Title Page

MAGNETICALLY CONTROLLED CAPSULE FOR ASSESSMENT OF GASTRIC MUCOSA IN SYMPTOMATIC PATIENTS (MAGNET)

Protocol Identifying Number: ISR- 191848

Principal Investigator:
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Investigator Initiated Research

Funded by AnX Robotica

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1. STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6), ISO 14155, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and FDA regulations: 21 CFR part 50, part 54 and part 56.

All personnel involved in the conduct of this study have completed human subjects' protection training.

2. SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name:

Title:

Sponsor:

Signed: _____ Date: _____

Name:

Title:

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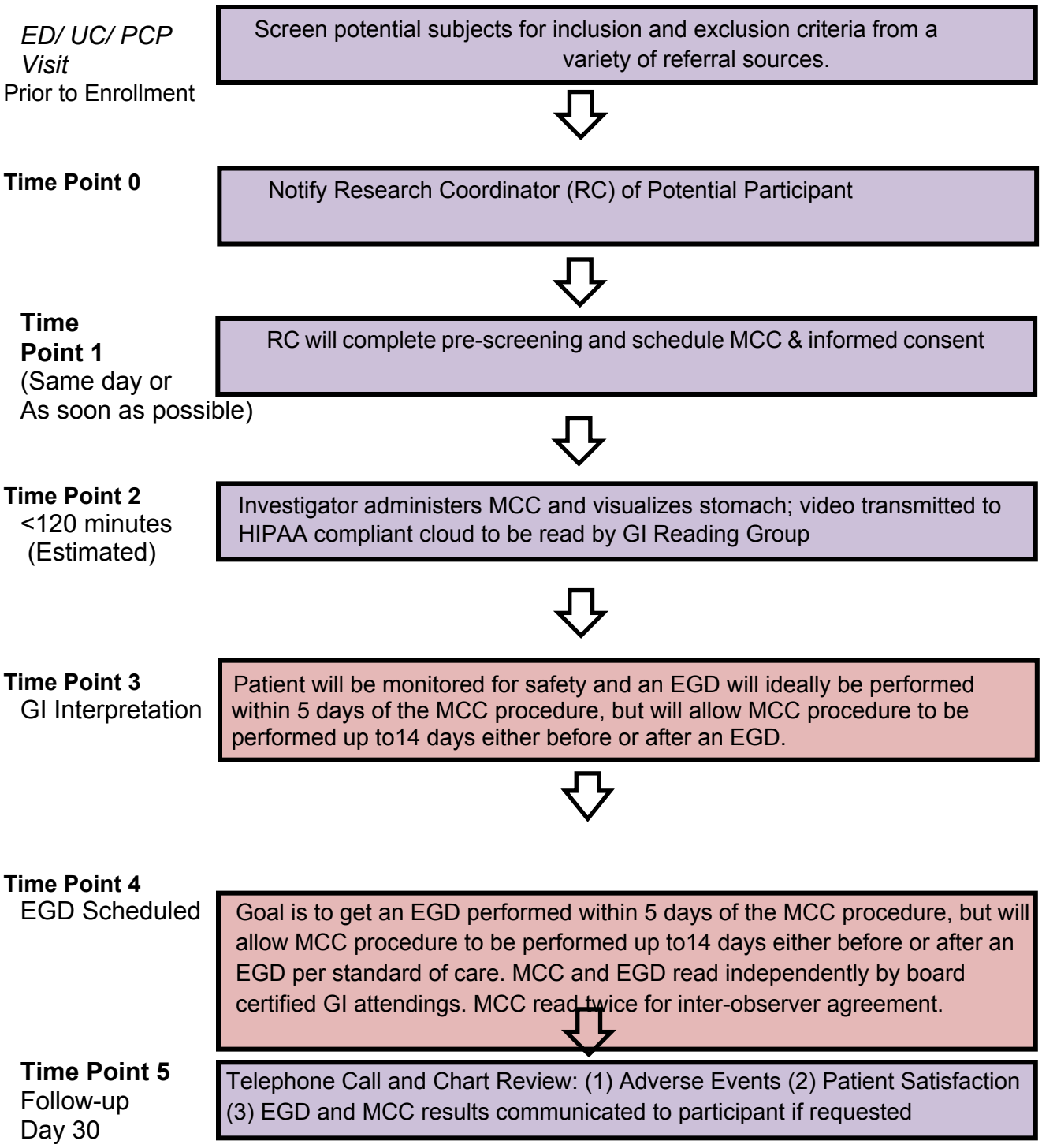
3. LIST OF ABBREVIATIONS

AC	Active Control
CFDA	Chinese Food and Drug Administration
CE	Capsule Endoscopy
CFR	Code of Federal Regulations
ED	Emergency Department
EGD	Esophagogastroduodenoscopy
FDA	Food and Drug Administration
GBS	Glasgow Blatchford Score
GI	Gastrointestinal
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MCC	Magnetically Controlled Capsule
PCP	Primary Care Physician
RC	Research Coordinator
ST	Standard (Risk Assessment)
UC	Urgent Care
UGIB	Upper GI Bleed
US	United States

4. PROTOCOL SUMMARY

Title:	**Magnetically Controlled Capsule For Assessment Of Gastric Mucosa In Symptomatic Patients: "MAGNET"**
Précis:	**This is a single-center prospective study examining the diagnostic utility of a single-use ingestible *magnetically controlled capsule* (MCC) endoscope (NaviCam™, AnX Robotica) which is remotely controlled by external hardware and software to visualize the mucosa of the stomach on patients with upper abdominal symptoms. Participants will be enrolled and tested at a central site referred from Emergency Departments (EDs), urgent cares (UCs) and primary care practices (PCPs) in the Washington, DC area and additional site(s) to be named. Total enrollment is estimated to be 72 patients with a goal of following all patients with a traditional endoscopy to confirm findings. Aim 1 is to establish feasibility of this novel outpatient testing. Aim 2 is to demonstrate high-quality visualization of gastric anatomic landmarks. Aim 3 is a pilot study to compare visualization of gastric anatomic landmarks and lesions of MCC follow-up traditional EGD. We currently anticipate enrolling 2-3 patients per week over 30 weeks.**
Objectives:	***Aim 1*: We aim to demonstrate feasibility of MCC in an outpatient primary and urgent care setting. Measured outcomes include duration of MCC test, linkage with EGD follow-up, image storage, image transfer, technician learning curve and documentation.** **Aim 2: We aim to show that MCC can identify and photograph regions of stomach consistent with established visualized scoring systems for anatomic landmarks.** ***Aim 3*: Pilot assessment of MCC compared to subsequent EGD to detect anatomic regions and gastric mucosal lesions.**
Population:	**An unselected pool of adult patients with an appropriate indication for upper endoscopy such as epigastric pain/burning, nausea and or vomiting, bloating, heartburn, iron deficiency anemia, unintended weight loss, abnormal imaging suggesting organic disease. In general, participants will be age ≥ 18, mixed gender, mixed race, hemodynamically stable with possible co-morbidities.**
Site Number	**1**
Study Duration:	**Time needed to reach sufficient study subjects plus additional time for analysis**
Subject Duration:	**30 days**
Estimated Time to Complete:	**12 months**

5. SCHEMATIC OF STUDY DESIGN:



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6. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

6.1. Background Information

Esophagogastroduodenoscopy (EGD) is one of the most common medical procedures and indications include epigastric pain, bloating, burning, heart-burn, excessive belching, nausea and/or, vomiting, anemia, weight loss. Access to EGD is limited by the cost, the need for an endoscopy specialist and the need for anesthesia. Lack of access to an EGD is a health disparity associated with increased gastric cancer mortality-to-incidence ratio (Tsai 2017). A novel approach to visualization of the upper GI tract is needed to increase access to care and improve diagnostic capabilities. Magnetically controlled capsule (MCC) is the first wireless ingestible capsule endoscope that is able to be directed by operator to visualize all anatomic areas of the stomach (NaviCam™, AnX Robotica). This study will be the first US study to examine the feasibility of using MCC in patients with relevant symptoms to the stomach. The goal is to ascertain if the diagnostic capabilities of the MCC compared to EGD are comparable for symptomatic patients who have clinical indications for an EGD.

MCC offers potential advantages over traditional EGD including the ability to be performed 24 hours a day without sedation and to be performed by a clinician. In addition, the MCC is less invasive, does not cause discomfort, and enables the patient to pursue normal daily activities after the procedure. Non-specialist physicians can administer the MCC and interpretation can be done in real-time or asynchronously by GI specialists. The MCC may impact decisions regarding the need for hospitalization, the need for additional diagnostic testing such as biopsy, the need for additional therapeutic interventions such as endoscopic hemostasis and polypectomy, and the need for further risk stratification of disease. The eventual work-flow may be similar to that of many current diagnostic tests such as radiologic examinations. This ability to transmit images could become especially important in rural communities or in communities that have limited access to a gastroenterologist or surgeon. Incorporation of the MCC into current practice could follow a trajectory similar to that of point-of-care ultrasonography, an imaging modality in which non-radiologist physicians have become increasingly skilled and for which indications continue to expand (Bennet 2018). The American Society of Gastrointestinal Endoscopy states that credentials for capsule endoscopy should be determined independently from other endoscopic procedures such as colonoscopy, sigmoidoscopy, or any other endoscopic procedure (ASGE 2005). The American Society for Gastrointestinal Endoscopy also emphasizes that sound medical training, appropriate patient selection, correct interpretation, and continued medical management for all patients. Capsule endoscopy requires only image interpretation and does not require procedural skill training associated with other

endoscopic procedures; therefore, ED physicians, urgent care physicians and primary care doctors and mid-level practitioners can meet these criteria with basic training.

Contraindications to the MCC are similar to contraindications for established capsule endoscopy (CE) which has been performed safely in a variety of clinical settings [3]. The only absolute contraindication is intestinal obstruction [4]. There is a low risk of non-natural excretion of capsules estimated at less than 1 in 100 [5]. In general, the CE procedure poses significantly less risk than traditional EGD, and multiple studies have shown that CE is well tolerated in patients with acute symptoms (Gralnek 2008, Sung 2016, Meltzer 2013).

The cost of the capsule is an important factor that may affect future use in the ED and clinics. The use of MCC in the ED, urgent care and primary care can potentially lead to more patients being safely managed in an outpatient setting. MCC may be especially cost-effective if it reduces hospital admissions, need for anesthesia, missed work days or overall EGDs. Future technological developments in the MCC may allow for operator to collect biopsy samples and perform therapeutic functions.

6.2. Rationale

In the United States, upper endoscopy is frequently performed for a variety of symptoms including heartburn, bloating, nausea, burping, and epigastric pain/burning. The prevalence of these symptoms may provide as much as 25% of a gastroenterologist's office practice. In general, the diagnostic yield of an EGD is low. Without alarm symptoms, as many as 70% of procedures are negative for significant findings. One major indication is testing for *H. pylori* for which EGD may be unnecessary, because *H. pylori* detection can be accomplished by fecal antigen testing or breath testing as accurately as biopsy and less expensively.

We believe there is an opportunity to improve the risk stratification of patients that undergo endoscopy through the use of MCC. Our primary hypothesis is that MCC allows for visualization of the stomach of symptomatic patients referred from the emergency, urgent care and primary care settings with clinical symptoms appropriate for endoscopy. A prospective study is proposed to evaluate the feasibility, safety and accuracy of this novel diagnostic modality.

6.3. Potential Risks and Benefits

6.3.1. Potential Risks

Patients for whom study enrollment may interfere with standard clinical care will not be enrolled. Alternatives to study participation are for patient to receive standard of care treatment for symptoms which includes only an EGD or barium studies. We have considered a variety of potential risks to participants including cognitive, affective,

physical, legal/confidentiality and economic risks. The NaviCam MCC is manufactured by AnX Robotica and has been granted marketing authorization by the FDA through the de-novo process to confirm its safety and effectiveness profile.

Since its introduction to the Chinese market after being approved by the Chinese Food and Drug Agency (CFD) in 2012, the NaviCam MCC was subject to a series of clinical studies. Published studies involving more than 500 people in China have been published comparing MCC to gastroscope. In a pilot study in 34 healthy volunteers (Liao et al. 2012), 75 to 100% of gastric mucosa was visualized in 27 (79.4%) people and 50% to 75% in 7 (20.6%) people. Visualization of the gastric cardia, fundus, body, angulus, antrum and pylorus were subjectively assessed as complete in 82.4%, 85.3%, 100.0%, 100.0%, 100.0% and 100.0% respectively. In a non-blinded comparative study in 68 patients (Zou et al. 2015) showed a diagnostic accuracy similar to standard gastroscopy: the positive percent agreement was 96.0%, and the negative percent agreement was 77.8%. The overall agreement was 91.2% with a κ value of 0.765 ($p<0.001$). A total of 68 pathological findings were detected, of which 53 were identified by both methods. In a multi-center comparative study in 350 patients (Liao et al. 2016), the NaviCam detected gastric focal lesions in the whole stomach with 90.4% sensitivity, 94.7% specificity, a PPV of 87.9%, a NPV of 95.9% and 93.4% accuracy. The NaviCam was preferred by almost all patients (95.7%), compared with gastroscopy. (Liao, 2016).

The physical risks associated with the NaviCam MCC are generally related to potential non-natural excretion. There is a small risk that the capsule could become stuck in the stomach or small intestine. Based on published and unpublished data of other types of capsule endoscopes, retained capsules have persisted in the GI tract for periods for many years without adverse event. In fact, a large retrospective review by Cheifetz, et al. found that a retained capsule is often asymptomatic or leads to a diagnosis. (Chifetz 2006). Furthermore, the device is made of biocompatible materials and its internal parts are non-toxic. The incidence of capsule retention has been reported to be less than 1% but this figure may be higher in Crohn's disease or other conditions. The rate of surgical/endoscopic removal was noted to be 0.75% (Barkin, 2002).

Patients who are at increased risk of capsule retention are not appropriate study subjects including people with swallowing disorders or with known or suspected gastrointestinal obstructions, strictures or fistulas. In general, if a patient does not pass the MCC naturally through the upper GI tract due to gastroparesis, an EGD will be sufficient to retrieve the capsule. Given that all study patients will receive an EGD as part of their standard work-up for the disease, this does not pose a significant increased risk. Any patient with dysphagia will be excluded because a retained capsule in the esophagus is at risk of aspiration.

Patients will be advised not to have an MRI for 30 days. For patients who are unsure whether they excreted the MCC, *an abdominal X-Ray or "Navicam capsule locator" may be required as an outpatient to confirm passage.*

In order to maximize safety for all study subjects, only consented and enrolled subjects will be administered the MCC under the supervision of a physician and a sub-investigator/trained research associate responsible to the PI. In addition, the MCC will be stored in a secure, limited access area. Product accountability log must include the protocol number, investigative site name, product name, medical units (i.e., capsules), serial number and subject ID number.

We believe the study poses a low privacy risk to subjects as all data will be encrypted and no PHI will be stored with data. Data will be stored in a REDCap database that allows for the common collection of data from multiple sites.

Finally, the study has a low economic risk since the device and the interpretation of the device are not being billed to the subject or his/her insurance company. The follow-up EGD is considered standard of care and will be billed to the patient's insurer. AnX Robotica, the manufacturer of the NaviCam has agreed to cover the cost of medical care and treatment for research injuries sustained by subjects enrolled in the study in accordance with the terms of the Clinical Trial Agreement and there is no economic risk expected as a result of unanticipated complications of the device as these will be covered by AnX Robotica, per the final negotiated terms in the Clinical Trial Agreement (currently under negotiation).

Major adverse events that occur will be reported directly to the principal investigator and overall study coordinator within 24 hours. Minor adverse events include inability to tolerate the MCC capsule, discomfort swallowing capsule, issues regarding video capture, issues regarding video transmission, erroneous video interpretation that has no significant impact on clinical care, protocol deviations, reactions to medication (pro-motility agent), delays in endoscopy interpretation, delays in EGD and others. All minor adverse events will be shared with the entire research team at regularly scheduled monthly calls or sooner at the PI's discretion.

Any major adverse events that occur will be reported directly to the principal investigator who will be available to study subjects 24 hours a day. Severe adverse events will be reported to the entire research team, the sponsor, the DSMB and to IRB within 24 hours. Updates will be provided after a full investigation is completed. SAE's will also be reported to the FDA. Potential major adverse events include delayed definitive care, and capsule retention in the small bowel, and any serious outcome that may be related to study protocol. A DSMB will be formed that includes experts in primary care, emergency medicine, and gastroenterology and research methodology. DSMB of approximately 3-5 multi-disciplinary persons will meet every 6 months during which a report will be produced by PI and as needed for SAE's.

6.3.2. Potential Benefits

Immediate potential benefits include a focused effort by the research team to visualize the stomach for all subjects and help ensure appropriate follow-up. Long-term potential benefits include more effective and efficient management of a variety of conditions that are common in the population.

Recently, the advantage of diagnostic tools that decrease exposure of healthcare providers to infectious diseases such as COVID-19 has become clearer.

6.3.3. Discussion

The evaluation of suspected symptoms in the stomach often requires an EGD by a gastroenterologist or surgeon and which may also entail hospitalization and procedural sedation by an anesthesiologist. While this traditional process is safe and effective, it is not efficient for low-risk patients and not timely for all high-risk patients. The opportunity to bring NaviCam MCC to the front-lines of US medical care may change how we manage GI symptoms. This trial is an important step toward demonstrating that NaviCam MCC is a safe and effective tool to diagnose patients who have upper GI symptoms and improve quality of care for those patients.

7. OBJECTIVES

7.1. Primary Objective

- ✓ Aim 1) To demonstrate feasibility of MCC in an outpatient setting for patients with upper abdominal symptoms
- ✓ Aim 2) To demonstrate high-quality visualization of gastric anatomic regions.
- ✓ Aim 3) To pilot a comparison of MCC versus EGD regarding the ability to visualize both gastric anatomic regions and gastric lesions.

7.2. Secondary Objective

1) To perform a cost-effective analysis of MCC v EGD.
2) To measure patient satisfaction for EGD v MCC.
3) To measure 30-day safety.
4) To compare international trials that compared EGD to MCC for detection of gastric lesions.
5) To measure the time required to visualize the stomach for MCC versus EGD.

8. STUDY OUTCOME MEASURES

8.1. Primary Outcome:

Aim 1: Pilot and Feasibility Stage.

1) *Implementation*: Installation, Training, Site Requirements
2) *Practicality*: Duration of MCC test (minutes), Technician "learning curve," Clinical Staff and Patient Satisfaction, Duration of fasting required
3) *Integration*: Scheduling MCC, Linkage with EGD follow-up, Image storage, Image transfer, Documentation of Interpretation, Photo-documentation, Database development

Aim 2: High-Quality Visualization (90%) of Gastric Anatomic Landmarks

Defined as visualization and photo-documentation of the following anatomical landmarks:

1) Lower Esophagus / Z line
2) Cardia / fundus
3) Body, lesser curvature AND/OR Body, greater curvature
4) Anterior / Posterior walls
5) Angularis
6) Antrum
7) Pylorus
8) Duodenal Bulb
9) Duodenal Ampulla

Aim 3: MCC versus EGD for visualization of anatomic landmarks (see above) and gastric lesions in symptomatic patients

Defined as visualization and photo-documentation of the following structures and diseases:

1) Visible Lesions (Paris Classification if relevant)
2) Ulcers (Forrest Classification) erosions
3) Gastric Atrophy
4) Gastric Varices
5) Gastritis*
7) Submucosal lesions
8) "Does patient need a follow-up EGD?" Y/N (Opinion of endoscopist interpreting MCC based on MCC findings.)

* (not erythema but 'chicken wire' pattern intramucosal change in vascular pattern or hemorrhagic)

8.2. Secondary Outcomes:

(1) Cost-effective analysis

(2) 30-day follow-up for adverse events and safety
(3) Patient Satisfaction of MCC versus EGD
(4) Replication of similar sensitivity and specificity of MCC to EGD to prior trials outside of the US for (a) Ulcers; (b) Cancer; (c) Inflammatory Changes
(5) Time spent visualizing the stomach for MCC versus EGD (minutes)
(6) Visualization of the duodenum
(7) Hiatus hernia

8.3. Selected Outcomes Measures (see data collection sheets)

8.3.1. Procedure time.

- When measuring procedure time of EGD and MCC, we will consider all components of procedure including anesthesia, prep, cleaning and preparing room for next patient and turn-around time. We will also measure total time for staff and for the clinician.

8.3.2. Training to perform MCC.

- How long? How many cases needed? Is there a learning curve to speed and accuracy?

8.3.3. Fasting and MCC prep

- NPO Midnight the day before MCC.

8.3.4. Scoring Anatomic Regions.

After confirming that gastric emptying has been achieved with overnight fast -- we will use the 5-point visualization score described in Ching, 2019 for the following anatomic regions

- Lower Esophagus / Z line
- Corpus
  - Greater curvature
  - Lesser Curvature
- Anterior Wall
- Posterior Wall
- Proximal stomach
  - Cardia/Fundus
- Distal Stomach
  - Antrum/Pylorus/Angularis
- Duodenum
  - Bulb
  - Ampulla

8.3.5. Scoring Gastric Mucosal lesions.

("yes/no")

- Visible Lesions (Paris Classification if relevant)
- Ulcers (+/- Forrest Classification)
- Gastric Atrophy
- Gastric Varices
- Gastritis*
- Hiatus hernia
- Submucosal lesions
- Plus: Does patient need endoscopic intervention?

8.3.6. Lesions picked up by MCC and not by EGD.

- Healing lesions (especially ulcers) are natural course of disease therefore we assume that some

lesions will be detected by capsule but not by EGD if EGD is done a few days later. With photo-documentation and two independent readers, we hope to assure that this phenomenon is a natural course of lesion and not a "false-positive" by MCC.

8.3.7. Measuring patient satisfaction (see *MAGNET7 and 8*, day 7 and 30).

- I felt the research team answered all my questions. Yes No
- Did you feel any pain with swallowing? Yes No
- How difficult was it to swallow the capsule? Very Easy Moderately Easy Neutral Moderately Difficult Very Difficult
- Did you feel discomfort after swallowing while operator moved the capsule? Yes No
- Did you notice the capsule pass during a bowel movement?? Yes No
- Any other issues? Yes No
- If yes, what were the issues? _____
- How much time in total approximately did you have to take out during your day for the capsule endoscopy procedure? ___ (we do not ask this)
- Did you feel like you needed to miss work after the capsule endoscopy procedure? Yes No
- (we do not ask this)
- Did you need someone to take you home after the capsule endoscopy procedure? Yes No

(we do not ask this) In the future, if both studies were equally accurate and you needed another examination of your stomach, would you prefer to have a traditional EGD or a capsule? EGD Capsule. Why?

9. STUDY DESIGN

9.1. Study Design

Prospective Study of Diagnostic Utility of MCC

9.2. Proposed Site

George Washington University (GWU) Medical Faculty Associates (MFA) in Washington, DC.

9.3. Patient Safety

The study will be conducted in compliance with the Declaration of Helsinki, ICH-GCP guidelines, ISO 14155, and US regulations. Study design will be approved by the local IRB at each participating institution prior to commencement.

9.4. Study procedure:

1. Screen potential adult patients with an appropriate indication for upper endoscopy such as epigastric pain/burning, nausea and or vomiting, bloating, heartburn, iron deficiency anemia, unintended weight loss, abnormal imaging suggesting organic disease from a larger pool of patients seen in an ED, Urgent Care, Primary Care and GI Clinic patients. In some settings, a research assistant will be on site to perform the screen. In other settings, the clinical staff will perform the screen or potential patients will be contacted by phone by RC. (Form used*: Magnet 1*)

2. Patients screened who are eligible will be approached about potential interest. (*See full list of inclusion/ exclusion criteria).* In some circumstances, patients will be given contact information for the research coordinator (RC), who will contact them as soon as possible to schedule MCC. In other circumstances, the research assistant will contact RC and attempt to schedule MCC before patient leaves the clinical setting.

3. RC will contact patients to complete screening, confirm eligibility, obtain verbal consent, and schedule both MCC and EGD (if EGD is not already scheduled). Formal written consent will be obtained by patient at the MCC location (2120 L Street, NW, suite 200).

4. Participants arrive at the MCC location for final screen, sign written consent and undergo MCC. All consented patients will be given a study ID and recorded in enrollment log. (Form used*: Magnet 3)* The patient's demographics and images will be stored in a HIPAA compliant fashion.

    - BRIEF DESCRIPTION OF MCC PROCEDURE. The patient will be NPO midnight. They will come to the facility and will ingest the capsule per manufacturer's protocol. (Manufacturer's protocol says that the person will take 10ml of simethicone in 100ml of water 40min before capsule is ingested. The capsule will then be controlled externally by magnetic field by the examining health care provider in such a way that the major regions of the stomach are photo-documented with still images and video. This may involve changing the position of the patient and the

possible ingestion of additional water. The sequence of the examination

will be pre-determined, and each area will have a predetermined number of images obtained as suggested by Gastroenterology Society guidelines.

5. Patient data collected will include the following elements: chief complaint of patient, history of present illness, past medical history, current medications (only PPIs and pain medication)..
6. At completion of MCC, video will be archived and patient satisfaction will be assessed. Capsule endoscopy will NOT be used for clinical decisions.
7. Patients will be instructed to return to the physician sooner, if concerning signs develop. A 7 and 30-day follow-up call and chart review is only performed if person is lost to follow-up will be conducted to check for symptom resolution and adverse events.
8. Esophagogastroduodenoscopy (EGD) will be performed as soon as possible in an appropriate endoscopy facility by an experienced endoscopist.
9. Endoscopic images will be stored in secure serve for later comparison with MCC images.

Summary of Research Strategy

- PRE-SCREEN (DAY -7 to DAY -1)
  - Upper Abdominal Pain or Related Symptoms (Indications for an EGD)
    - Performed in ED, UC, PCP offices or GI clinic

- SCREEN (DAY -7 -> DAY 0)
  - More thorough screening questions and scheduling by RC (<24 hours)
    - Performed by Telephone

- ENROLL (DAY 0)
  - Signed Informed Consent procedure, more detailed questions and MCC Procedure performed
    - Occurs at the GWU Medical Faculty Associates Building on 2120 L street.
    - NaviCam MCC performed by trained Clinician.
    - Reviewed by a Gastroenterologist.
    - Scheduled for an EGD will ideally be performed within 5 days of the MCC procedure, but will allow MCC procedure to be performed up to14 days either before or after an EGD (paid by insurance as standard of care).

- FOLLOW-UP (DAY 1-30)

- Day 7 and Day 30: Telephone Call plus CRISP Chart Review, only if lost to follow-up.

10. STUDY ENROLLMENT AND WITHDRAWAL

10.1. Subject Inclusion Criteria

1. Individuals aged ≥ 18 years with upper GI symptoms (epigastric pain, bloating, burning, heart-burn, excessive belching, nausea and/or, vomiting, anemia, and weight loss) appropriate for an upper endoscopy evaluation.
2. Able to speak English
3. Able to understand and sign consent form
4. Able to undergo standard outpatient endoscopy
5. Indications for EGD Low blood (unexplained anemia)
   - Blood in vomit (hematemesis)
   - Upper abdominal or chest pain
   - Indigestion (dyspepsia)
   - GERD
   - Suspected ulcer
   - Unexplained weight loss
   - Gastric biopsy
   - Other

10.2. Subject Exclusion Criteria

Individuals with one or more of the following will not be eligible for participation in the study:

1. Hemodynamic shock
2. Active hematemesis
3. Dysphagia, swallowing disorder
4. Suspected bowel obstruction or perforation
5. Gastroparesis
6. Crohn's disease
7. Prior GI tract surgery that changes the gastrointestinal anatomy (e.g., Billroth I or II, esophagectomy, gastrectomy, bariatric procedure and small intestinal resection)
8. Presumed pregnant, trying to conceive or currently breastfeeding
9. Altered mental status (e.g., hepatic encephalopathy) that limits the ability to swallow a capsule
10. Expected to have Magnetic Resonance Imaging examination within 30 days.
11. No reliable contact information – no phone, no permanent address.
12. Pacemaker or ICD

13. BMI ≥ 38

10.3. Strategies for Recruitment and Retention

Email notifications will be sent to GW providers on the study to help recruit eligible patients at GW EDs, urgent care facilities and PCP offices. Existing RA's stationed in those units will help spread the word about potential eligibility (i.e. stable for outpatient work-up, symptoms related to UGI tract.) Pre-screening will take place onsite. Full consent and interview for inclusion and exclusion criteria will occur by lead RC and PI at site of NaviCam.

10.4. Subject Withdrawal

10.4.1. Reasons for Withdrawal

A subject can withdraw at any time and for any reason. Subject should provide written notice to PI as to withdrawal intent. The PI can withdraw a patient from the study for noncompliance issues or serious medical conflicts.

10.4.2. Handling of Subject Withdrawals

If subject withdraws from the study, no further contact will be attempted or made by study staff. If patient is withdrawn from study by PI for non-compliance or health related concerns, study staff will notify subject via phone call and/or IRB approved letter, if direct contact cannot be made.

10.4.3. Premature Termination or Suspension of Study

Notification of all study subjects. No further data collection.

11. DATA ENTRY SYSTEM

For this protocol, REDCap database will be used for data entry screens corresponding to the study forms that will be developed and maintained by GWU. Clinical center staff will enter de-identified data into the REDCap database.

12. ASSESSMENT OF SAFETY

12.1. Unanticipated Adverse Events

An unanticipated adverse event is an effect on health or safety caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence in the protocol, or any other unanticipated problem associated with a device that relates to the rights, safety, or welfare of subjects in the clinical study.

12.2. Assessment of Adverse Events

All adverse events will be graded for severity as follows:
Mild: Sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities.
Moderate: Sign or symptom, which may be ameliorated by simple therapeutic measures; yet, may interfere with usual activity.
Severe: Sign or symptom that are intense or debilitating and that interfere with usual activities. Recovery is usually aided by therapeutic measures.

The relationship of the adverse event to the study device is defined as follows:
Probably related: Follows a reasonable temporal sequence from study device use delivery/retrieval and cannot be reasonably explained by known characteristics of the subject's clinical data.
Possibly related: Follows a reasonable temporal sequence from study device delivery/retrieval but could have been produced by the subject's clinical state regardless of the study device.
Not related: No relationship to study device activation is perceived.

12.3. Serious Adverse Events

Adverse events will be reported within 24 hours to the Study PI, the local IRB and the sponsor.
Additional procedures are warranted for cases of serious adverse events which is defined by the FDA as an adverse event that:
a) Led to death,
b) Led to serious deterioration in the health of the subject, that either resulted in:
    1) A life-threatening illness or injury, or
    2) A permanent impairment of a body structure or a body function, or
    3) In-patient or prolonged hospitalization, or
    4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect

12.4. Reporting Procedures

All device related serious adverse events should be reported to the PI, Sponsor, GWU IRB, and FDA.

Unanticipated adverse events should be reported to the PI, Sponsor, and GWU IRB in a timely manner.

13. HYPOTHESIS AND ANALYSIS

13.1. Study Hypothesis

Aim 1: We hypothesize that initiation of MCC pilot study will be feasible defined by outcomes related to (A) implementation, (B) Practicality and (C) Integration.

Aim 2: We hypothesize that MCC will meet established quality measures (≥90%) for visualization of stomach anatomy landmarks.

Aim 3: We hypothesize that the MCC will be similar to EGD at visualization of gastric lesions and/or disease.

13.2. Sample Size Considerations

The sample size for this Proof of Concept study was not chosen for statistical consideration, as there are no formal statistical inferences planned. The size of the study is judged adequate for the preliminary evaluation objectives. All 72 participants will receive the MCC and will be referred to follow-up EGD. The base-line prevalence of lesions and the estimated loss to follow-up will provide information for formal sample size calculation for follow-up study.

We did not use a statistical justification but a practical justification to choose 72 participants. All 72 will get the MCC unless they are unable to tolerate the capsule. The issue of drop-out is relevant only to Aim 3 which pilots the concept of non-inferiority compared to subsequent EGD. We did not power this study to prove non-inferiority --- this study will allow us to estimate baseline lesion prevalence and the likely drop-out rate. Moving forward, we be able to calculate an accurate sample size for a future larger definitive non-inferiority study.

For patients in whom visualization is limited by incomplete gastric emptying, we will record fasting time but exclude patient from assessment of MCC accuracy.

13.3. Cost-Effective Analysis

A cost-effective model will be constructed to compare MCC with traditional endoscopy. Full analysis plan is forthcoming.

14. STUDY OVERSIGHT

A Data Safety Monitoring Board (DSMB) consisting of appropriately qualified independent experts has been appointed by the PI to provide review of data on patient safety and study progress. The membership roster is maintained by site PI and study coordinator and is available from them as needed. PI will provide reports including adverse events.

The Data and Safety Monitoring Board provides ongoing evaluation of the study progress including patient accrual and retention, monitoring of adverse events, and the adequacy and efficiency of the analysis plan to discern outcomes that might require study modifications, or result in early cessation of the study due to its benefits or harms. The DSMB does not evaluate the scientific merit or methodology of the study, nor does it directly participate in the execution of a study's protocol, monitor the budget, or approve sub-protocols or other modifications to the study.

The major responsibilities of the Board are:

- To review the data analysis plan and make recommendations for additions or changes to the plan.
- To assess the performance of the site and make appropriate recommendations regarding continuation, probationary status, or termination.
- To consider patient accrual, overall study progress (timeline and follow-up participation), adverse effects and patient safety, and proper monitoring and reporting by the study team as these affect the ethical treatment of participants or the ethical conduct of research.
- Report to the PI on any perceived problems with study conduct, enrollment, sample size, and data collection.

14.1. Monthly Reports

Monthly Recruitment Reports - reports of the number of people screened and enrolled by month. Reports detailing recruitment, baseline patient characteristics, data quality, incidence of missing data and adherence to study protocol. Sponsor will have access to monthly status reports.

14.2. Annual Reports

Data and Safety Monitoring Board (DSMB) Reports - The DSMB will prepare a written report which includes patient recruitment, baseline patient characteristics, center performance information with respect to data quality, timeliness of data submission and protocol adherence (in addition to safety and efficacy data). The reports also include adverse events, loss to follow-up and all outcome variables as described previously in this protocol.

15. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of ICH E6, Section 6.5 of ISO 14155, and regulatory and institutional requirements for the protection of confidentiality of subjects.

16. QUALITY CONTROL AND QUALITY ASSURANCE

QC procedures will be implemented on data entry system and data QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

17. ETHICS/PROTECTION OF HUMAN SUBJECTS

17.1. Good Clinical Practices

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

17.2. 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 in the study.

17.3. Informed Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study or select to withdraw their consent. The consent process will be documented in the clinical or research record.

17.4. Exclusion of Women, Minorities, and Children (Special Populations)

Adults ≥18 years of age will be included. Refer to Section 10 “Study Enrollment and Withdrawal” for the full inclusion and exclusion criteria.

18. PARTICIPANT CONFIDENTIALITY

All records will be confidential. Subjects will not be identified in any reports or publications of this study. It is possible that representatives of regulatory agencies and from the study’s sponsor may come to (the university/hospital) to review study information. In that situation, copies of the relevant parts of the study records will be

released with all identifying information removed. Access to study records will be limited to those who need the information for purposes of this study, as well as the patient's healthcare providers should they need access to the information. All records are kept in a secure location and access is limited to research study personnel.

19. DATA HANDLING AND RECORD KEEPING

19.1. Data Management Responsibilities

The site will maintain appropriate medical and research records for this trial in compliance with ICH E6, ISO 14155, and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in this study, the site will permit authorized representatives of the PI to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, recorded videos of upper GI tract, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. Except for videos and digital images, all data will be collected on CRFs and a RedCap database.

Study participation will also be recorded in the medical record to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial.

19.2. Data Capture Methods

Data will be captured both via handwritten source documents and a centralized web-based data entry system. The centralized web system will be Redcap and will be administered by GWUH.

19.3. Schedule and Content of Reports

The recruitment and follow-up period will begin in November 2019 and continue through October 2021. Data queries will be generated and resolved during this time period through August 2022. Data close-out will be performed immediately following the end of the recruitment period.

19.4. Study Records Retention

Study records will be maintained for at least 6 years post study closure and per IRB specifications.

19.5. Protocol Deviations

Protocol deviations will be maintained through protocol deviations source documentation that is entered into the centralized databased. Protocol deviations will also be reported directly to study PI within 24 hours.

20. PUBLICATION/DATA SHARING POLICY

This study will ultimately lead to peer-reviewed journal manuscripts and peer-reviewed meeting presentations with a digital archive PubMed Central upon acceptance for publication.

1) Pilot and Feasibility

2) High Quality Photo-documentation with MCC

3) Non-Inferiority Pilot Study of Anatomic Landmarks

4) Non-Inferiority Study of Gastric Lesions

5) Patient Satisfaction Study

6) Cost-effective Analysis

7) Multi-center Pragmatic Patient Centered Outcomes Study (Additional Patients and Sites required)

21. REFERENCES

White CM, Kilgore ML. NaviCam ESO Versus Esophagogastroduodenoscopy (EGD) in Esophageal Variceal Screening: A Decision Analysis. J Clin Gastroenterol. 2009 Aug 5. PubMed PMID: 19661814.

Moglia A, Menciassi A, Dario P, Cuschieri A. Capsule endoscopy: progress update and challenges ahead. Nat Rev Gastroenterol Hepatol. 2009 Jun;6(6):353-62. Review. PubMed PMID: 19434097.

Lapalus MG. Esophageal capsule endoscopy vs. EGD for the evaluation of portal hypertension: a French prospective multicenter comparative study. Am J Gastroenterol. 2009 May;104(5):1112-8.

Seddighzadeh A, Wolf AT, Parasuraman S, Shetty R, Vallurupalli N, Reddy S, Goldhaber SZ. Gastrointestinal complications after 3 months of dual antiplatelet therapy for drug-eluting stents as assessed by wireless capsule endoscopy. Clin Appl Thromb Hemost. 2009 Mar-Apr;15(2):171-6. PubMed PMID: 19117963.

Westerhof J, Koornstra JJ, Weersma RK. Capsule endoscopy: a review from the clinician's perspectives. Minerva Gastroenterol Dietol. 2008 Jun;54(2):189-207. Review. PubMed PMID: 18319691.

Gralnek IM, Adler SN, Yassin K, Koslowsky B, Metzger Y, Eliakim R. Detecting esophageal disease with second-generation capsule endoscopy: initial evaluation of the NaviCam ESO 2. Endoscopy. 2008 Apr; 40(4):275-9. PubMed PMID: 18389444.

Sung J.J.Y., Tang R.S.Y., Ching J.Y.L., Rainer T.H., Lau J.Y.W. Use of capsule endoscopy in the emergency department as a triage of patients with GI bleeding. (2016) Gastrointestinal Endoscopy, 84 (6), pp. 907-913.

Cheifetz AS, Lewis BS. Capsule endoscopy retention: Is it a complication? J Clin Gastroenterol. 2006;40:688-691.

Meltzer AC, Ali MA, Kresiberg RB, et al. Video capsule endoscopy in the emergency department: A prospective study of acute upper gastrointestinal hemorrhage. Ann Emerg Med. 2013.

Tsai MC, Wang CC, Lee HL, et al. Health disparities are associated with gastric cancer mortality-to-incidence ratios in 57 countries. World J Gastroenterol. 2017;23(44):7881–7887. doi:10.3748/wjg.v23.i44.7881

Bennett CE, Samavedam S, Jayaprakash N, Kogan A, Gajic O, Sekiguchi H. When to incorporate point-of-care ultrasound (POCUS) into the initial assessment of acutely ill patients: a pilot crossover study to compare 2 POCUS-assisted simulation protocols. Cardiovasc Ultrasound. 2018;16(1):14. Published 2018 Sep 11. doi:10.1186/s12947-018-0132-0

Barkin JS, Friedman S. Am J Gastroentrol 2002; 97:A83

ASGE. Guidelines for Credentialing and Granting Privileges for Capsule Endoscopy Gastrointest Endosc 2005;61:503-505

Articles on NaviCam MCC

Zhuan Liao et. al.: Feasibility and safety of magnetic-controlled capsule endoscopy system in examination of human stomach: a pilot study in healthy volunteers; J Interv Gastroenterol 2:4, 155-160; October/November/December 2012

Wen-Bin Zou et al; Magnetic-controlled capsule endoscopy vs. gastroscopy for gastric diseases: a two-center self-controlled comparative trial; Endoscopy online, 2015

Yuting Qian et al.; Combination of Five Body Positions Can Effectively Improve the Rate of Gastric Mucosa's Complete Visualization by Applying Magnetic-Guided Capsule Endoscopy; Gastroenterology Research and Practice, Volume 2016

Yanping Tang et al.; The Clinical Utility of Magnetically Controlled Capsule Endoscopy in Pediatric Patients; Gastrointestinal Endoscopy, Volume 83, No. 5S : 2016

Huasheng Lai et al.; Association between patient characteristics and magnetically controlled capsule endoscopy findings; 2018 Saudi journal of Gastroenterology

Shu-Guang Zhua et al.; Gastric preparation for magnetically controlled capsule endoscopy: A prospective, randomized single-blinded controlled trial; Digestive and Liver Disease 50 (2018) 42–47

Yuting Qian et al.; Magnetic-Guided Capsule Endoscopy in the Diagnosis of Gastrointestinal Diseases in Minors; Gastroenterology Research and Practice Volume 2018

Yuan-Chen Wang et al.; Repetitive Position Change Improves Gastric Cleanliness for Magnetically Controlled Capsule Gastroscopy; Digestive Diseases and Sciences, Published online: 17 December 2018

Xue Chen et al.; Screening for Gastric and Small Intestinal Mucosal Injury with Magnetically Controlled Capsule Endoscopy in Asymptomatic Patients Taking Enteric-Coated Aspirin; Gastroenterology Research and Practice Volume 2018

An-Jing Zhao et al.; Screening for gastric cancer with magnetically controlled capsule gastroscopy in asymptomatic individuals; Gastrointestinal Endoscopy, Volume 88, No. 3, 2018

H-L Ching et al.; Robot Magnet-Controlled Upper GI Capsule Endoscopy Using Ankon NaviCam® System First Reported Experience Outside China; Gut 2017;66(Suppl 2):A1–A288

Zhuan Liao, ..., Zhao-Shen Li. Accuracy of Magnetically Controlled Capsule Endoscopy, Compared With Conventional Gastroscopy, in Detection of Gastric Diseases, Clinical Gastroenterology and Hepatology, Volume 14, Issue 9, 2016. Pages 1266-1273.e1

22. APPENDICES

22.1. APPENDIX A: Schedule of Events

2019-2021

- Consensus building, Protocol Development, FDA letter IRB submission (+/- IDE)
- Contract between primary sites GWU MFA and AnX Robotica
- DSMB formation, steering committee convene, central MCC reading team call schedule established for January 2020 to January 2021; hiring of staff
- MCC training and Site Visit by PI and team
- Enrollment kick off
- Monthly Calls for entire team, Status reports
- Target Enrollment Reached, End recruitment DSMB report prepared
- Data Cleaning
- First manuscript Draft Prepared
- Manuscript Submitted (To be discussed: Dissemination plan)

22.2. APPENDIX B – Document List (per request)

Magnet 1: Magnet potential patient form

Magnet 2: Patient eligibility screening

Magnet 3: Patient Data Collection Form

Magnet 4: Anatomic and Lesion Assessment (A)

Magnet 5: Anatomic and Lesion Assessment (B)

Magnet 6: EGD and Lesion Assessment (C)

Magnet 7: Patient Follow-up Call Day 7

Magnet 8: Patient Follow-up Call Day 30

Magnet 9: Patient CRISP Chart Review

Magnet 10: Adverse Event Form/ Serious Event Form

Magnet 11: Protocol Deviation

Magnet 12: Lost to Follow-up