A randomized controlled trial of metoclopramide versus placebo during gastrojejunostomy tube placement for facilitating guidewire advancement through the pylorus

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List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
FDA	Food and Drug Administration
GJ	Gastrojejunostomy
HIPAA	Heath Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IDS	Investigational Drug Services
IR	Interventional Radiology
IRB	Institutional Review Board
ITT	Intention To Treat
PHI	Protected Health Information
PI	Principle Investigator
QI	Quality Improvement
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UP	Unanticipated Problem

Statement of Compliance

The trial will be conducted in accordance with the ICH, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Putman Seed Fund Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

Print/Type Name

Signed:

Date:

Protocol Summary

Title: A randomized controlled trial of metoclopramide versus placebo during gastrojejunostomy tube placement for facilitating guidewire advancement through the pylorus.

Precis: A total of 110 patients undergoing gastrojejunostomy (GJ) tube placement as part of routine clinical care will be randomized in 1:1 fashion to receive a one-time dose of metoclopramide (10mg in 10 mL Saline IV) or placebo (10 mL Saline IV) to determine whether this promotility agent aids in advancing a guidewire through the pylorus. Patients and physicians performing the GJ tube placement procedure will be blind to treatment assignment. Fluoroscopy dose during the procedure will be compared between the metoclopramide and placebo groups.

Objectives: The primary objective is to determine whether promotility agents (e.g. metoclopramide) can facilitate passage of a guidewire through the pylorus during GJ placement procedures. Secondary objectives include determination of whether promotility agents can reduce total procedure fluoroscopy time and radiation dose by reducing the time needed to pass a guidewire through the pylorus. Additional secondary objectives include determination of whether promotility agents impair gastric insufflation during GJ placement.

Endpoints: Fluoroscopy time required to advance a guidewire through the pylorus (primary endpoint). Time to insufflate the stomach, total procedure fluoroscopy time, total procedure air kerma, total procedure time, drug related adverse events (AEs), and failure to successfully place a GJ tube (secondary endpoints).

Population: 110 male and female Duke University Hospital inpatients over the age of 18 undergoing GJ tube placement as part of routine clinical care

Phase: 2

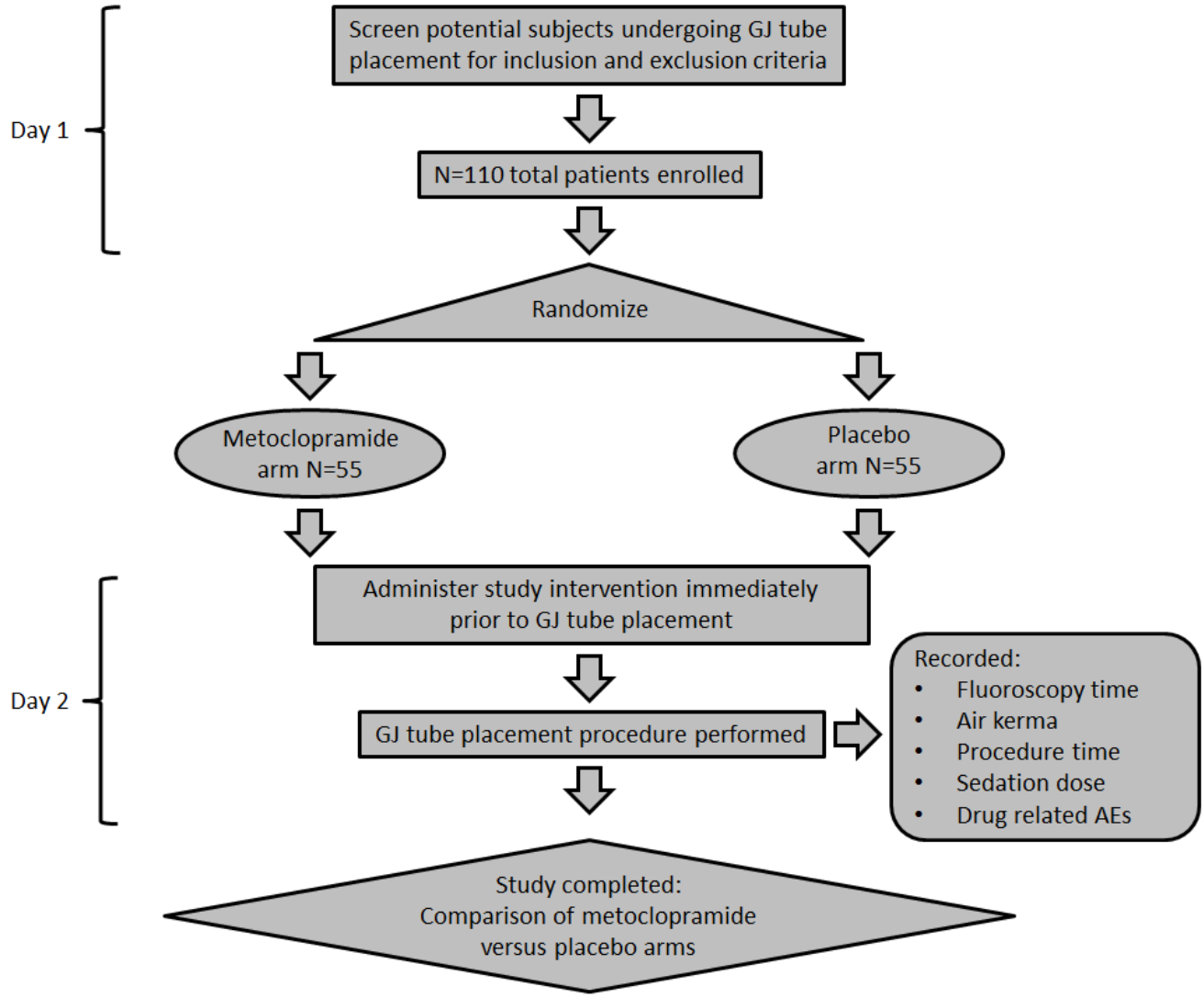
Number of Sites Enrolling Participants: 1

Description of Study Agent: One-time dose of metoclopramine 10 mg IV or placebo (saline IV)

Study Duration: Approximately 30 months

Participant Duration: Approximately 1 day

Schematic of Study Design



1 Key Roles

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2 Introduction: Background Information and Scientific Rationale

2.1 Background Information

Metoclopramide is an antiemetic and promotility agent which acts via muscarinic and dopaminergic receptors[1]. Promotility agents such as metoclopramide are widely used to increase intestinal peristalsis in patients with digestive disorders such as gastroesophageal reflux or diabetic gastroparesis[2]. In addition to their usage in these chronic conditions, single doses of these agents have been shown to be efficacious in causing acute emptying of the stomach through the pylorus into the duodenum. Specifically, previous meta-analyses of randomized controlled trials have found that a single dose of erythromycin or metoclopramide is effective at emptying the stomach of blood and improving visualization during endoscopy for upper gastrointestinal tract bleeding[3,4]. Similarly, a previous randomized controlled trial demonstrated that a single dose of 10 to 20 mg metoclopramide IV or domperidone increases the rate at which nasoenteric tubes spontaneously pass through the pylorus from 27 to 55%[5]. Single dose metoclopramide is also indicated for reducing transit time during small bowel follow through examinations[6].

Gastrojejunostomy (GJ) tube placement is a commonly performed procedure for providing nutritional support in patients unable to tolerate gastric feeds due to gastric outlet or duodenal obstruction or severe gastroesophageal reflux[7]. When performed percutaneously, this procedure involves advancing a guidewire from the gastrostomy skin entry site through the pylorus, a time consuming and tedious task. A variety of wire, catheter, and device related techniques have been described to facilitate wire intubation of the pylorus[8], but this remains a rate limiting step which typically accounts for over half the total fluoroscopy time and a third of the total procedure time.

Adjuvant pharmacological agents such as metoclopramide which promote gastric peristalsis, pyloric relaxation, and duodenal peristalsis may aid in advancing a guidewire from the stomach to the proximal jejunum, thus reducing radiation dose and procedure time during GJ placement procedures.

2.2 Rationale

As described above, advancing a guidewire into the duodenum is a rate limiting step during GJ tube placement procedures which is frequently hindered due to spasm of the pylorus. The hypothesis of this study is that a single dose of metoclopramide (10 mg IV) at the time of GJ tube placement will reduce the fluoroscopy time required to advance a wire through the pylorus (primary outcome). It is further hypothesized that if this rate limiting step is facilitated, the total procedure fluoroscopy time, radiation dose in terms of air kerma, and total procedure time may also be decreased (secondary outcomes).

The proposed intervention, a one-time dose of metoclopramide 10 mg IV, matches the FDA indication for this medication for diabetic gastroparesis, prevention of postoperative nausea and vomiting, radiological small bowel follow through examinations, and for postpyloric nasoenteric feeding tube placement.

Although there is strong a priori rationale to suspect that metoclopramide may be superior to placebo in facilitating guidewire passage through the pylorus, it remains unclear whether this agent will be effective in the setting of GJ tube placement. Although the most time consuming step in GJ tube placement is advancement of a guidewire through the pylorus, standard technique involves insufflation of the with air prior to gastric puncture[9]. Occasionally, an anti-peristaltic agent such as glucagon is utilized to trap air in the stomach to facilitate gastric insufflation[9]. Gastric insufflation may be hindered by administration of a promotility agent such as metoclopramide. Thus, a placebo control arm is necessary to rigorously test the stated hypothesis.

2.3 Potential Risks and Benefits

2.3.1 Known Potential Risks

Adverse reactions to metoclopramide include[10]:

- Cardiovascular: Atrioventricular block, bradycardia, congestive heart failure, flushing (following high IV doses), hypertension, hypotension, supraventricular tachycardia
- Central nervous system: Drowsiness (~10% to 70%; dose related), dystonic reaction (<1% to 25%; dose and age related), lassitude (~10%), restlessness (~10%), fatigue (2% to 10%), headache (4% to 5%), dizziness (1% to 4%), somnolence (2% to 3%), akathisia, confusion, depression, drug-induced Parkinson's disease, hallucination (rare), insomnia, neuroleptic malignant syndrome (rare), seizure, suicidal ideation, tardive dyskinesia
- Dermatologic: Skin rash, 13rticarial
- Endocrine & metabolic: Amenorrhea, fluid retention, galactorrhea, gynecomastia, hyperprolactinemia, porphyria
- Gastrointestinal: Nausea (4% to 6%), vomiting (1% to 2%), diarrhea
- Genitourinary: Impotence, urinary frequency, urinary incontinence
- Hematologic & oncologic: Agranulocytosis, leukopenia, methemoglobinemia, neutropenia, sulfhemoglobinemia
- Hepatic: Hepatotoxicity (rare)
- Hypersensitivity: Angioedema (rare), hypersensitivity reaction
- Neuromuscular & skeletal: Laryngospasm (rare)
- Ophthalmic: Visual disturbance
- Respiratory: Bronchospasm, laryngeal edema (rare)

Most adverse reactions, including the risk of tardive dyskinesia, are associated with increased duration of treatment and cumulative dose. In a recent randomized placebo controlled trial utilizing a one-time dose of 10-20 mg metoclopramide IV, among 100 patients receiving this agent there were 4 drug associated events (lethargy n=2, dysphoria n=1, tremor n=1) which were not significantly different in frequency compared to the placebo group[5]. Given the study design involving a one-time dose of 10 mg metoclopramide IV, long term risks are considered unlikely.

2.3.1 Known Potential Benefits

Known potential benefits of metoclopramide use include prevention of postoperative nausea and vomiting, and FDA approved indication for this medication. Further benefits include potentiation of opioid mediated analgesia[11].

3 Objectives and Purpose

Primary objective: To determine whether a one-time dose of metoclopramide 10 mg IV reduces the fluoroscopy time necessary to advance a guidewire through the pylorus compared to placebo control during GJ tube placement.

Secondary objectives: To determine whether a one-time dose of metoclopramide 10 mg IV, by facilitating wire advancement through the pylorus, reduces total procedure fluoroscopy time, total procedure radiation dose (air kerma), and total procedure time.

4 Study Design and Endpoints

4.1 Description of the Study Design

The proposed study is a single center randomized, double blind, placebo controlled phase 2 trial. Two study groups will be present: the experimental arm receiving a single dose of metoclopramide 10 mg IV and the control arm receiving a single dose of placebo (saline IV, identical volume and labeling).

4.2 Study Endpoints

4.2.1 Primary Endpoint

The primary endpoint of the study will be the fluoroscopy time required to advance a guidewire through the pylorus, defined by the fluoroscopy time at which the guidewire first enters the duodenum minus the fluoroscopy time at which initial gastric needle puncture was performed. This metric is selected as the primary endpoint because it represents the most time consuming step in GJ placement procedures. Furthermore, this metric is most closely linked to the hypothesized mechanism of benefit of promotility agents, and will therefore aid in producing a clearly interpretable study result.

4.2.2 Secondary Endpoints

Secondary endpoints of the study will include time to insufflate the stomach, the total procedure fluoroscopy time, the total procedure radiation dose in terms of air kerma, the total procedure time, and drug related AEs. As described above, promotility agents may hinder gastric insufflation; therefore this secondary endpoint will be measured. Although potentially of greater clinical importance, total procedure fluoroscopy time, air kerma, and total procedure time demonstrate greater variability than the time needed for guidewire advancement through the pylorus, and are therefore less suitable as the primary endpoint. The most important sources of this additional of variability include operator experience and patient body habitus. Powering the study to overcome these extraneous sources of variability would require much larger sample

sizes. Nonetheless, these secondary endpoints will provide an important framework for interpreting the overall clinical benefit, or lack thereof, for routine use of promotility agents during GJ tube placement. AEs during GJ placement and in the immediate post procedural time period will be recorded. Any failed attempts at GJ placement will be recorded.

4.2.3 Exploratory Endpoints

No exploratory endpoints are planned.

5 Study Enrollment and Withdrawal

5.1 Participant Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Provision of signed and dated informed consent form by participant or legal representative
- Stated willingness to comply with all study procedures and availability for the duration of the study
- Male or female, age greater or equal to 18
- Inpatient at Duke University Hospital
- Undergoing GJ tube placement as part of routine clinical care

Women and members of minority groups and their subpopulations will be offered the opportunity to participate in the study in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects.

5.2 Participant Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Allergic reaction to metoclopramide
- Pheochromocytoma
- QTc prolongation
- Seizure disorder
- Extrapyramidal symptoms
- Pregnancy

5.3 Strategies for Recruitment and Retention

Target sample size will be 110 inpatients at Duke University Hospital. Potential patients will be identified by the Interventional Radiology (IR) clinical team at the time of referral for GJ placement. The study will be briefly described to the patient by the treating IR physician, and potentially interested patients will be given written information about the study. Patients who remain potentially interested will be contacted by a member of the study team for the consent

discussion. We anticipate accrual of approximately 50 patients per year in this single site study. All patients undergoing GJ tube placement as part of their routine clinical care will be offered participating assuming that inclusion criteria are met and no exclusion criteria are present. Therefore, we expect the study population to reflect the demographics of the Duke University Hospital inpatient population, which includes both women and minorities. Patients undergoing GJ tube placement include some individuals with cognitive impairment. Because of the potential benefits of study participation, these vulnerable patients will not be denied the opportunity to participate. For these cognitively impaired individuals, written informed consent for study participation will be obtained from the same legally authorized representative consenting for GJ tube placement. No compensation will be provided for study participation. As the study is short in duration, no strategies for participant retention are required.

5.4 Participant Withdrawal or Termination

5.4.1 Reasons for Withdrawal or Termination

An investigator may terminate participation in the study if:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 Handling of Participant Withdrawals or Termination

Given the short duration of the study, participant withdrawals or termination are expected to be uncommon. Patients who withdraw from the study between the time of consent and the time of metoclopramide or placebo administration will not have undergone any study related intervention. Therefore, replacement of these participants will be permitted. Any patients who receive metoclopramide or placebo at the time of the procedure and withdraw prior to completion of the procedure or in whom the GJ tube placement procedure is aborted will be analyzed according to the principle of intention-to-treat.

5.5 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IRB.

6 Study Agent

6.1 Study Agent and Control Description

6.1.1 Acquisition

Metoclopramide 10 mg IV and placebo (saline) will be obtained from Duke University Hospital Pharmacy.

6.1.2 Formulation, Appearance, Packaging, and Labeling

Both metoclopramide and placebo will be obtained in identical appearing 10 mL syringes.

6.1.3 Product Storage and Stability

Metoclopramide injection is stored at 20 to 25^0 C and is stable for at least 21 days[12].

6.1.4 Preparation

Metoclopramide and placebo will be purchased from Duke University Hospital Pharmacy.

6.1.5 Dosing and Administration

A single 10 mg dose of metoclopramide or placebo will be administered at the time of the GJ tube placement procedure by a dedicated nurse whose sole role during the procedure is administration of medications and patient monitoring.

6.1.6 Route of Administration

Metoclopramide or placebo will be administered IV.

6.1.7 Starting Dose and Dose Escalation Schedule

No additional doses of metoclopramide or placebo will be administered and no dose escalation will occur.

6.1.8 Dose Adjustments/Modifications/Delays

No dose adjustments or modifications will occur.

6.1.9 Duration of Therapy

Duration of therapy will involve a single dose of metoclopramide or placebo.

6.1.10 Tracking of Dose

As no adjustments will occur after the one-time dose of metoclopramide or placebo, no procedures for monitoring dosing and adherence are necessary.

6.1.11 Device Specific Considerations

Not applicable.

6.2 Study Agent Accountability Procedures

Study participants will be randomized to the study or control arm via a random number generator when they are enrolled.

The dedicated IR nurse, whose sole role during the procedure is administration of medications and patient monitoring, will be informed prior to the procedure which arm the patient is enrolled in. They will administer a prepared 10 mL intervention syringe at the time of the GJ tube placement along with other pre-procedural sedation medication, and record the intervention administered (whether metoclopramide or saline) in the patient's electronic medical record.

The patient and physician performing the procedure will be blinded to the intervention.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

The following will study specific procedures will occur:

- After potentially interested study participants are identified by the treating IR physician, a member of the study team will review the electronic medical record to determine eligibility for the study based on inclusion and exclusion criteria.
- At the time of the GJ tube placement procedure, immediately prior to the start of the procedure, a one-time dose of metoclopramide 10 mg IV or placebo will be administered along with sedation medications.

7.1.2 Standard of Care Study Procedures

The following occur as standard of care for all patients undergoing GJ tube placement:

- After receiving a referral for GJ tube placement by the clinical team, the treating IR physician performs a history and physical examination to evaluate the patient's candidacy for the procedure
- Patients deemed a candidate for GJ tube placement undergo placement of a nasoenteric tube the night before the procedure. Barium (300 mL E-Z-Paque) is administered PO the night before the procedure or PR the morning of the procedure to opacify the transverse colon.
- At the time of the GJ tube placement procedure, fentanyl and midazolam are administered IV and titrated to achieve moderate sedation.
- The GJ tube placement begins with insufflation of the stomach with air through the nasoenteric tube. The stomach is then pexied to the anterior abdominal wall using T-fasteners. The stomach is then punctured with a needle. A guidewire is inserted through

the needle and advanced through the pylorus and into proximal jejunum. The gastrostomy is serially dilated over the guidewire, and an 18 to 22 French gastrojejunostomy tube is inserted over the guidewire.

- After the completion of the procedure, the patient is discharged from the IR procedure room once sedation medications wear off to a Richmond Agitation Scale of -1 (awake but drowsy). The patient is transferred to an IR recovery bed or a monitored hospital bed and evaluated by nursing staff every 15 minutes for 1 hours then every 30 minutes for 2 hours then hourly until achieving baseline mental status.
- The gastrostomy lumen of the GJ tube is set to intermittent low wall suction for 24 hours and the patient is NPO for 24 hours to prevent gastric ileus and leakage of gastric contents around the tube. After 24 hours, if the patient has a benign abdominal assessment by history and physical examination, the GJ tube may be used. The patient is then discharged from routine IR care, and is reevaluated by the treating IR service on an as needed basis only if clinical problems arise.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

No screening or study related laboratory evaluations will be performed.

7.2.2 Other Assays or Procedures

Not applicable.

7.2.3 Specimen Preparation, Handling, and Storage

Not applicable.

7.2.3 Specimen Shipment

Not applicable.

7.3 Study Schedule

7.3.1 Screening

Patients referred to IR for GJ tube placement are evaluated with a history and physical examination by the treating IR physician at least 1 day prior to the procedure. The study will be briefly described to the patient by the treating IR physician. Patients potentially interested in study participation will then be provided with written material describing the study, and will be referred to a member of the study team. The study team member will then screen the patient for eligibility based on a review of the electronic medical record. In accordance with IRB and HIPAA regulations, no PHI will be recorded during this screening evaluation.

7.3.2 Enrollment/Baseline

On the evening prior to or morning of the GJ tube placement procedure, patients who remain potentially interested in participating in the study will meet with a member of the study team and informed written consent will be obtained from subjects who elect to participate.

7.3.3 Follow-Up

Administration of a one-time dose of metoclopramide 10 mg IV or placebo will occur at the time of GJ tube placement, immediately prior to initiation of the procedure. Study follow-up will include the GJ tube placement procedure itself and span 24 hours following placement. Events recorded during the GJ tube placement procedure will include: fluoroscopy time required to advance a guidewire through the pylorus; total procedure fluoroscopy time; total procedure air kerma; total procedure time; sedation medication doses; drug related AEs; successful completion of GJ tube placement or failure of the procedure. Events recorded over the following 24 hours will include AEs identified during routine standard of care monitoring following the procedure.

7.3.4 Final Study Visit

Completion of study related follow up will occur 24 hours after GJ tube placement.

7.3.5 Early Termination Visit

Not applicable.

7.3.6 Unscheduled Visit

Not applicable.

7.3.7 Schedule of Events Table

Procedures	Screening (Day 0)	GJ Tube Placement Procedure (Day 1)	Final Follow-Up (Day 2)
Informed Consent	X		
Demographics	X		
Randomization	X		
Administer Metoclopramide or Placebo		X	
Record Fluoroscopy Time, Air Kerma, Procedure Time		X	
Adverse Event Evaluation		X	X

7.4 Justification for Sensitive Procedures

Given the paucity of published data on use of promotility agents to facilitate guidewire advancement through the pylorus during GJ placement procedures, as well as reports of the

potential benefit of the antiperistaltic agent glucagon to facilitate gastric insufflation during GJ placement procedures[9], it is possible that promotility agents may hinder GJ placement. Therefore, a placebo control is justified to rigorously test the study's hypothesis.

7.5 Concomitant Medications, Treatments, and Procedures

All concomitant medications administered during the GJ tube placement procedure will be recorded on the case report forms (CRFs).

7.5.1 Precautionary Medications, Treatments, and Procedures

Not applicable.

7.6 Prohibited Medications, Treatments, and Procedures

Treatment with concomitant glucagon during the GJ tube placement procedure will not be permitted unless discussed with and approved by the study PI.

7.7 Prophylactic Medications, Treatments, and Procedures

Not applicable.

7.8 Rescue Medications, Treatments, and Procedures

Not applicable.

7.9 Participant Access to Study Agent at Study Closure

Not applicable.

8 Assessment of Safety

8.1 Specification of Safety Parameters

Safety parameters included as secondary endpoints include drug related AEs and failed GJ tube placement (see Section 4.2).

8.1.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, prolongation of hospitalization, or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or result in prolongation of hospitalization may be considered serious when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may

require medical or surgical intervention to prevent on of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment, tardive dyskinesia, or peritonitis due to gastric perforation or spillage of gastric contents.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related study documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant populations being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and
- Suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

8.2 Classification of an Adverse Event (AE)

8.2.1 Severity of Event

Adverse events will be graded according to the following guidelines to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgement. The degree of certainty about causality will be graded using the categories below:

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after

administration of the drug, is unlikely to be attributed to concurrent disease or other drugs.

- Possibly Related – There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related" as appropriate.
- Unlikely to be Related – A clinical event whose temporal relationship to drug administration makes a causal relationship improbable (e.g. the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or underlying disease provides plausible explanations (e.g. the participant's clinical condition or other concomitant treatments).
- Not Related – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

James Ronald, MD PhD, and Nicholas DuRocher, MD, will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during the GJ tube placement procedure or routine clinical monitoring after the procedure. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Ups will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of

study participation. Events will be followed for outcome information until resolution or stabilization.

8.4 Reporting Procedures

8.4.1 Adverse Event Reporting

For any problem or AE requiring prompt reporting to the IRB but not meeting criteria for a SAE, within ten business days of the investigator becoming aware of the event, study personnel will send to the IRB a Safety Event submission in the eIRB.

8.4.2 Serious Adverse Event Reporting

The study clinician will complete a SAE Form within the following timelines:

- Immediately (within 24 hours) upon learning of an unanticipated study-related death, study personnel will notify the IRB via e-mail or fax by providing a brief summary of the event. Then, within 1 week (five business days), study personnel will send to the IRB a Safety Event submission in the eIRB.
- For a reportable SAE, study personnel will notify the IRB within five business days of the investigator becoming aware of the event. Study personnel will send a Safety Event submission in the eIRB.

All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the IRB and should be provided as soon as possible.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the criteria for Ups require the creation and completion of an UP report form. The PI will report UPs to the IRB. The UP report will include the following information:

Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, Ups will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 1 week (5 business days) of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within ten business days of the investigator becoming aware of the problem.

8.4.4 Events of Special Interest

Not applicable.

8.4.5 Reporting of Pregnancy

Not applicable.

8.5 Study Halting Rules

Administration of study agent will be halted when three SAEs determined to be "definitely related" or "probably related" to metoclopramide are identified. The study may also be halted for futility or efficacy based on interim statistical analysis (see Sections 10.4.7.1 Safety Review and 10.4.7.2 Efficacy Review).

8.6 Safety Oversight

Safety oversight will be under the direction of the PI who has appropriate expertise in GJ tube placement procedures and in post procedure care. Safety oversight will occur continuously throughout the study.

9 Clinical Monitoring

Study audits may be performed to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s). Audits may be performed at any time at the discretion of the Duke University Health System IRB.

10 Statistical Considerations

10.1 Statistical and Analytic Plans

A separate SAP will not be created. See below for detailed description of the statistical analysis plan.

10.2 Statistical Hypotheses

- Primary Efficacy Endpoint: The null hypothesis is that there is no difference between the metoclopramide and placebo groups in the mean fluoroscopy time required to advance a guidewire from the stomach through the pylorus during GJ tube placement (i.e. H_0: $\mu_1 = \mu_2$ where μ_1 is the mean fluoroscopy time in the placebo group and μ_2 is the mean fluoroscopy time in the metoclopramide group). The alternative hypothesis is that there is a difference between the metoclopramide and placebo groups in the mean fluoroscopy time required to advance a from the stomach guidewire through the pylorus during GJ tube placement (i.e. H_1: $\mu_1 \neq \mu_2$).
- Secondary Endpoints:
    - Total procedure fluoroscopy time: The null hypothesis is that there is no difference between the metoclopramide and placebo groups in the mean total procedure fluoroscopy time (i.e. H_0: $\mu_1 = \mu_2$ where μ_1 and μ_2 represent the mean

total procedure fluoroscopy time in the placebo and metoclopramide groups, respectively). The alternative hypothesis is that there is a difference between the metoclopramide and placebo groups in the mean total procedure fluoroscopy time (i.e. H_1: $\mu_1 \neq \mu_2$).

- Total procedure air kerma: The null hypothesis is that there is no difference between the metoclopramide and placebo groups in the mean total procedure air kerma (i.e. H_0: $\mu_1 = \mu_2$ where μ_1 and μ_2 represent the mean total procedure air kerma in the placebo and metoclopramide groups, respectively). The alternative hypothesis is that there is a difference between the metoclopramide and placebo groups in the mean total procedure air kerma (i.e. H_1: $\mu_1 \neq \mu_2$).
- Total procedure time: The null hypothesis is that there is no difference between the metoclopramide and placebo groups in the mean total procedure time (i.e. H_0: $\mu_1 = \mu_2$ where μ_1 and μ_2 represent the mean total procedure time in the placebo and metoclopramide groups, respectively). The alternative hypothesis is that there is a difference between the metoclopramide and placebo groups in the mean total procedure time (i.e. H_1: $\mu_1 \neq \mu_2$).
- Drug related AEs: The null hypothesis is that there is no difference between the proportion of participants experiencing drug related AEs in the metoclopramide and placebo groups (i.e. H_0: $p_1 = p_2$ where p_1 and p_2 represent the proportion of participants experiencing a drug related AE in the placebo and metoclopramide groups, respectively). The alternative hypothesis is that there is a difference between the proportion of participants experiencing drug related AEs in the metoclopramide and placebo groups (i.e. H_1: $p_1 \neq p_2$).
- GJ tube placement procedure failures: The null hypothesis is that there is no difference between the proportion of participants in whom GJ tube placement is unsuccessful in the metoclopramide and placebo groups (i.e. H_0: $p_1 = p_2$ where p_1 and p_2 represent the proportion of participants in whom there is failure to place a GJ tube in the placebo and metoclopramide groups, respectively). The alternative hypothesis is that there is a difference between the proportion of participants in whom GJ tube placement is unsuccessful in the metoclopramide and placebo groups (i.e. H_1: $p_1 \neq p_2$).

10.3 Analysis Datasets

The analysis dataset will involve all randomized participants (i.e. Intention-to-Treat (ITT) analysis dataset).

10.4 Description of Statistical Methods

10.4.1 General Approach

The general approach of the study is a randomized, double blind, placebo controlled trial.

- For descriptive statistics, including patient demographics, means and standard deviations will be reported for continuous variables and percentages will be reported for categorical variables.

- For inferential tests of the difference of two means (i.e. H_0: $\mu_1 = \mu_2$ versus H_1: $\mu_1 \neq \mu_2$), two-sided unpaired T-tests will be performed.
- For inferential tests of the difference of proportions between groups (i.e. H_0: $p_1 = p_2$ versus H_1: $p_1 \neq p_2$), two-sided Fisher's exact tests will be performed.
- For all inferential tests, a two-sided p-value less than 0.05 will be considered significant.

10.4.2 Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is the fluoroscopy time required to advance a guidewire through the pylorus, defined as the fluoroscopy time at needle puncture of the stomach to the fluoroscopy time when the guidewire first enters the duodenum. The mean fluoroscopy time required to advance a guidewire through the pylorus will be computed in the placebo group (μ_1) and the metoclopramide group (μ_1) where groups are defined by ITT. The null hypothesis of no difference in fluoroscopy time to advance a guidewire through the pylorus (i.e. H_0: $\mu_1 = \mu_2$) will be tested using a two-sided unpaired T-test. A p-value less than 0.05 will constitute rejection of the null hypothesis in favor of the alternative hypothesis (i.e. H_1: $\mu_1 \neq \mu_2$).

10.4.3 Analysis of the Secondary Endpoints

Continuous variable secondary efficacy endpoints will include total procedure fluoroscopy time, total procedure air kerma, and total procedure time. Total procedure fluoroscopy time will be defined as the fluoroscopy time at the start of gastric insufflation to fluoroscopy time at completion of the procedure. Total procedure air kerma will be defined as the air kerma at the completion of the procedure minus the air kerma at the start of gastric insufflation. Total procedure time will be defined as the time at the start of gastric insufflation to time of completion of the procedure. For each continuous variable secondary efficacy endpoint, the test of the null hypothesis of no difference in means between the placebo and metoclopramide ITT groups (i.e. H_0: $\mu_1 = \mu_2$) versus the alternative hypothesis (i.e. H_1: $\mu_1 \neq \mu_2$) will be performed using a two-sided unpaired T-test. A p-value less than 0.05 will constitute rejection of the null hypothesis in favor of the alternative hypothesis.

Discrete variable secondary efficacy endpoints will include the number of patients experiencing drug related AEs and the number of in whom there is failure of GJ tube placement. Drug related AE will be defined as an AE of any severity that is classified as "Definitely Related", "Probably Related", or "Possibly Related". Any procedure in which a GJ tube is not successfully placed will be classified as a failure. For each discrete variable secondary secondary efficacy endpoint, the test of the null hypothesis of no difference in proportions between the placebo and metoclopramide ITT groups (i.e. H_0: $p_1 = p_2$) versus the alternative hypothesis (i.e. H_1: $p_1 \neq p_2$) will be performed using a two-sided Fisher's exact test. A p-value less than 0.05 will constitute rejection of the null hypothesis in favor of the alternative hypothesis.

10.4.4 Safety Analyses

Analyses of AEs will be performed as described above in Section 10.4.3 Analysis of Secondary Efficacy Endpoints.

10.4.5 Adherence and Retention Analyses

Not applicable.

10.4.6 Baseline Descriptive Statistics

The placebo and metoclopramide groups will be compared on baseline characteristics, including demographics and comorbidities, using means and standard deviations for continuous variables and percentages for categorical variables. Inferential tests to assess differences in baseline characteristics of the groups will be performed using T-tests for continuous variables and Fisher's exact tests for categorical variables.

10.4.7 Planned Interim Analyses

10.4.7.1 Safety Review

As described above in Section 8.5 Study Halting Rules, if three SAEs related to metoclopramide are identified the study will be halted. In addition, a single planned interim analysis will be performed after accrual of 55 patients and conditional power will be computed. If the conditional power to detect a 3 minute reduction in the fluoroscopy time required to advance a guidewire through the pylorus in the metoclopramide group (i.e. H_1:$\mu_1 - \mu_2 = 3$) drops below 0.2, the study will be halted. This halting for futility rule will also ensure that the study will be terminated if metoclopramide produces a hindrance to advancing a guidewire through the pylorus compared to placebo. Conditional power will be computed as follows[13]:

$$P(\theta) = \Phi\left(\frac{Z_k\sqrt{I_k} - z_{1-\frac{\alpha}{2}}\sqrt{I_K} + \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right) + \Phi\left(\frac{-Z_k\sqrt{I_k} - z_{1-\frac{\alpha}{2}}\sqrt{I_K} - \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right)$$

where θ is the parameter being tested (i.e. $\mu_1 - \mu_2$), I_k is the information at the interim analysis, I_K is the final information at the completion of the study, Z_k is the test statistic calculated from the observed data at the interim analysis, $z_{1-\alpha}$ is the standard normal distribution value for the test with a type I error rate of α, and Φ represents the cumulative distribution function for the standard normal distribution. The interim and final information levels are computed as follows:

$$I_k = \left(\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}\right)^{-1} \text{ and } I_K = \left(\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}\right)^{-1}$$

where σ_1^2 and σ_2^2 represent the variance in the placebo and metoclopramide groups and n_1, n_2, N_1, and N_2 represent the sample sizes of the placebo and metoclopramide groups at the interim and final analyses. If at the interim analysis $P(\theta=3)<0.2$, the study will be halted.

10.4.7.2 Efficacy Review

At the single interim analysis, the Haybittle-Peto criteria will be utilized to stop for efficacy[14]. Specifically, if a p-value less than 0.001 is obtained, the study will be halted. With the simple Haybittle-Peto rule, given the stringency of the stopping criterion, no adjustement is made in the α level at the completion of the study (i.e. a p-value less than 0.05 will be considered significant).

10.4.8 Additional Sub-Group Analysis

Not applicable.

10.4.9 Multiple Comparison/Multiplicity

Not applicable.

10.4.10 Tabulation of Individual Response Data

Not applicable.

10.4.11 Exploratory Analyses

Not applicable.

10.5 Sample Size

The target sample size is estimated to provide statistical power for the primary outcome, the fluoroscopy time required to advance a guidewire through the pylorus. Based on an IR QI database, we estimate that the average fluoroscopy time required to advance a guidewire through the pylorus is 5.3 minutes with a standard deviation of 5.7. In order to provide a clinically meaningful reduction in fluoroscopy time, we assume an effect size of $\mu_1 - \mu_2 = 3$ minutes under the alternative hypothesis. We therefore estimate that 55 patients in the metoclopramide group and 55 patients in the placebo group would be required to produce approximately 80% power to achieve a p-value < 0.05 in a two-sided unpaired T-test of H_0: $\mu_1 = \mu_2$ versus H_1: $\mu_1 \neq \mu_2$[15].

Based on the IR QI database, in 2016 315 enteral access placement procedures were performed, approximately 75% of which were GJ tube placements. Allowing for potential patients declining participation, we expect to easily accrue approximately 50 patients a year with completion of the study in approximately 2 years.

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

Randomization codes will be generated and maintained by Duke University Health System IDS. Randomization of subjects between the placebo group and metoclopramide groups will be performed in a 1:1 fashion. Replacement will be permitted for subjects who drop out between the time of study consent and the GJ tube placement procedure (i.e. for patients in whom no study related intervention is performed).

The IR physician performing the procedure, the IR technologist recording procedural events and times, and the patient will be blinded to treatment assignment.

10.6.2 Evaluation of Success of Blinding

Not applicable.

10.6.3 Breaking the Study Blind/Participant Code

As described above in Sections 8.5 Study Halting Rules, the blind will be broken in patients experiencing SAEs to determine if these patients received metoclopramide. Intentional and unintentional breaking of the blind will be reported to the PI and IRB.

11 Source Documents and Access to Source Data/Documents

Source data will include CRFs and the electronic medical record. CRFs will include Duke medical record number, a study subject identifier, the time of medication administration, the fluoroscopy time, air kerma, and time at the following procedural events: start of gastric insufflation; needle puncture of the stomach for guidewire insertion; guidewire intubation of the duodenum; procedure completion. The CRF will also record any procedures that were aborted or in which a GJ tube was not successfully placed. Demographic information will be obtained from the electronic medical record. A record of study participation will also be documented in the electronic medical record.

12 Quality Assurance and Quality Control

Quality control procedures will be implemented beginning with the data entry into CRFs. Any missing data or data anomalies will be reviewed by the PI and will be communicated to study members for clarification/resolution. The study team will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the IRB.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting

intervention/administering study product. The written informed consent form is submitted with this protocol to the IRB.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval from the PI and IRB.

Representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, stored in locked file cabinets in the locked IR office suite and on a secured password protected computer in the PI's locked office.

13.4.1 Research Use of Stored Human Samples, Specimens or Data

- Intended use of data collected during this study will be to reduce radiation dose and procedure time during GJ tube placement procedures.
- Storage: No biological specimens will be obtained during this study. Data will be stored on the PI's password protected computer in a locked office.

13.5 Future Use of Stored Specimens

Not applicable.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study team and PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, the original entry will be crossed out with a single line, and initialed and dated. Erasing, overwriting, or correction fluid will not be permitted on original documents.

Clinical data will be entered into the PI's password protected computer in a locked office in the IR suite in Duke University Hospital. No data will be stored, transmitted, or shared with non-study personnel, on non-secured or non-Duke University Health System computers.

14.2 Study Records Retention

Study documents will be retained for a minimum of 6 years following completion of the study in accordance with IRB regulations.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study team. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. Protocol deviations will be sent to the local IRB per their guidelines.

14.4 Publication and Data Sharing

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. In addition, in accordance of with Food and Drug Administration Amendments Act of 2007 which mandates that a "responsible party" (i.e., the PI) register and report results of certain "applicable clinical trials" (including trials of drugs and biologics: controlled, clinical investigations, other than Phase I investigations of a

product subject to FDA regulation), the trial will be registered with ClinicalTrials.gov and results reported.

15 Study Administration

15.1 Study Leadership

The PI will govern the conduct of the study. The study will be subject to Duke University Health System IRB oversight.

16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

17 Literature References

1. Cunningham RS. 5-HT3-receptor antagonists: a review of pharmacology and clinical efficacy. Oncol Nurs Forum 1997;24:33-40.
2. Ramirez B, Richter JE. Review article: promotility drugs in the treatment of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1993;7:5-20.
3. Bai Y, Guo JF, Li ZS. Meta-analysis: erythromycin before endoscopy for acute upper gastrointestinal bleeding. Aliment Pharmacol Ther 2011;34:166-171.
4. Barkun AN, Bardou M, Martel M, Gralnek IM, Sung JJ. Prokinetics in acute upper GI bleeding: a meta-analysis. Gastrointest Endosc 2010;72:1138-1145.
5. Hu B, Ye H, Sun C, et al. Metoclopramide or domperidone improves post-pyloric placement of spiral nasojejunal tubes in critically ill patients: a prospective, multicenter, open-label, randomized, controlled clinical trial. Crit Care 2015;19:61.
6. Paul N, Rawlinson J, Keir M. The use of metoclopramide for the small bowel meal examination: pre-procedural versus peri-procedural oral administration. Br J Radiol 1996;69:1130-1133.
7. Itkin M, DeLegge MH, Fang JC, et al. Multidisciplinary practical guidelines for gastrointestinal access for enteral nutrition and decompression from the Society of Interventional Radiology and American Gastroenterological Association (AGA) Institute, with endorsement by Canadian Interventional Radiological Association (CIRA) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE). J Vasc Interv Radiol 2011;22:1089-1106.
8. Donnelly LF, Klosterman LA, Ball WS, Jr., Bisset GS, 3rd. Comparison of duodenal intubation techniques during conversion of gastrostomy to gastrojejunostomy tubes in children. AJR Am J Roentgenol 1997;169:1633-1634.
9. Lyon SM, Pascoe DM. Percutaneous gastrostomy and gastrojejunostomy. Semin Intervent Radiol 2004;21:181-189.
10. UpToDate Metoclopramide: Drug Information.
11. Appadu BL, Lambert DG. Analgesia induced by metoclopramide. Br J Anaesth 1993;71:774.

12. Gupta VCP. Chemical stability of metoclopramide hydrochloride injection diluted with 0.9% sodium chloride injection in polypropylene syringes at room temperature. Int J Pharm Compd 2005;9:72-74.
13. C. J, Turnbull BW. Group Sequential Methods with Applications to Clinical Trials. Boca Raton, FL: Chapman & Hall/CRC, 2000.
14. Pocock SJ. When (not) to stop a clinical trial for benefit. Jama 2005;294:2228-2230.
15. Rosner B. Fundamentals of Biostatistics. 7th ed. Boston, MA: Brooks/Cole, Cengage Learning, 2010.