographic guidance. Electro-cautery assisted delivery system, which allows direct placement of the LAMS without need for wire placement or predilation, is also available for the LAMS (AXIOS-EC™ stent) (Figure 1, 2).

Indications of using LAMS include drainage of pancreatic fluid collections, recanalization of benign and malignant colorectal obstructions, and forming gastrogastrostomy, gastroenterostomy, and cholecystogastrostomy fistulas²¹. This device and its delivery system has been previously approved by FDA for drainage of pancreatic fluid.^{22,23}

4.a.v. Standard of care device

Self-expandable metal stent is a flexible cylindrical device produced in different diameters and lengths. The stent is available in silicon-covered and uncovered varieties; however, only the uncovered SEMS will be used in this study. The stent is basically a nitinol mesh knitted with elastic alloy that slowly expands at body temperature after deployment. Biliary tree, esophagus, stomach, duodenum and colon are organs in which

SEMS is used to treat luminal obstructions²⁴. The SEMS stent has two 27 mm flanges, one proximal and one distal, to reduce the risk of stent migration. Three models of uncovered duodenal SEMS stents will be used in this study: Boston Scientific, WallFlex™ Duodenal Stent, M00565010, 60 mm; Boston Scientific, WallFlex™ Duodenal Stent, M00565020, 90 mm; Boston Scientific, WallFlex™ Duodenal Stent, M00565030, 120 mm. Wallflex™ Enteral Duodenal Stent has been approved by FDA for the intended use of palliative treatment of gastroduodenal obstructions caused by malignant neoplasm, 510(k) number, K062750. The indication of the use of Wallflex™ Enteral Duodenal Stent in this study is palliative treatment of malignant gastroduodenal obstructions which is matched with the intended use of the FDA approval.

4.a.vi. EUS-GE technique

All patients who are randomized to the EUS-GE arm of the study will receive intravenous antibiotics immediately prior to the procedure. EUS-GE will be performed in an endoscopy unit or in an operating room under either conscious sedation, monitored anesthesia care, or general anesthesia. All procedures will be performed using therapeutic echoendoscopes by expert endoscopists at tertiary care centers with or without trainee involvement. One of the following technical approaches will be used:

- Direct gastroenterostomy (DGE)

DGE entails direct puncture of a small bowel loop adjacent to the gastric wall using a therapeutic echoendoscope. To facilitate the puncture, a forward viewing gastroscope is first inserted and fluid infused into the small bowel distal to the obstruction. Generally, a total of 500 ml of fluid using a combination of saline and contrast (with or without methylene blue) is infused. At the discretion of the endoscopist, a standard, commercially available EUS 19-gauge needle can then be used as a “finder” needle to locate a small bowel loop closest to the stomach by aspiration of blue-tinged fluid confirming the correct puncture site. The puncture position may then be confirmed via enterogram. The needle is withdrawn while keeping the endoscope in a stable position. A cautery-assisted

LAMS (Axios stent, Boston Scientific Corporation Inc., Marlborough, MA, USA) is then inserted directly across the stomach and into the small bowel followed by stent deployment forming the gastroenterostomy.

- Balloon assisted gastroenterostomy (BAGE)

The BAGE method has been developed with the hope of improving small bowel access and possibly facilitating stent insertion with the help of a guidewire. A standard, commercially available stone retrieval or dilating balloon or a dedicated double balloon instrument is inserted over a wire across the obstruction. Following inflation of the balloon with contrast fluid, EUS-guided puncture of the balloon or of the fluid-filled small bowel loop between the two balloons (in case of the double balloon method) is performed transgastrically with a 19-gauge needle. A guidewire is then advanced deep into the small bowel to guide subsequent insertion of a LAMS. In case of the double balloon method, there will not be a need to advance a wire prior to LAMS insertion.

Other assisted techniques may also be utilized. These include balloon trap technique in which the wire is coiled within the balloon which is pulled along with the wire to apply traction for easy stent advancement and deployment. Alternatively, a pediatric upper scope can be advanced to grasp the wire after the small bowel is punctured. This also allows for wire traction. For the BAGE method, LAMS can be deployed either over a guidewire (AXIOS™ stent), or directly with the cautery-enhanced LAMS (AXIOS-EC™ stent), creating the gastroenterostomy.

4.a.vii. ES technique

All endoscopic stenting (ES) procedures will be performed with a therapeutic gastroscope or duodenoscope under conscious sedation, monitored anesthesia care, or general anesthesia. Once the area of stenosis is reached, the length of the obstruction will be estimated by advancing the endoscope through the obstruction when possible or measured with fluoroscopy and contrast injection. A guidewire will then be advanced through the obstruction and an

enteral SEMS will be deployed under direct endoscopic visualization and fluoroscopic guidance. The stent will not be dilated with a balloon.

4.a.viii. **Post procedure process**

A liquid diet is allowed after the procedure and advanced to a low-residue diet, as tolerated. Stable outpatients may be discharged home if they can tolerate full liquid diet after the procedure. All others will remain hospitalized and can be discharged when at least full liquid diet is tolerated. Any post-procedural complication and the length of hospital stay post procedure will be recorded. During hospitalization, unblinded study investigator coordinator will visit patients one day post-procedure and two days post-procedure to record full fluid diet attempts and any post procedure complication using the case report form. Before discharge, patient will be notified about possible symptoms that they may experience and any other signs that might indicate potential adverse events. In addition to that, patients are given a clear instruction about their clinical follow-up schedule as well as follow-up phone calls from the investigators.

4.a.ix. Study plan and timing

Figure 4 provides an overview of the study assessments, follow-ups and, procedures. Results from any protocol-specified evaluations, including patient's regular medical care or study-specific assessments, will be recorded on the case report form (CRF). The investigators may schedule unplanned visits, in addition to those listed on the study plan table, in order to protect the safety of the subject or collect more accurate information.

- **Baseline assessments**

Baseline assessments will be performed within 36 hours before the procedure. In this phase, patients will be asked to define their gastric outlet obstruction score (GOOS) and complete Short Form-36 (SF-36) quality of life questionnaire. Biliary obstruction in participants presenting with jaundice or history of jaundice will also be recorded including time of appearance, liver enzymes and treatment characteristics. Treatment characteristics

include type of procedure (EUS-BD, ERCP, or PTBD), date of procedure, success and complications of procedure.

- Interventional procedure evaluation

During the procedure, the length of the obstruction will be evaluated by the endoscopist. X-ray imaging may also be used for evaluation of the length of the obstruction. Length of procedure will be measured as the time interval between randomization to the successful deployment of stent (including possible stent dilation and treatment for bleeding or other AEs). Identifying and assessment of adverse events will begin from the time that informed consent is obtained. Following stent deployment, “Technical Success” will be determined endoscopically and/or radiographically.

If the EUS-GE technique with LAMS is used, then the following items will be recorded: the type of technique (direct vs balloon assisted), the use of wire and balloon dilation, and the part of the small bowel that was punctured (second part of duodenum, the third part of duodenum, or the jejunum).

If the ES with SEMS is used, then the following items will be recorded: if the stricture passed by the endoscope, dilation of the stricture before stent deployment, and the place of proximal flange deployment (pre-pylorus vs post-pylorus).

- Follow-up assessments

“Clinical Success” will be assessed after the patient’s discharge from hospital at 1 week. Patients will be contacted at 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, and 12 months after the procedure to evaluate the GOO score. There will be a grace period of +/- 4 days for the weekly follow ups and +/- 1 week for monthly follow ups. If patient data is not collected for one visit, “N/A” will be recorded and subsequent visits will be collected. Evaluation of the adverse events will begin from the time that informed consent is obtained and will continue till the end of the study or participant’s death. To assess the quality of life, the SF-36 questionnaire will be completed at 1 month and at 3 months after the procedure by calling the patients known to be still alive. The study coordinator who will record the data during the procedure and will contact participants for follow-ups, for

assessing the quality of life, GOO scoring, and any AEs, will also remain unblinded. To reduce the observer bias, study coordinators will contact patients using the case report form..

4.a.x. Study assessments

Patient's data will be recorded on the CRF sheet as indicated in the protocol by the study coordinator. After making sure of the accuracy, completeness and timeliness of the recorded data, the study coordinator will sign the form indicating its completion. A copy of the completed CRF will be archived and data will be entered into redcap in a timely manner.

- Background and disease history

Participant's demographics, history of anticoagulant use (type, dosage, and the time of the last dose as well as the medication re-starting time), type of malignancy, and other comorbidities will be thoroughly recorded in the CRF before the procedure. Characteristics of the obstruction including location (pylorus, first or second part of the duodenum, or jejunum), GOO severity score, and prior treatments for the obstruction (i.e. duodenal stenting) will be recorded as well. Please refer to the most up to date version of the CRF for which data to collect.

- Quality of life

Quality of life (QOL) will be assessed by Short Form-36 (SF-36) quality of life questionnaire before procedure, at one month and at 3 months after the procedure to compare the change of QOL. The SF-36 questionnaire will be filled by the patient and if needed, one of the investigators will help the participants with the questionnaire.

- Technical success

Following the procedure, the endoscopist will determine if the procedure is successful based on endoscopy results and/or imaging. Technical success will be defined as adequate

positioning and deployment of the stent as determined endoscopically and radiographically.

- Clinical success

Clinical success is defined by the improvement of at least 1 point in the gastric outlet obstruction score within 7 days after stent insertion.

Prior to discharge, while the patient is alert and stable, a fluid meal will be allowed to the patient and advanced to a low-residue diet, as tolerated.

- Gastric outlet obstruction (GOO) and the severity of GOO

An unblinded study member will interview the participants before procedure and 1 day, 2 days, 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, and 12 months after the procedure to evaluate the symptoms of GOO (such as nausea, vomiting, and inability to tolerate PO intake), and to assess the severity of GOO based on gastric outlet obstruction severity system (GOOSS) (see Section 2).

GOO will be confirmed endoscopically and/or radiographically. The need for unplanned re-intervention (endoscopic or surgical) to treat GOO will be considered as a surrogate for GOO. GOO before and after two weeks after the procedure will be considered as persistent and recurrent GOO, respectively.

4.a.xi. Assessment of safety of procedures (Adverse events)

In this trial we will use two independent evaluation systems for classification and grading of AEs: 1) ASGE lexicon's severity grading system⁷ and 2) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0²⁵. Each AE will be evaluated by both ASGE and CTCAE systems.

CTCAE system will be used for safety and monitoring purposes. Severity, timing, and relationship of the AE to the procedure will be evaluated by CTCAE system for safety monitoring and reporting AE to team members. Details about evaluation and reporting AEs based on CTCAE has been explained in details in the Section 9.c.

In addition to CTCAE system, all AEs will be also evaluated using ASGE lexicon. The safety of EUS-GE procedure, as one of the study's endpoints, will be evaluated by frequency and severity of AEs which are related to the procedures. ASGE system is well accepted by gastroenterology society, and previous studies on EUS-GE and ES have generally reported their results based on ASGE system. Therefore, in order to be able to compare our results with the previous studies, we will use ASGE lexicon to evaluate, compare, and report safety as an outcome of this trial. In this section, the details of evaluation and grading of AEs based on ASGE lexicon.

In order to evaluate timing, attribution, and severity of AEs using ASGE system, all required information including the timing, the type of AE, the treatment used for managing the AE, ICU/ward admission and its duration, physical examination and imaging findings, lab results, repeated endoscopy and its findings, surgical intervention, and any other related findings will be recorded.

In order to prevent any bias that could impact the evaluation of AEs, recorded data from all participating centers will be sent to the Sponsor Investigator. The Sponsor-investigator will evaluate timing, attribution, and severity of all reported AEs. Upon request, additional required data will be provided for evaluating the AEs. The SI will have access to unblinded data for assessing the severity, timing, and attribution of AEs.

- Timing

Events can occur pre-procedure, intra-procedure (from entering the preparation area through leaving the endoscopy room), post-procedure (up to 7 days), and late (any time after 7 days). For delayed events, the number of days after the procedure will be documented.

- Attribution to the intervention

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.

- Unlikely - The AE is doubtfully related to the study treatment.

- Severity

Severity is graded by the degree of consequent disturbance to the patient and any changes in the plan of care, as shown in Table 1. AEs should be followed until their death to assess severity and should include the reason and the outcome of any new procedure.

Table 1. Severity of adverse events based on ASGE system⁷

Consequence	Severity grade			
	Mild	Moderate	Severe	Fatal
Procedure aborted (or not started) because of an adverse event	x			
Post-procedure medical consultation	x			
Unplanned anesthesia/ventilation support, i.e. endotracheal intubation during conscious sedation		x		
Temporary ventilation support by bagging or nasal airway during conscious sedation, and endotracheal intubation during a modified anesthesia care procedure are not adverse events		x		
Unplanned hospital admission or prolongation of hospital stay for lesser or equal to 3 nights	x			
Unplanned admission or prolongation for 4-10 nights		x		
Unplanned admission or prolongation for greater than 10 nights			X	
ICU admission for 1 night		x		
ICU admission greater than 1 night			X	
Transfusion		x		
Repeat endoscopy for an adverse event		x		
Interventional radiology for an adverse event		x		
Interventional treatment for integument injuries		x		
Surgery for an adverse event			X	
Permanent disability (specify)			X	
Death				x

4.a.xii. Regulatory and ethical consideration

Prior to initiation of a site, approval from appropriate regulatory agencies will be obtained to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with ICH Good Clinical Practice (GCP), the guiding principles of the current version of the Declaration of Helsinki, and all applicable subject privacy requirements. This includes, but is not limited to the following:

- Signed informed consent must be obtained for each subject prior to participation in the study
- The IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including the investigational device.
- Investigator reporting requirements (e.g. reporting of SAEs and protocol deviations to the IRB)

Respective IRBs should approve the final study protocol, including the final version of the Informed Consent Form and any other materials to be provided to the patients. Copies of IRB approvals should be forwarded to the Coordinating Center.

4.a.xiii. Consent process

The consent form describes each portion of this study and provide sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, is obtained before the participant is involved in any study-related procedure.

Before obtaining the consent form, the investigator will provide a full and clear explanation to the participant regarding the items in the consent form, including:

- The anticipated risks and benefits of the investigational product,
- Duration of participation in the study and the follow-up schedule,
- The right of patient to withdraw from the trial at any time,
- That patient's refusal of or withdrawal from participation in the trial does not cause any disadvantage to her/him,
- In the event of trial-related injury, all necessary treatments are available for the participant

- The privacy of participants is kept
- Monitors and IRB are given access to the participant's documents on condition that confidentiality of the patient is fully secured.

The patient is given sufficient time to consider participation in the trial. The Investigator obtains written consent from the patient after confirming that the patient understands the contents of the consent form. The consent form shall be signed and dated by the participant and by the investigator obtaining the consent. The participant shall be given a copy of the signed and dated consent document. The original signed copy of the consent document will be retained in the medical record or research file.

b. Study duration and number of study visits required of research participants.

Study duration is 7 years. Patient-subject enrollment duration is 1 year. One pre-procedure assessment and 9 post-procedure assessments will be performed. Figure 4 provides an overview of the study assessments, follow-ups and, procedures. In addition to the study assessments and follow-ups per routine clinical practice assessments and follow-ups will be performed

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Patients will be blinded to the result of randomization in order to minimize bias in answering the follow-up questions. Blinding of the endoscopists is not possible as he or she will be performing the procedure. The statistician will remain blinded throughout the study. The study coordinator who will record the data during the procedure and will contact participants for follow-ups, for assessing the quality of life, GOO scoring, and any AEs, will also remain un-blinded. To reduce the observer bias, study coordinators will contact patients using the case report form.

Experts who adjudicate the AEs as an outcome measure, may have access to unblinded data for assessing the severity, timing, and attribution of AEs. DSMB will be unblinded, and the Principal Investigator of each site will unblind the reports to the DSMB. The Principal Investigator at each site will be unblinded to have access to data required for reporting the AEs. The statistician analyst will be provided with subject codes and remain blinded.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A

- e. Justification for inclusion of a placebo or non-treatment group.

This is not applicable to this study. All patients are presenting for a procedure they require.

- f. Definition of treatment failure or participant removal criteria.

Treatment failure is defined as inability to accurately position and deploy the stent at the discretion of the endoscopist. In these cases, patients may cross over to EUS-GE or ES (depending on their initial randomization) assuming a major procedural complication has not occurred that would preclude additional endoscopic intervention.

- g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

No change in medical care will be expected.

5. Inclusion/Exclusion Criteria

Inclusion Criteria

- Capability of understanding and complying with the study requirements, including filling the quality of life questionnaire and signing the informed consent form.
- Adult patients with malignant, symptomatic gastric outlet obstruction due to unresectable malignant lesion
- Gastric outlet obstruction scoring system (GOOSS) score of 0 (no oral intake) or 1 (liquids only)
- Age ≥ 18 and ≤ 80 years.

Exclusion Criteria

- Evidence of other strictures in the gastrointestinal (GI) tract
- Previous gastric, periampullary or duodenal surgery
- World Health Organization (WHO) performance score of 4 (patient is 100% of time in bed)
- Life expectancy of less than 3 months based on the endoscopist's opinion.
- Cancer extending into the body of the stomach, 4th portion of the duodenum or proximal jejunum around the ligament of Treitz
- Large volume ascites

- Inability to tolerate sedated upper endoscopy due to cardiopulmonary instability, severe pulmonary disease or other severe comorbidities
- Pregnant or breastfeeding women (women of childbearing age will undergo urine pregnancy testing as part of the standard of care)
- Uncorrectable coagulopathy defined by INR > 1.5 or platelet < 50000/ μ l
- Complete GOO evidenced by inability to either pass a wire across the stricture and/or inability to opacify small bowel distal to the malignant stricture
- Resectable or borderline resectable tumors
- One of the two techniques (EUS-GE and ES) cannot be performed (at the discretion of endoscopist)

The general information of all excluded cases (including age, sex, and tumor type) as well as the reason for exclusion will be recorded. If an exclusion criteria is discovered in the procedure room then the patient will be considered a screening failure and “off study”.

6. Drugs/ Substances/ Devices

- a. The rationale for choosing the drug and dose or for choosing the device to be used.

Self-expandable metal stent (SEMS) is a flexible cylindrical device produced in different diameters and lengths. The stent is available in silicon-covered and uncovered varieties. The stent is basically a nitinol mesh knitted with elastic alloy that slowly expands at body temperature after deployment. Biliary tree, esophagus, stomach, duodenum and colon are organs in which SEMS is used to treat luminal obstructions²⁴.

- b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

As reported in the section 9.a, studies have shown that the rate of SAEs of EUS-GE with LAMS is comparable to ES with SEMS. Specifically, in a study that compared these two methods, rate of SAEs of EUS-GE and ES were 10% and 9.6%, respectively ($p = 0.95$)¹⁶. However, data on safety of EUS-GE are limited to retrospective case series with small sample sizes.

LAMS stent (AXIOS™ stent) and its electrocautery-enhanced delivery system (AXIOS-EC™ stent) has been approved by FDA for endoscopic drainage of symptomatic pancreatic pseudocysts for maximum of 60 days²². The usage of LAMS for pancreatic collections has been limited to 60 days as pancreatic fluid will generally resolve in a short period of time after deployment of the LAMS stent. For example, in a retrospective case series the median time for resolution of pancreatic fluid collection was 35-days following the deployment of LAMS²⁶.

However, when LAMS is used for creating a gastroenterostomy, the stent will be kept at the anastomosis site because, unlike drainage of pancreatic collections, gastroenterostomy anastomosis, created by LAMS, is intended to remain patent and functional until patient's death.

We believe that remaining of the LAMS for a long-time period in the anastomosis site will not cause additional risks to the patients because GI lumen can support the LAMS on its both sides. Retrospective studies investigating LAMS for gastroenterostomy support our claim as no SAEs related to the long-time presence of the LAMS (i.e. stent migration) was reported to ^{5,6,14-16}.

Moreover, a clinical trial which compared LAMS removal after pancreatic fluid resolution vs keeping the LAMS even after fluid resolution (up to 28 month), showed that the two groups were not different in terms of safety and efficacy²⁷.

The main advantage of EUS-GE over ES is the lower rate of re-intervention due to recurrent obstruction. Although ES provides relief of GOO, re-obstruction, which require further interventions, is its major drawback. The lower rate of re-intervention after managing malignant GOO is very important since the patients with end stage malignancy should be managed in a way to provide comfort, fewer invasive interventions, and shorter length of hospital stay.

The rate of re-intervention for EUS-GE on malignant GOO varies from 0 to 9.5 percent in different case series (Table 2). On the other hand, according to three ²⁸⁻³⁰. In a study which compared EUS-GE with ES retrospectively, the rate of re-intervention was significantly lower among EUS-GE cases (4.3% vs 28.6%, p=0.015)¹⁶. Promising results regarding safety and effectiveness of EUS-GE plus its considerably lower rate of re-

intervention need is the main justification for performing EUS-GE with LAMS to palliate malignant GOO.

- c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

- a. *Primary outcome variable:*

The primary outcome is rate of GOO recurrence manifested by recurrence of nausea, vomiting, and inability to tolerate PO intake up to 3 months after the procedure confirmed either endoscopically and/or radiographically leading to reintervention.

Secondary outcome variables:

1. Safety (rate and severity of adverse events); Technical success; clinical success; GOO recurrence; re-intervention rates; length of procedure; length of hospital stay; overall survival after procedure; quality of life change after procedure; and type of diet tolerated after procedure; time to achieve any oral diet tolerance full liquid tolerance and time to achieve full liquid diet tolerance any oral diet tolerance.; Stent dysfunction rate(defined as the restenosis of the stent due to tumor ingrowth or overgrowth, stent migration, or fracture); duration of stent patency (Calculated from the time of stent placement to the time of stent dysfunction)

- b. *Statistical plan including sample size justification:*

7.c.i. Statistical design – Model

This is a randomized active control trial, and the primary outcome is the rate of gastric outlet obstruction (GOO) recurrence. The rate of symptomatic recurrence of GOO will be compared at 3 months after the procedure between the EUS-GE with LAMS and ES with SEMS groups.

7.c.ii. Null and alternative hypotheses

The null hypothesis is that EUS-GE is equal to ES with respect to recurrence rate of gastric outlet obstruction:

H0: $C=T$ (C is equal to T)

The alternative hypothesis is that EUS-GE is not equal to ES with respect to recurrence rate of gastric outlet obstruction:

H1: $C \neq T$ (C is not equal to T)

Where C and T are GOO recurrence rates of ES and EUS-GE, respectively.

7.c.iii. Sample size calculation

Two-sided 5% significance level and 80% power were used for sample size calculation.

We plan for an overall Type 1 error rate of 5% for GOO recurrence rate. Based on previous published studies we assumed 4% and 23% recurrent GOO 3 months after the EUS-GE and ES, respectively. The sample size was calculated with the final p threshold, to have 80% power to detect a clinically meaningful difference in recurrence rate of 23% in the EUS-GE group versus 4% in the ES group; therefore, the estimated required sample size is 50 completers per group.

In order to exclude participants with life expectancy of less than 3 months, we exclude very sick patients including the patients who have life expectancy of less than 3 months based on the endoscopist's opinion (see Section 5). A total of 10 % drop out rate has been estimated for this trial. Considering all above-mentioned assumptions, a total of 112 participants (56 in each arm) will be randomized into treatment groups.

7.c.iv. Randomization

Randomization will be done by center via REDCap and will be in variable blocks of four to eight. The coordinating center (i.e. Johns Hopkins Hospital) will share access to the REDCap randomization instrument and centers will only have access to their own Data

Access Group. Participants will be randomly allocated, with a 1:1 ratio, either to EUS-GE or ES group.

7.c.v. Primary analyses

Recurrent obstruction is the primary outcome of this study (see Section 2). The primary outcome will be evaluated with intention-to-treat analyses on all randomized patients-regardless of whether they have received treatment or whether they have adhered to the randomized group.

Per-protocol analyses will be also performed and its results will be compared to intention-to-treat analyses to assess the robustness of primary analyses. Per-protocol analyses only account participants who adhered to the randomized group and were successfully followed for two weeks.

Chi2 statistical test will be used to compare the GOO recurrence rate between the treatment arms. Multiple regression models will be performed to evaluate the potential predictors of the primary outcome. The primary outcome will be tested at $\alpha = 0.05$, two-tailed.

7.c.vi. Secondary analyses

Secondary outcomes were defined in Section 2. Continuous variables will be reported as mean +/- standard deviation or median (IQR), with inferential analysis performed using t test or non-parametric tests. Categorical variables will be reported as frequencies and proportions with inferential analysis performed using Chi-square test (or Fisher's exact test if required). The rate of adverse events will be compared using Poisson or negative binomial regression. To compare time-to-event outcomes (i.e. recurrent GOO), the Kaplan-Meier and cox regression methods will be used; the latter allows us to adjust for demographic and clinical predictors. Post-intervention survival will be calculated from the date of intervention (EUS-GE or ES) to the date of the intended event. To compare the quality of life change between the two techniques, we will use regression analysis adjusting

for pre-intervention quality of life. Finally, logistic regression will be used to calculate odds ratios for demographic and clinical predictors. A level of significance of $p < 0.05$ will be adopted for the secondary outcomes.

For all secondary outcomes both intention-to-treat and per-protocol analyses will be performed.

7.c.vii. Safety analyses

Safety will be evaluated by the frequency of Adverse event and its severity based on ASGE lexicon (See section 4.a.xi). For each treatment group, separate summaries will be provided for all device related, procedure related, total AEs, and SAEs by severity and timing. Intention-to-treat and per-protocol analyses will be performed to investigate the safety of the procedures. Statistical methods described in Section 11.7 will be used for safety analysis. Details on the approach to handling missing data for safety analyses are provided in Section 11.9.

7.c.viii. Handling missing data

Our goal is to obtain complete follow-up of adverse events, recurrent GOO, and GOO score. All lost to follow-up patients will be treated as censored at the time of last known follow-up. Patients will be considered “lost to follow-up” after missing two consecutive data collection visits. If patient data is not collected for one visit, “N/A” will be recorded and subsequent visits will be collected.

Values will be imputed for the primary and secondary outcomes using relevant imputation methods. Then, in order to explore the impact of missing data, sensitivity analyses for primary and secondary outcomes will be performed.

8. MULTICENTER GUIDELINES

The coordinating center's PI shall internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation.

8.a. Coordinating center responsibilities

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all the participating centers met all requirements as outlined in the monitoring plan before starting patient enrollment, and all participating institutions are using the correct version of the protocol.
- Assuring that all participating centers adhere to the study protocol, especially with respect to eligibility, consent process, and completeness of data collection after enrollment of 5-10 patients and after enrollment is complete.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE).
- Reviewing data from all sites, including coordinating and participating centers.

8.b. Participating center responsibilities

The principal investigator of each participating center is responsible to monitor the trial continuously to assure:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.

- Collecting and submitting data to the coordinating center according to the schedule specified by the protocol.

The Sponsor-investigator will consider off site monitoring where appropriate. This may include conference calls and upon sending de-identified CRFs in order to monitor the trial sites. On-site visits may be conducted based on the center's performance criteria, especially regarding to adverse event reporting (e.g. sites with considerably higher or lower reports of serious adverse events related to others).

9. Risks

- a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Both EUS-GE with LAMS and ES with SEMS are considered therapeutic endoscopy, which is considered invasive procedures with potential risks to the patient. The risks of ES have been well described as it has been used for years and it is considered as the standard of care.

Three large systematic review and meta-analysis have reported a total of 25-28 percent SAEs for²⁸⁻³⁰ mentioned the following complications as the main adverse events of ES:

- Stent related complications including re-obstruction by tumor ingrowth, stent migration, insufficient stent expansion, stent compression by tumor pressure, food occlusion, stent fracture, and other stent related complications.
- Perforation
- Bleeding
- Pain
- Biliary obstruction

EUS-GE with LAMS, however, is a novel technique and its safety on human subjects can only be estimated from 6 case series. According to our review of literature, the reported SAEs related to this technique are stent misdeployment, pneumoperitoneum, peritonitis, bleeding, pain, and unplanned re-intervention mainly due to recurrent obstruction. Table 2 provides a summary of adverse events in all case series on EUS-GE. As expected, the rate of SAEs tends to be higher in studies which were performed only on malignant

obstructions. In addition to the mentioned AEs, we believe that infection can be the other potential procedure related AE. According to our review of the literature, there have been no reports on allergic reaction to AXIOS LAMS in the literature so far.

In addition to the potential risks mentioned above, we observed a SAE in one of the participating centers, Hospital Universitario Rio Hortega, Spain. Patient enrolment was started in the Hospital Universitario Rio Hortega after obtaining approval from the “Ethic Committee of Investigation Using Medications” (reference number, EC-094-17), and granting protocol-based approval for off-label use of Axios LAMS stent. The SAE was GI bleeding that resulted in death. The SAE was evaluated as possibly associated with the procedure.

Table 2: Outcome of the main series on endoscopic ultrasound-guided gastroenterostomy for gastric outlet obstruction

Study	Number of patients (patients with malignant obstruction)	follow-up time (days)	Stent misdeployment	Pneumoperitoneum	Peritonitis	Bleeding	Pain	Unplanned reintervention
Khashab ⁵	10 (3)	Mean 150 (range 96-227)	None	None	None	None	None	None
Itoi ¹⁴	20 (20)	Median 100 (range 44–233 days)	None	1 (5%)	None	None	None	None
Tyberg ¹⁵	26 (26)	Mean 55 (range 0–32)	None	None	1 (3.8%), resulting in death	1 (3.8%)	1 (3.8%)	None
Chen ¹⁶	30 (30)	Median 103 (IQR 54-187)	3 (10%)	None	None	None	None	1 (4.3%)
Chen ⁶	74 (49)	Median 114 (IQR 45-206)	5 (6.8 %)	None	None	None	None	7 (9.5%)
Barthet ¹⁷	3 (2)	-	0	0	0	0	0	-

b. Steps taken to minimize the risks.

In order to minimize the risks which are related to the endoscopist, including stent misdeployment and stent migration, procedures will be performed by board certified gastroenterologists trained in advanced endoscopy who are experienced with both EUS-GE and ES procedures. Adherence to the standard of practice of the Johns Hopkins Hospital and Division of Gastroenterology and Hepatology will be kept during the study.

Only tertiary centers with known expertise in pancreaticobiliary diseases and interventional EUS will be included. Endoscopists should have performed at least 20 enteral stenting and 10 EUS-guided gastroenterostomy procedures prior to enrollment

Only tertiary centers with known expertise in pancreaticobiliary diseases and interventional EUS will be included. Endoscopists should have performed at least 20 enteral stenting and 10 EUS-guided gastroenterostomy procedures prior to enrollment.

To decrease the rate of acute and subacute bleeding during or post procedure, patients who are on anti-coagulant or anti-platelets will be asked to discontinue and restart the medication based on the proper half-life of the drug genres. Patients with unknown recent baseline Complete Blood Count values, will be asked to do the laboratory test. If required, CBC test might be repeated for patient's post-procedure to rule out any significant Hemoglobin or Hematocrit drop. Major bleedings during or post procedure will be addressed by appropriate measures including endoscopic or surgical measures and blood transfusion as needed.

To minimize the risk of infection, patients who are randomized to the EUS-GE arm will be given IV antibiotics prior the procedure in the endoscopy room. Patients will be asked for any history of allergic reactions to antibiotics, and in case of any allergies to a specific first line antibiotic, the patient will be given another first line antibiotic in order to protect him/her from potential allergic reactions.

Tumor ingrowth and stent migration are the most common causes of re-obstruction after ES with SEMS. Only uncovered WallFlex stent (Boston Scientific, Natick, Massachusetts, United States) will be used in this trial. In order to minimize the risk of re-obstruction, the Wallflex stent has two flanges at the proximal and distal ends which decrease the chance of stent migration. In case of tumor ingrowth or stent migration which result in recurrent obstruction, patient will be treated per standard of care and will be offered repeat enteral stenting (ES) and gastrojejunostomy procedures.

c. Plan for reporting unanticipated problems or study deviations.

9.c.i. Adverse event recording/reporting

The AEs will be evaluated according to both CTCAE and ASGE lexicon. ASGE lexicon will be used to define and grade AEs in order to determine the safety of EUS-GE and ES procedures.

On the other hand, CTCAE, which is widely accepted tool to evaluate adverse events in oncology patients, will be used for safety and monitoring purposes of the trial. Participants will be patients with unresectable malignant tumors that have resulted in GOO; therefore, CTCAE, which is a more conservative evaluation system in comparison to ASGE lexicon, will be used to define and assess AEs for safety and monitoring purposes in order to further protect the participants. The following section will explain how CTCAE v 5.0 will be used to evaluate and record AEs and report them to team members and IRB.

9.c.ii. Definitions

- Adverse Event (AE): An AE is an event that prevents completion of the planned procedure and/or results in admission to hospital, prolongation of existing hospital stay, and the need for another procedure (needing sedation/anesthesia), or subsequent medical consultation.
- Serious adverse event (SAE): Any adverse event that demand any kind of additional intervention, hospitalization, or prolongation of hospitalization, and/or results in limiting activity of daily living, disability, life-threatening outcome, or death. SAE is determined as grade 2 to 5 of CTCAE v5.0.
- Adverse Event Related to the research procedure (attribution): There is a reasonable possibility that the adverse event may have been related to the investigational device/procedure. The PI will determine if the AE is related to the research procedure.
- Unanticipated adverse device effect (UADE): “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan

or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21 CFR 812.3(s))

- Unexpected adverse event: Any adverse event that the frequency, specificity, or severity of which is not consistent with the risk information described in the clinical study protocol.
- Unexpected death: is defined as the death of a participant under circumstances that was not related to a risk of participation listed in the protocol or the consent document that was signed by the patient. The cause of the unexpected death is more likely not related to the procedure under investigation itself.
- Expected death: an “expected death” is a term used to define the death of a participant that occurred due to the nature of participant’s known underlying disease or condition as well as if it caused by a possible risk of the study procedure as described in the protocol and the consent form.

9.c.iii. Eliciting data

The principal investigators are responsible to make sure that all co-investigators are familiar with the possible adverse events and have the clear directions of reporting and documenting them.

Adverse events will be collected by the following means:

- Participants will be contacted at one day, two days, 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, and 12 months after the procedure by an unblinded investigator to determine if any AEs have occurred.
- Participants will be assessed for AEs during all the routine post-procedure clinical visits with their endoscopists.

9.c.iv. Recording and assessing adverse events

All observed or reported adverse events, regardless of their severity or causal relationship to the investigational device and the procedure, will be documented in the subject’s Adverse Event Form. For all adverse events, sufficient information will be provided to permit 1) an accurate determination of the severity of the adverse events

(i.e., whether the AE meets the criteria for a serious adverse event), and 2) an assessment of the casual relationship between the adverse event and the investigational device.

Principal investigator of each participating center is responsible for reviewing documented adverse events and any abnormal findings to determine; 1) if the abnormal findings should be classified as an AE, 2) if the AE is attributable to the procedure or devices, and 3) the severity of AEs.

9.c.v. Adverse event severity

Revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0²⁵ will be used to evaluate severity of AEs for reporting and safety purposes. CTCAE uses a range of grades from 1 to 5 to define the severity of AEs:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Activities of Daily Living (ADL):

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self-care ADL refer to bathing, dressing*

9.c.vi. Assignment and attribution of adverse events

The PI is responsible for deciding if an AE is related to the research procedure (i.e. interventional procedure/device). If the PI's final determination of causality is

unknown or the relationship is questionable to the investigational device or other study treatment or diagnostic procedures, the adverse event will be considered to be associated with the use of the investigational device.

9.c.vii. Reporting adverse events

It is the responsibility of each participating investigator to report serious adverse events to the respective IRB and the investigator-sponsor as described below.

- Reporting to the investigator-sponsor

All adverse events that will occur during or within twelve months of the procedure will be reported to the investigator-sponsor as described below:

➤ Serious Adverse Event Reporting:

Serious adverse events that occur during or within twelve months of the procedure and meet one of the following criteria will be reported to the investigator-sponsor.

- A. Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and attributable or possibly attributable to the intervention.
- B. All Grade 4 (life-threatening or disabling) Events – All adverse events in this category will be reported unless it is expected and specifically listed in the protocol.
- C. All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial.
- D. All adverse events that meets the criteria of UADE.

Participating investigators must report each serious adverse event (SAE) to the Investigator-sponsor **within two business days of the SAE occurrence** using Serious Adverse Event Form. If the participating investigator does not become aware of the serious adverse event

immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event **within one business day of learning of it** and document the time of his or her first awareness of the adverse event. AEs will be reported to:

Mouen Khashab, MD
Office: 443-287-1960
Fax: 443-683-8335
Email: mkhasha1@jhmi.edu
Emergency Contact#: 443-509-3388

Within the subsequent 1-2 business day from initial report, the participating investigator must provide follow-up information on the reported adverse event. Follow-up information will describe how the event was treated, whether the event has resolved or continues, and whether the participant will continue or discontinue study participation.

Sponsor-investigator (who is also the PI of the JHH center), in turn, will report such adverse events to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor-investigator first receives notice of the events.

FDA form 3500A
(<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>) will be used for reporting SAEs to FDA.

➤ Non-serious Adverse Event Reporting

All non-serious adverse events will be recorded on Adverse Event Form. Non-serious AEs will not be reported on Serious Adverse Event Form. As a part of ongoing safety review conducted by the Sponsor-investigator, any reported non-serious AE that is determined by the sponsor investigator as a SAE will be treated as a SAE. The Sponsor-investigator may request complementary information in order to determine the severity of the AE.

- Reporting to Institutional Review Board (IRB)

In accordance with applicable IRB policies, principal investigator of each participating center will report any AE, including observed and reported AEs, to the respective IRB if the AE has the following conditions:

- Is defined as serious adverse event
- Is unexpected
- Associated with the investigational device/procedure or diagnostic product. Principal investigators will report AEs as soon as possible, but in no event later than 10 calendar days

All deaths, whether expected or unexpected, which occur within 30 days after the procedure will be reported to the IRB. The PI is responsible for reporting the study deaths. Unexpected and expected deaths will be reported no longer than 3 and 10 days, respectively.

In order to comply with local IRB policies, each participating center will follow additional regulations demanded by the respective IRB.

Within 3 calendar days, a copy of the submitted adverse event report form will be forwarded to the Sponsor-investigator:

Mouen Khashab, MD

Office: 443-287-1960

Fax: 443-683-8335

Email: mkhasha1@jhmi.edu

Emergency Contact#: 443-509-3388

- Reporting to the Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

9.c.viii. Data and monitoring safety plan

The study will be conducted in compliance with the protocol, the guiding principles of the current version of the Declaration of Helsinki, FDA regulations and guidelines, and Good Clinical Practice (GCP) guidelines which require the following:

- The rights and well-being of human subjects are protected
- We will ensure that our reported data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol, with GCP, and with applicable regulatory requirements.

The main goal of monitoring the EUS-GE with LAMS is 1) to assure compliance with the protocol requirements and 2) immediate detection and management of serious adverse events (FDA, 21CFR 812.46).

A quality assurance monitoring of this trial may be conducted by the sponsor, sponsor's designees, or IRBs authorities. The quality assurance monitor will have access to all medical records, trial-related files and correspondence, and the informed consent documentations.

9.c.ix. Data safety monitoring board (DSMB)

Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least annually by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB Recommendation letter will state the timeline for the next required review. The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial, recommendations will be made in writing to the Study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research, will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate.

After enrolling of one third of the planned participants, DSMB will review all the serious adverse events and the recruitment process based on the proposed schedule.

- d. Legal risks such as the risks that would be associated with breach of confidentiality.
There are no legal risks associated with participation in this study.

All measures to protect confidentiality will be taken. Collected data will be handled in an anonymous manner with adherence to HIPAA guidelines. All the study mandated data points without any patient identification information will be recorded and collected using research electronic data capture and shared with the lead coordinating center. Data will be transferred to a SAFE desktop for storage and further actions including data analysis.

- e. Financial risks to the participants.
None

10. Benefits

- a. Description of the probable benefits for the participant and for society.

Potential improvement in decision making for patients with malignant GOO, which would finally lead to the improvement of patient outcome.

11. Payment and Remuneration

- a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

According to the prospective reimbursement analysis performed by Epic Billing Grid of the Johns Hopkins Medical Institutions, all items, services and procedures will be performed as part of the patients standard clinical care and will be authorized through the normal insurance clearance process prior to procedure.

The amount that patients will be charged for this device is 4,000 for the 15 mm AXIOS or 5,000 for the 20 mm AXIOS stent, which will be authorized through the normal insurance clearance process.

12. Costs

- a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

All procedures are part of routine clinical care and will be billed to the patient's insurance company.

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