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A single-center, feasibility study to evaluate the use and safety of the Percutaneous Ultrasound Gastrostomy technique

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List of Abbreviations

AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EHM	External Handheld Magnet
FDA	United States Food & Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
hCG	Human Chorionic Gonadotropin
HR	Heart Rate
IBC	Internal Balloon Catheter
IR	Interventional Radiology
REB	Research Ethics Board
LAR	Legally Authorized Representative
PEG	Percutaneous Endoscopic Gastrostomy
PUG	Percutaneous Ultrasound Gastrostomy
SAE	Serious Adverse Event

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Protocol Synopsis

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Protocol	Version 1.0
Title	A single-center, feasibility study to evaluate the use and safety of the Percutaneous Ultrasound Gastrostomy technique
Brief title	Percutaneous Ultrasound Gastrostomy technique
Sponsor	CoapTech
Investigation Type	Medical Device / Procedure
Study Type	Interventional

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Purpose and Rationale	The purpose of this study is to evaluate the performance, safety and tolerability of the Percutaneous Ultrasound Gastrostomy (PUG) procedure that utilizes a novel device in conjunction with widely available ultrasound technology. The CoapTech device consists of a gastric catheter with a balloon enclosing a magnetic bar at its distal end and an external, handheld magnet. The gastric catheter is passed through the mouth and into the stomach. The external magnet is then used to maneuver the balloon to the desired location, with feedback and guidance from real-time ultrasound visualization. With the external magnet coupled, or "coapted", to the magnet within the gastric tube balloon, the gastric tube balloon will be in place within the stomach pushing it flush against the internal abdominal wall. This allows for complete ultrasound visualization from skin-to-stomach, facilitating safe percutaneous puncture into the stomach and guidewire-assisted placement of the gastrostomy tube. In this study, subjects will have the procedure performed to assess the performance of the device and aspects of the technique as well as determining safety and tolerability. The phased study approach is as follows: • Phase 1: 5 subjects, performed in specialty suite • Phase 2: up to additional 20 subjects, performed at the bedside (or in specialty suite, if appropriate) • Phase 3: TBD (will require protocol amendment) More than 200,000 gastrostomy tubes are placed each year in the United States, and that number is expected to increase as the proportion of the population that is elderly grows (Roche et al 2003, Goldberg et al 2005, Lynch et al 2004). Percutaneous endoscopic gastrostomy (PEG) has become the most common method for placement of a gastrostomy tube. This requires the use of specialized equipment and the availability of physicians specifically trained in this procedure. The CoapTech device and the Percutaneous Ultrasound Gastrostomy (PUG) technique are designed to reduce the need for specialized equipment as well as to reduce the training required to perform the procedure.

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Primary Objective(s)	To assess the safety and feasibility of gastrostomy tube placement using the PUG technique and the CoapTech device. The primary outcome of interest will be number and severity of device-related adverse events. *Any adverse events during the immediate procedural and post-procedural period with a score of 3 or greater ("serious") will be considered unsafe. Of that set, any adverse safety events during the immediate procedural and post-procedural period with a "relatedness to intervention" score of 3 or greater ("probably related") will be considered device-related. See Table 3.*

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Secondary Objectives	1) While acknowledging that the study is underpowered, to perform a preliminary direct comparison of the following between the PUG placement and a retrospective cohort of matched controls who undergo gastrostomy placement using the percutaneous radiologic gastrostomy (PRG) push gastropexy technique. a) Serious complication rate: a composite rate inclusive of inadvertent puncture of important structures, damage to structures requiring surgical repair and development of infectious complications during the immediate post-procedure period. Important structures are defined a priori as liver, larger blood vessels (that require operative repair or result in significant blood loss in the opinion of the operator), small or large bowel, spleen, etc.. b) Serious adverse events, individually described as: i) Misplacement harm ii) Infection (Sepsis, Peritonitis) iii) Tissue / Organ Damage iv) Requirement for Salvage Surgery and which type(s) v) Other 2) To describe the preliminary rate of other complications during the immediate procedural period between the PUG placement and a historical cohort of matched controls who underwent gastrostomy placement using the PRG technique. a) Tube rupture b) Retained foreign body due to procedure 3) To compare the preliminary cost and operational factors during the immediate procedural period and overall hospital stay between the PUG placement and a retrospective cohort of matched controls who undergo gastrostomy placement using the PRG technique, including:

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	a) Length of stay after gastrostomy insertion b) Total variable direct costs by cost category (e.g. medications, suite time, etc.) 4) To assess preliminary human factors properties through immediate procedural period data including: a) Overall procedure time b) Physician feedback via surveys on usage properties
Study Design	Single-center, non-randomized, non-blinded feasibility and safety pilot study
Population	The study population will consist of male and female patients (≥18 years old) admitted to the hospital and in whom it has been determined by the clinical care team that gastrostomy tube placement is indicated for the administration of nutrition or medications.
Comparator	The comparator group will consist of a matched historical cohort of patients who had gastrostomy tube placement performed using the PRG procedure
Inclusion Criteria	• Informed consent must be obtained before any study-specific assessment is performed • Male or female ≥18 years of age • BMI ≤30, AND BMI ≥20 • Indication for gastrostomy tube placement determined to be present by the primary clinical care team • Patient determined to be an appropriate candidate for gastrostomy by the study team • Women of childbearing potential must have negative serum or urine pregnancy test during the current hospitalization

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Exclusion Criteria	• BMI > 30, OR BMI < 20 • Temperature ≥ 38 C • Systolic BP < 100 or > 180 mmHg • Heart Rate < 50 or > 110 • Presence of a contraindication to being in proximity to a magnet (e.g. pacemaker). • History of prior gastrostomy, gastrectomy (partial or complete), or abdominal trauma or upper-abdominal surgery. • Patients with hematocrit <25%, or a history of blood transfusion within the 14 days prior to screening, or active life-threatening GI bleeding. • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. • Involvement in other investigational trials within 30 days prior to screening. • Any other medical condition(s) that may put the patient at risk or influence study results in the investigator's opinion, or that the investigator deems unsuitable for the study. For example, large or collapsed transverse colon overlapping anterior stomach on pre-existing radiographic scan. • Anticipated discharge <36 hrs from gastrostomy
Investigational and Reference Therapy	Investigational: Placement of gastrostomy tube using the CoapTech device and the PUG technique Reference: A historical cohort of matched patients who underwent PRG placement.

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Efficacy Assessments	Primary efficacy assessment:
	
	Describing the feasibility and safety of gastrostomy tube placement using the PUG technique and the CoapTech device.
	
	Key preliminary and secondary efficacy assessments
	
	• Description of occurrences of procedure termination
	  ○ Termination according to protocol
	  ○ Termination due to other reasons
	• Description of any reasons for delays in performance of procedure
	• Determination of overall rate of any adverse events and relatedness-to-device
	• Description of occurrences of inadvertent puncture of vital organs during performance of procedure
	• Description of occurrences of infectious complications
	• Description of occurrences of salvage surgery performed due to complication of procedure
	• Description of occurrences of requirements for sedation and analgesia during performance of procedure

Patient Assessments	• Physical examination • Vital signs • Height and weight • Calculation of BMI • Abdominal circumference • Laboratory evaluations • Electrocardiogram, if appropriate • Gastrostomy tract depth (measured under ultrasound during procedure)

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Other assessments	• Preliminary healthcare resource utilization (Costs)
	  ○ Direct costs of procedure
	  ○ Environment (e.g. Suite time, etc.)
	  ○ Laboratory costs
	  ○ Medication cost
	  ○ Provider costs
	  ○ Device costs (estimated)
	• Length of total ICU and length of total hospital stay after determination made to have gastrostomy tube placed
	• Indications for gastrostomy placement

Data Analysis	The primary safety variables are the number and severity of enrolled subjects who have a serious, device-related adverse event during placement of a gastrostomy tube using the PUG procedure. The primary feasibility/efficacy variable is the number of enrolled subjects who have successful placement of a gastrostomy tube using the PUG procedure. Key secondary efficacy variables will be assessed by using common descriptive statistics to a historical cohort of matched subjects who have undergone PRG placement. Data assessments are planned at the end of Phase 1 (n=5), after the 7th subject in Phase 2 (n=12), and at the end of Phase 2 (n≤25).

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Introduction

Background

Gastrostomy feeding is an established means of delivering adequate nutrition to patients with an inability to meet their metabolic requirements due to inadequate oral intake. Additionally, the gastrostomy tube can be utilized for medication administration in patients unable to otherwise tolerate oral intake. Traditionally, placement of gastrostomy tubes has been performed endoscopically, radiologically or by either laparoscopic or open surgical techniques. More than 200,000 gastrostomy tubes are placed each year in the United States, and that number is expected to increase as the proportion of the population that is elderly grows (Roche et al 2003, Goldberg et al 2005, Lynch et al 2004).

Previous studies have failed to identify a clearly superior technique for placement of feeding tubes (Bravo 2016, Yuan 2016). Percutaneous endoscopic gastrostomy (PEG) was first described by Gauderer et al. in 1980 in a case series of 12 children as an alternative to laparotomy in high-risk patients (Gauderer 1980). There is a high overall success rate of PEG placement at 95-100% (Itkin 2011). Percutaneous endoscopic gastrostomy (PEG) has become the most common method for placement of a gastrostomy tube. This requires the use of specialized equipment and the availability of physicians specifically trained in this procedure. The number of procedures performed yearly to place feeding tubes is expected to rise as the population ages and as some treatments have resulted in some diseases become chronic states rather than invariably fatal conditions.

Challenges to performance of gastrostomy tube placement include the requirement for specialized equipment, specialized areas designated to have this procedure performed as well as the need for proceduralists who are specifically trained in this technique.

The CoapTech device was developed in an effort to reduce the complicated requirements associated with other techniques of gastrostomy placement so that when clinically indicated the procedure can be performed in a safe and timely manner by a wide range of clinicians with various training backgrounds.

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Purpose

This is a single-center, non-randomized, non-blinded feasibility study to evaluate the performance, safety and tolerability of the Percutaneous Ultrasound Gastrostomy (PUG) procedure that utilizes a novel device in conjunction with widely available ultrasound technology. The procedure will be performed in up to 25 eligible subjects. Patients will be followed for 2 days following performance of PUG to assess for potential complications. If the patient remains hospitalized they will be assessed at date of discharge or Day 30 (whichever is earlier) for potential complications.

Study Objectives

Primary Objective

- To assess the feasibility and safety of gastrostomy tube placement using the PUG technique and the CoapTech device. The primary outcome of interest will be number and severity of device-related adverse events. *Any adverse events during the immediate procedural and post-procedural period with a score of 3 or greater ("serious") will be considered unsafe. Of that set, any adverse safety events during the immediate procedural and post-procedural period with a "relatedness to intervention" score of 3 or greater ("probably related") will be considered device-related. See Table 3 for scoring system details.*

Key Secondary Objectives

- Description of occurrences of procedure termination
    - Termination according to protocol
    - Termination due to other reasons
- Description of any reasons for delays in performance of procedure
- Determination of categorical rates of serious complications during the immediate procedural period of 48 hours
    - Serious adverse events include but are not limited to the following:
        - inadvertent puncture of important structures
        - damage to structures requiring surgical repair and
        - development of infectious complications.
    - Important structures are defined a priori as liver, larger blood vessels (that require operative repair or result in significant blood loss in the opinion of the operator), or local organs including small or large bowel, spleen, colon, etc.
    - Serious adverse events will be described as:
        - Misplacement harm
        - Infection (Sepsis, Peritonitis)
        - Tissue / Organ Damage
        - Requirement for Salvage Surgery and which type(s)
        - Other
- Description of occurrences of inadvertent puncture of vital organs during performance of procedure

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- Description of occurrences of infectious complications
- Description of occurrences of salvage surgery performed due to complication of procedure
- Description of occurrences of requirements for sedation and analgesia during performance of procedure
- Description of reasons for delays in performance of the procedure.

Exploratory Objectives

- To evaluate the costs associated with performance of gastrostomy placement using the PUG technique
    - Direct costs of procedure
    - Environment (e.g. Suite time, etc.)
    - Laboratory costs
    - Medication costs
    - Provider costs
    - Equipment costs (other than device)
- Description of length of total ICU and hospital length-of-stay after determination made to have gastrostomy placed
- To assess satisfaction of the clinical care team with the performance of the procedure and human factors of the device.

Investigational Plan

Study Design

After assessing eligibility during the screening period, patients who meet the study inclusion and exclusion criteria will be eligible to have gastrostomy tube placement using the PUG technique with the CoapTech device. Proceduralists who have been trained in the performance of the technique will be contacted to arrange a time to have the procedure performed.

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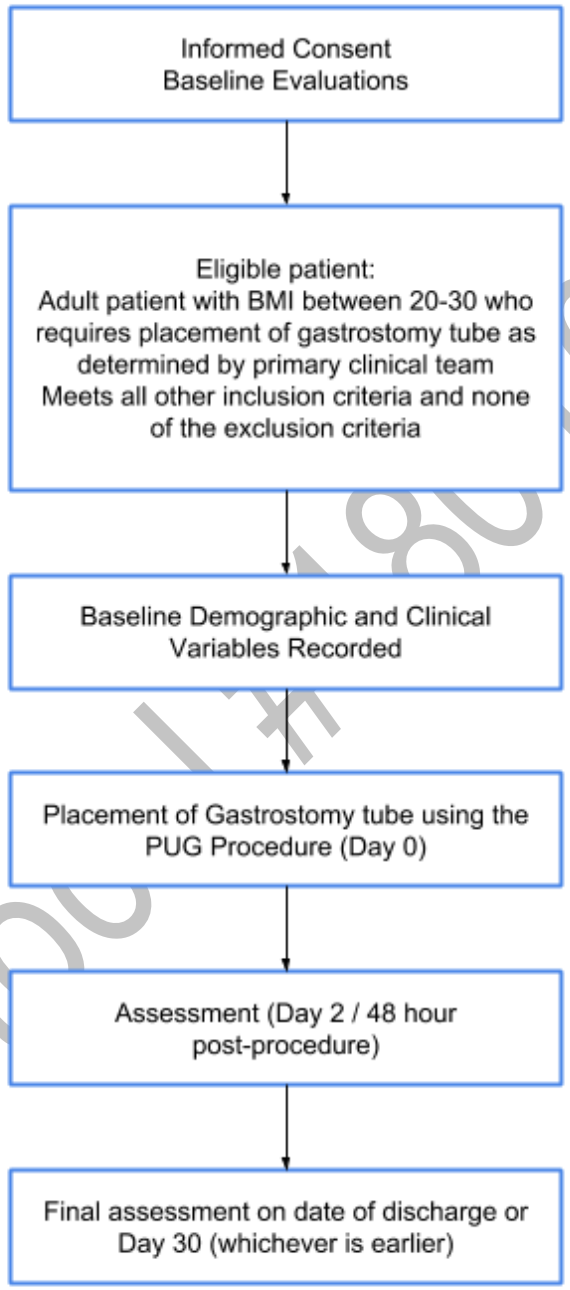
Figure 1. Study Design Timeline



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Rationale of Study Design

A single arm, prospective, feasibility and safety pilot study was chosen for this first in-human clinical trial of the PUG procedure. If the study were designed to show reduced rates of complications for the PUG procedure compared to PRG then an unachievable number of subjects would be required to be enrolled. A table was generated demonstrating the number of patients required to show that there is a reduction in complications from 3 to 1%. In order to reject a null hypothesis that there is no reduction in complications of the PUG procedure, 1000 subjects would be required to be enrolled with 500 subjects in each arm of the trial. A trial of this size would not be a reasonable first use in human study. The current study will utilize a matched retrospective cohort of patients who had gastrostomy tube placement performed using the PRG procedure for comparison.

The 25-patient study is divided into two phases. The five patients were selected for phase 1 (n=5) as it should allow for sufficient experience with the PUG technique in a controlled environment that will allow for immediate assessment with fluoroscopy or conversion to PRG if needed. With adequate experience from Phase 1, Phase 2 will then allow for some of the PUG procedures to be performed outside of the interventional radiology suite to assess the unique capability of the PUG procedure.

Table 1. Enrollment Required for Prospective Comparison of PUG vs PEG

Total Patients Enrolled (N)	Patients randomized to PUG	Patients randomized to PEG	Expected # of Serious Complications in PUG patients if true rate = 1%	Expected # of Serious Complications in PEG patients if true rate = 3%	95% CI for PUG rate	95% CI for PEG rate	P - value for Null hypothesis PUG rate > PEG rate
8000	4000	4000	40	120	(0.7% - 1.4%)	(2.5% - 3.6%)	<0.0001
1000	500	500	5	15	(0.4% - 2.5%)	(1.8% - 5.0%)	0.02
600	300	300	3	9	(0.3% - 3.1%)	(1.5% - 5.8%)	0.07
400	200	200	2	6	(0.1% - 3.9%)	(1.2% - 6.7%)	0.14

Risks and Benefits

The potential risks of the proposed PUG procedure include those that exist in the current standard of care: infection, bleeding and unwanted damage to organs surrounding the stomach. Similarly, as with any gastrostomy approach, there are anesthesia risks. The FDA acknowledged the PUG procedure's safety factors as technically equivalent to PEG, but also identified the new risk of magnetic pressure applied to the stomach tissues during the PUG procedure. Theoretically, excessive pressure on the stomach wall caused by magnetic coaptation forces could cause injury to the stomach and surrounding tissues including abrasions, bruising and ischemia. These risks are considered minimal based on prior data from live canine, bench top, and cadaver tests, which demonstrated no clinically significant tissue damage. In terms of anesthesia risks,

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PUG is expected to be performed under procedural/moderate sedation, but this level may be increased based upon clinical indication. Therefore, the anesthesia risk for PUG is considered to be no different (i.e., greater) than current gastrostomy (PEG or PRG) procedures.

The benefits for the patient of using PUG are potentially significant. Enabling ultrasound visualization categorically increases safety with PUG, as opposed to PEG, which is performed with a “blind stick” (via transillumination and palpation) or percutaneous radiology-guided gastrostomy (PRG) which only uses projectional fluoroscopy for transgastric needle guidance. With real-time ultrasound visualization, the operator will be able to directly visualize critical structures (Liver, colon, inferior epigastric arteries, etc) to ensure they are not inadvertently punctured. Additionally, the PUG balloon catheter is provided as a sterile, single-use disposable. This eliminates reprocessing risks common to endoscopy-based procedures. Finally, unlike PRG & PEG, this technique for gastrostomy tube insertion could be performed bedside and would not require critically ill patients to leave the safety of the ICU department to have the tube inserted, as it currently required.

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Population

The study population will consist of male and female patients (≥18 years old) admitted to the participating study site and in whom the primary clinical team has determined that a gastrostomy tube should be placed. The study will focus on patients with a BMI of 20-30 to avoid complications associated with extremes in body habitus.

Inclusion Criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

- Informed consent must be obtained before any study-specific assessment is performed
- Male or female ≥18 years of age
- 20≤ BMI ≤30
- Indication for gastrostomy tube placement determined to be present by the primary clinical care team
- Patient determined to be an appropriate candidate for gastrostomy by the study team
- Women of childbearing potential must have negative serum or urine pregnancy test during the current hospitalization

Exclusion Criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study.

- BMI > 30, or BMI < 20
- Temperature ≥ 38 C
- Systolic BP < 100 or > 180 mmHg
- Heart Rate < 50 or > 110
- Presence of a contraindication to being in proximity to a magnet (e.g. pacemaker).
- History of prior gastrostomy, gastrectomy (partial or complete), or abdominal trauma or upper-abdominal surgery.
- Patients with hematocrit <25%, or a history of blood transfusion within the 14 days prior to screening, or active life-threatening GI bleeding.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
- Involvement in other investigational trials within 30 days prior to screening.
- Any other medical condition(s) that may put the patient at risk or influence study results in the investigator's opinion, or that the investigator deems unsuitable for

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the study. For example, large or collapsed transverse colon overlapping anterior stomach on pre-existing radiographic scan.
- Anticipated discharge < 36 hours from gastrostomy.

Method of Assigning Subjects to Treatment Groups
All patients enrolled in the study will have the PUG procedure performed. There is no prospectively enrolled comparator group.

Procedural Team

The PUG procedure will be performed by a member of the study team trained to perform the procedure. The proceduralists consist of physicians trained in either critical care or interventional radiology (IR). The proceduralist assigned will be based on scheduling and availability of the entire proceduralist team. Patients consenting to the study who reside on general medical floors will have PUG performed in the IR or specialty suites.

Demographics

Patient demographic information including sex, date of birth, and race will be collected prior to the patient having the PUG procedure performed.

Medical History

Medical history will be recorded in the Case Report Forms (CRFs). Important medical events, illnesses and medications will be recorded on the appropriate CRF pages. Any existing medical condition present prior to performance of the PUG procedure will be reported as medical history.

Height & Weight

Height and weight will be recorded for all patients.

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Description of CoapTech Device

The device consists of several components (a balloon catheter, an external handheld magnet, and a guidewire), which are described individually below (Fig. 2 and Fig. 3).

Internal Balloon Catheter (IBC)

The disposable internal component of the device consists of a balloon catheter (16 Fr, polyurethane) that is placed through the patient's mouth, down through the esophagus, and into the stomach (Fig. 4). At the catheter's distal end, the balloon encloses a bar magnet (dimensions, 0.150" diameter x 1.750" length). The proximal end of the tube is fitted with a luer lock port through which a spring-tempered stainless steel wire stylet is installed along the length of the tubing. The stylet aids in manual placement of the IBC into the stomach by preventing curling of the tube upon itself. The luer lock port is used during the procedure to introduce fluid into the ultra-thin polyurethane balloon that surrounds the magnet at the distal end of the catheter. The balloon surrounding the magnet can be seen on ultrasound only when it is in direct apposition to the wall of the stomach during coaptation. Any air between the ultrasound probe and the fluid-filled balloon prevents identification of the balloon.

External Handheld Magnet

The non-disposable component of the device is the external handheld magnet (EHM), consisting of a large magnet enclosed in a plastic housing shaped for ergonomic handling. To maintain sterility, the EHM is protected by a disposable sterile cover (provided with kit). The EHM is placed on that patient's abdominal wall to attract the magnetic tip of the IBC to the anterior stomach.

Guidewire

The guidewire is composed of a plastic dispenser loaded with a 0.031-inch diameter, 261-cm long flexible (nickel titanium and stainless steel) wire. In its natural state, the tip of the guidewire is coiled into a pigtail shape with an approximate 1.2-cm diameter and two full rotations. The guidewire fits through a standard 18G needle.

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Figure 2. Device components and description

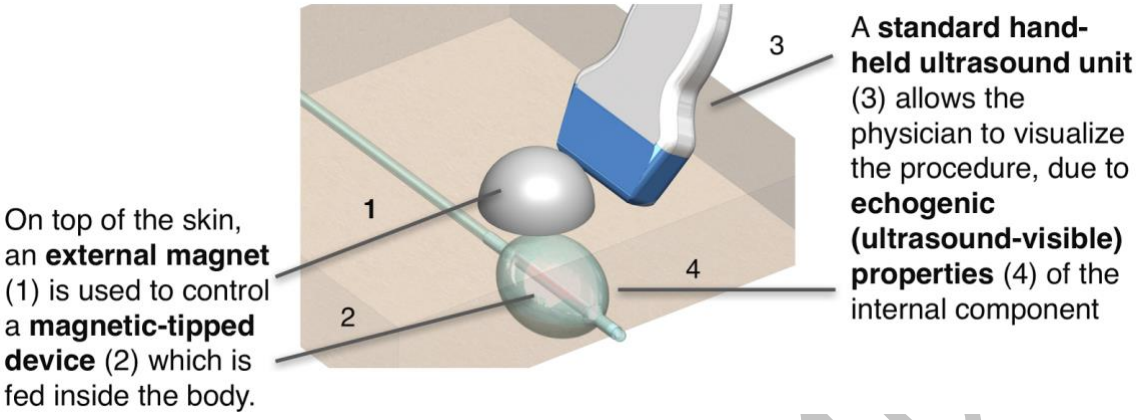

Figure 3. Internal Balloon Catheter (left) and External Handheld Magnet (right)

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Treatment per medical protocol

1. STOP if any contraindications to percutaneous gastrostomy or magnetic fields (such as a pacemaker) are present.
2. Insert a temporary feeding tube using standard gastric tube insertion technique(s) and confirm placement below the ribs with auscultation. If unable to complete, STOP.
3. Remove the balloon catheter from sterile packaging. Lubricate the catheter liberally. Insert the catheter orally using standard gastric tube insertion technique(s). If sensing resistance, STOP. Once completed, remove the inner stylet.
4. Prepare the site according to the surgical guidelines of your institution.
5. Prep the handheld magnet by placing it in a sterile drape or transducer cover.
6. Confirm catheter placement in stomach by moving the handheld magnet along the abdomen **below the ribs** and feeling for coaptation with the balloon catheter (i.e. trans-cavity magnetic attraction and alignment). If coaptation is not obvious, fill the balloon (approximately 25mL) with methylene blue dyed sterile water or saline and attempt to find the balloon catheter by ultrasound. If unable to achieve coaptation or confirm by ultrasound, STOP. **NOTE**: time under coaptation is expected to be less than 10 minutes.
7. Insufflate the stomach with air using the preplaced temporary gastric tube. If unable to appropriately insufflate, STOP.
8. If the balloon has not been inflated under prior steps, infuse approximately 25mL of methylene blue dyed sterile water or saline into the balloon catheter. If needed, first gently aspirate the balloon catheter to remove air from the balloon. **NOTE:** adding more than 35mL of fluid into the balloon catheter may impact visualization.
9. Use ultrasound to visualize the balloon. To enhance visualization, agitate the fluid by pressing repeatedly on the external tubing or pumping the syringe (up to 5mL of fluid in and out). If unable to visualize the balloon on ultrasound, STOP.
10. For gastrostomy tract formation, make minor adjustments to balloon location using the handheld magnet, as needed. Verify with ultrasound that no bowel, viscera or vessels are overlaying the stomach at the planned gastrostomy tract. Note the balloon depth on ultrasound to estimate the gastrostomy tract length. Record the planned tract length. If unable to identify a safe tract site, STOP.
11. Inject local anesthetic at the planned gastrostomy site if needed for patient comfort. Create a gastrostomy tract using an access needle attached to a syringe. Under real-time ultrasound guidance, advance the needle to target the balloon's center while gently aspirating. Confirm placement in balloon by aspirating blue dyed water or saline into the syringe. If unable to aspirate, STOP.
12. Hold the access needle in position while removing the syringe.
13. Insert curled end of guidewire into the access needle. To achieve this, pull the guidewire back into the feeder tip, which will temporarily straighten the guidewire

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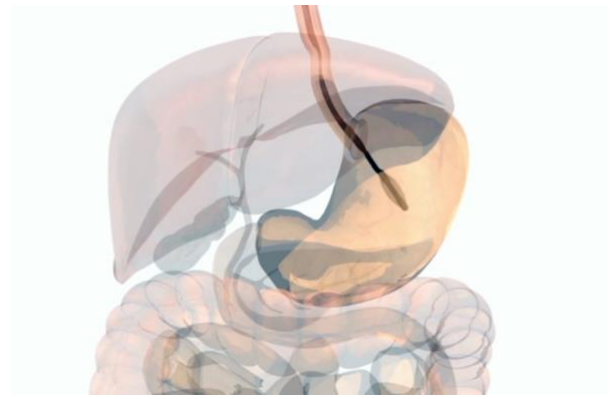
tip. Insert until resistance is relieved, or approximately 5 cm beyond the needle. If excessive resistance is present, STOP.

14. Gently remove the needle, leaving the guidewire in place.
15. Deflate the balloon by aspirating all fluid from the external port.
16. Remove the handheld magnet and place it safely away from the patient and other magnetic material.
17. Gently advance the guidewire while simultaneously retracting the balloon catheter from the mouth. This should be done slowly and at equal rates (as much as possible). Upon completion of this step, the curled guidewire tip will have exited the mouth with the balloon catheter, with the other end of the guidewire exiting via the gastrostomy tract. If coupling of the guidewire and balloon is lost during this process, remove the guidewire from the stomach and STOP.
18. In order to push the gastrostomy tube over the guidewire, cut off the curled end of the guidewire at the shaded section. Discard the curl and balloon catheter. **CAUTION**: cutting outside the shaded region could cause unraveling of the guidewire.
19. Follow standard percutaneous gastrostomy PUSH (Sachs-Vine) technique, with gastrostomy PUSH kit.
20. In situations where coaptive ultrasound has identified a safe gastrostomy tract region, and the PUSH technique is ultimately not feasible or fails, gastrostomy tube placement may be completed using gastropexy. Using a gastropexy kit, place gastropexy anchors followed by standard insertion technique.

Figure 4. Clinical workflow of PUG procedure

Step 1. IBC insertion: Internal balloon catheter (IBC) is inserted orally down the esophagus using standard procedures for orogastric tube insertion. Stomach is insufflated.	

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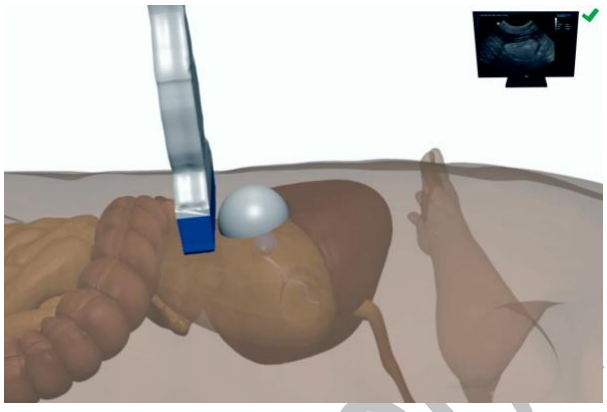
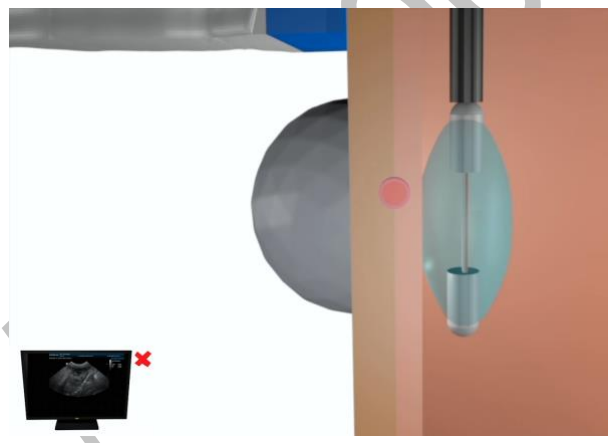
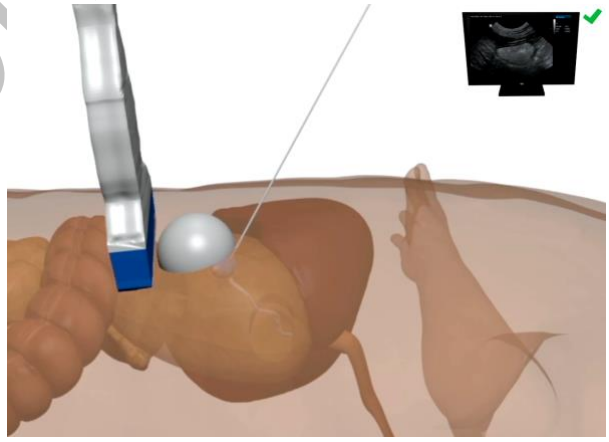
Step 2. Coaptation: External magnet (displayed here as rounded white structure) pulls stomach against the abdominal wall by magnetic force.	
Step 3. Visual confirmation: Balloon is filled with saline and a safe gastrostomy tract location is identified through ultrasound of the stomach and balloon. Moving the external magnet will make minor adjustments to the position of the IBC, to avoid certain anatomy.	
Step 4. Puncture and coupling: Needle and guidewire are inserted through stomach with ultrasound visualization and coupled with IBC through pigtail mechanism.	
Step 5+. The final steps of the PUG procedure are consistent with those of the Sacks-Vine technique used in the PEG procedure.	

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Assessments

Efficacy Assessment

The primary safety variables are the number and severity of enrolled subjects who have a serious, device-related adverse event during placement of a gastrostomy tube using the PUG procedure.

The primary feasibility/efficacy variable is the number of enrolled subjects who have successful placement of a gastrostomy tube using the PUG procedure.

Other Assessment – Procedure Failures

In cases where the PUG procedure fails to have successful placement of a gastrostomy tube, reasons for the failure will be determined. These reasons will be divided into those pertaining to the procedure/device itself and those reasons external to the procedure/device.

Other Assessment – Resource Utilization

The costs associated with performance of gastrostomy placement using the PUG technique will be assessed. This includes:

- Direct costs of procedure
- Environment (e.g. Suite time, etc.)
- Laboratory costs
- Medication costs
- Provider costs
- Equipment costs (other than device)

Other Assessment – Clinical Team Survey

A brief survey will be administered to the primary clinical team to assess satisfaction with the procedure and provide human factors feedback.

Subject Evaluation

Physical Exam
A physical examination will be performed by the study team at baseline, immediately following recovery from the PUG procedure and at Day 2 following PUG procedure. If

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the patient remains in the hospital longer than 2 days then another physical examination will be performed at the time of discharge or on Day 30, whichever comes first.

Physical examinations will include a review of the patient's general appearance, as well as evaluation of the following body systems (see Table 2). Any abnormalities observed at baseline should be recorded on the Medical History Form of the Case Report Form (CRF). Any post-baseline new or worsening abnormalities should be recorded as an Adverse Event (AE).

Table 2 Assessments for Physical Examination

Assessment	Assessment
General appearance	Chest and lungs
Head and neck	Heart
Eyes	Abdomen
Ears	Extremities
Nose	Nervous System
Throat	Skin

Vital Signs
Pulse rate and systolic and diastolic blood pressure will be measured and recorded on the CRF at baseline, immediately prior to the PUG procedure, during the PUG procedure according to institutional norms, immediately following recovery from the PUG procedure, at Day 2 assessment and at the final assessment if the patient remains hospitalized (up to Day 30).

Clinical Laboratory Tests
Serum chemistry and hematology blood tests are performed as per usual care protocol. Results of these tests will be noted in the CRFs.

Electrocardiogram
For enrolled patients coming from an inpatient ICU, as part of usual care, a standard 12-lead ECG will be performed prior to performance of the PUG procedure. Interpretation of the tracing will be made by a member of the study team who is a qualified physician skilled in ECG interpretation. The interpretation of the 12-lead ECG will be documented by the study team member in the CRF. A copy of the ECG tracing should be labeled with the study and patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on the CRF as appropriate. In the event that there are significant abnormalities present on the ECG and the study

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team member performing the interpretation is not the same as the proceduralist then the study team member will notify the proceduralist prior to commencing the study procedure.

Pregnancy Testing
Female patients must have a negative urine or serum pregnancy test in order to be enrolled in the study. Those females who have had a total hysterectomy or bilateral oophorectomy, or who are 2 years post-menopausal do not require a pregnancy test. Results of any pregnancy testing will be noted in the CRF.

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Concomitant Medications, Therapies, and Interventions
All therapies/interventions administered to and medical/surgical procedures performed on the study patients from the time of informed consent through the follow-up contact will be documented on the CRF.

All prescription and over-the-counter medications being taken by patients during the study are regarded as concomitant medications and must be documented on the CRF following informed consent. For any medication that is administered, the investigator will document the drug name, amount, route of administration, frequency, and duration administered, as well as the reason for administering the medication.

Medical/surgical procedures performed during the study will also be recorded on the CRF, along with the date and time, and reason for the intervention. This includes airway interventions (intubation, tracheotomy, and cricothyrotomy).

Adverse Event Assessments

Adverse Event (AE)

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered related to the study procedure. This includes an exacerbation of a pre-existing condition.

Adverse events include the following:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values that the investigator considers clinically significant (includes significant shifts from baseline within the range of normal that the investigator considers to be clinically important)
- Abnormalities in physical examination

Throughout the study, the investigator must record all AEs on the AE CRF, regardless of the severity or relationship to study procedure. The investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical

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laboratory values. In addition, AEs should also include those laboratory values that become out-of-range and are judged to be clinically significant.

Serious Adverse Event (SAE)

A *Serious Adverse Event* is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- is fatal; [results in **death****; NOTE: death is an outcome, not an event]
- is Life-Threatening [NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe]
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A life-threatening AE is defined as an AE that placed the patient, in the view of the initial reporter, at immediate risk of death from the AE as it occurred (ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).

Table 3. Adverse Events Scoring System

Pt Identifier	AE Onset	AE End	AE Code (MedRA, CTCAE)	Severity	SAE ? (Y/N)	Related-ness	Action Taken	Outcome	Comments

Severity of AE:
1 = Mild
2 = Moderate
3 = Severe
4 = Life threatening or disabling

Relatedness to Intervention:
0 = Definitely unrelated
1 = Unlikely
2 = Possibly related
3 = Probably related
4 = Definitely related

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Action Taken:
0 = None
1 = Dose modification
2 = Medical intervention (specify in comments)
3 = Hospitalization
4 = Intervention discontinued
5 = Other

Outcome:
1 = Resolved
2 = Recovered with minor sequelae
3 = Recovered with major sequelae
4 = Continuing treatment
5 = Condition worsening
6 = Patient death**

Pregnancy Reporting

Pregnancy is an exclusion to enrollment in the current study. If it is determined after enrollment that the study subject is pregnant then all study procedures will be terminated and the Research Ethics Board (REB) will be notified of the protocol deviation. The subject should be followed through the pregnancy for assessment of possible relationship of harm to the study treatment.

Any SAE experienced during pregnancy must be reported to the REB.

Ethical Considerations

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

Research Ethics Board

Before implementing this study, the protocol and the informed consent form must be reviewed by a properly constituted REB. A signed and dated statement that the protocol and informed consent have been approved by the REB must be on file at the site before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by the REB.
If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform CoapTech immediately that this request has been made.

Informed Consent

The Investigator must explain to each participant (or legally authorized representative, LAR) the nature of the study, the purpose, the procedures involved, the expected duration, the potential benefits and risks involved, and any discomfort it may entail. The study procedure should be identified as investigational (experimental) and that its rate of adverse events are not completely known. This information must be provided in

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language that the participant understands. Each participant must be informed that participation in the study is voluntary and that they may withdraw from the study at any time, and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician. The participant or LAR should read and consider the statement before signing and dating it and should be given a copy of the signed document. No participant can enter the study before Informed consent has been obtained.

The study seeks a waiver of consent for recruitment of patients to the comparison matched historical cohort of patients who received the standard of care, PRG, procedure. The involvement in this arm of the research study presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context. The same data will be collected in a retrospective fashion using electronic medical record and medical center data sources. Per the study protocol outlined elsewhere, no identifiable patient information will be collected to ensure confidentiality.

Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs or devices.

Protocol Amendments

Alterations to the protocol can only be made in a written protocol amendment that must be approved by the PI, CoapTech, and the REB. Only amendments that are required for imminent threat to patient safety may be implemented prior to REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, CoapTech should be notified of this action and the REB at the study site should be informed within 10 working days or less, if required by local regulations.

Data Handling and Record Keeping

Source data/documentation is defined as the first place that data is recorded. Any and all source documents must be maintained and be retrievable at the site. The Investigator must maintain source documents for each participant in the study.

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All data collected during the course of the study will be obtained from primary sources that have been recorded in written and electronic documents such as the participant's medical file. The results of physical exams, vital signs, laboratory findings, and ECG tracings will be recorded in the participant's medical and/or research files. Data collected on digital CRFs during the trial will be documented in an anonymous fashion, and study subjects will only be identified by subject numbers in places other than the initial demographic form. Study site will utilize digital CRFs stored on the secure and cloud based platform RedCap.

The source documents should contain all demographic and medical information including laboratory data, ECGs, etc., and the signed informed consent form, which should indicate the study number and title of the trial.

The Investigator(s) agree(s) to adhere to the document retention procedures by a signed contract. Essential documents include, but are not limited to REB-approved study protocol and subsequent amendments (if applicable), information given to study participants (REB approved informed consent form template, recruitment materials and any other written communications), CRFs, curriculum vitae for any person authorized by the Investigator to assist with trial activities, delegation of authority/site signature log, monitoring visit logs, laboratory reports (or equivalent), laboratory reference ranges, laboratory certifications, and any other pertinent documents.

Administrative Considerations

Investigators and Study Administrative Structure

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study related duties and functions. The investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

Research Ethics Board Approval

Before initiation of the study, the investigator must provide the sponsor with a copy of the written REB approval of the protocol and the informed consent form. This approval must refer to the informed consent form and to the study title, study number, and version and date of issue of the study protocol, as given by the sponsor on the cover page of the protocol.

Status reports must be submitted to the REB at least once per year. The REB must be notified of completion of the study; a final status report must be provided to the REB within 3 months of study completion or termination (or as required). A copy of these reports will be sent to the study clinical monitor. The investigator must maintain an

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accurate and complete record of all submissions made to the REB, including a list of all reports and documents submitted.

Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

Patient Information and Consent: Prospective Clinical Study

Before enrolling in the prospective clinical study, the patient or legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her.

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the patient or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements. The informed consent form must be in a language understandable to the patient or the patient's legally authorized representative(s) and must specify who informed the patient or the patient's legally authorized representative(s).

After reading the informed consent document, the patient or the patient's legally authorized representative(s) must give consent in writing. Consent must be confirmed at the time of consent by the personally dated signature of the patient, the patient's legally authorized representative(s) and by the personally dated signature of the person conducting the informed consent discussions.

If the patient or the patient's legally authorized representative(s) is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient or by a local legally recognized alternative (eg, the patient's thumbprint or mark) or by the personally dated signature of the patient's legally authorized representative. The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

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A copy of the signed and dated consent document(s) must be given to the patient or the patient's legal representative(s). The original signed and dated consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

Patient Information and Consent: Retrospective Matched Cohort

The study seeks a waiver of consent for recruitment of patients to the comparison matched historical cohort of patients who received the standard of care, PRG, procedure. The involvement in this arm of the research study presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context. The same data will be collected in a retrospective fashion using electronic medical record and medical center data sources. Per the study protocol outlined elsewhere, no identifiable patient information will be collected to ensure confidentiality.

Patient Confidentiality

Patient names will not be supplied to the sponsor. Only the patient number and patient initials will be recorded in the CRF, and if the patient name appears on any other document, it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be told that representatives of the sponsor, a designated contract research organization, the REB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

Case Report Forms and Study Records

Case report forms (digital/electronic) are provided for each patient. All forms must be filled out by authorized study personnel. All corrections to the original CRF entry must indicate the reason for change. The investigator is required to sign the CRF after all data have been captured for each patient. If corrections are made after review and signature by the investigator, he or she must be made aware of the changes, and his or her awareness documented by re-signing the CRF.

Data Monitoring Committee

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An independent DSMB will be established to provide an independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study. The DSMB will consist of, at the minimum, a physician knowledgeable in gastrostomy tube placement with additional expertise in clinical research methodology and safety.

The DSMB will adhere to a prospectively determined Charter, which will be written by the principal investigator and approved by the study sponsor and the DSMB. The Charter will define the responsibilities of the DSMB, the number and timing of the DSMB meetings, the conduct of the meetings, and the data sets to be reviewed by the DSMB.

At a minimum, the DSMB will review the study data when 50% enrollment has been achieved. All AEs and SAEs will be made available to the DSMB. The DSMB may also be asked to review on an ongoing basis other SAEs of concern.

The DSMB will provide the principal investigator and the study sponsor with summary reports after each meeting.

Protocol Violations/Deviations

The investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the REB and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the sponsor. Changes to the protocol will require written REB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The REB may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the REB. The sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

No protocol exemption will be granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact the sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the sponsor and may also be required to be submitted to the REB.

Premature Closure of the Study

If the sponsor, investigator, DSMB, or regulatory authorities discover conditions arising during the study, which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation

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between the sponsor and the investigator(s). In addition, a decision on the part of the sponsor to suspend or discontinue development of the investigational product may be made at any time.

Access to Source Documentation

Regulatory authorities, the REB, or the sponsor may request access to all source documents, CRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the CRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

Data Generation and Analysis

The clinical database will be developed and maintained by the principal investigator. The principal investigator will be responsible for performing study data management activities.

Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. The sponsor will notify the investigator if these documents must be retained for a longer period of time. It is the responsibility of the sponsor to inform the investigator or institution as to when these documents no longer need to be retained.

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Financial Disclosure

The investigator should disclose any financial interests in the sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the investigator by the sponsor, which will be signed and dated by the investigator, prior to the start of the study. Changes in status concerning financial interests during the study and after its completion will be disclosed by the Investigator in accordance 21 CFR Part 54.

Publication and Disclosure Policy

All information concerning the study material, such as patent applications, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor and not previously published are considered confidential and will remain the sole property of the sponsor. The investigator agrees to use this information only in accomplishing this study and will not use it for other purposes.

It is understood by the investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study in a timely manner.

The investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with the sponsor, provided the sponsor a copy of the draft document intended for publication, and obtained the written consent of the sponsor for such publication. All information obtained during the conduct of this study will be regarded as confidential.

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Version History

Version	Date	Description
1.0	21 Jun 2018	Initial Release
1.1	10 Aug 2018	Added Version and Date of Last Modification
1.2	04 Sept 2018	Added Clarification Text re: REB Recommendation

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