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Study Title: A prospective single blinded, pilot study, comparing a magnetically controlled capsule with or without a tether with conventional upper endoscopy for the diagnosis of patients with upper abdominal symptoms

Document Title: Clinical Study Protocol

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A prospective single blinded, pilot study, comparing a magnetically controlled capsule with or without a tether with conventional upper endoscopy for the diagnosis of patients with upper abdominal symptoms

CLINICAL STUDY PROTOCOL

Protocol Version	04
Date	23 February 2022
Investigational Device	NaviCam UpperGI Capsule
Sponsor	AnX Robotica Corp.
Manufacturer	AnX Robotica Corp. 6010 W Spring Creek Pkwy Plano, TX 75024Phone: 859-801-8517

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 and ICH guidelines

Investigator:

Name: _____

Address: _____

Signature:_____ Date: _____

Sponsor:

Name: _____.

Address: 6010 W Spring Creek Pkwy, Plano, TX 75024

Signature:_____ Date: _____

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ABBREVIATIONS

CRF	Case Report Form
EGD	Esophagogastroduodenoscopy
ICF	Informed Consent Form
ID	Identity
IRB	Institutional Review Board
MCC	Magnetically Controlled Capsule
SAE	Serious Adverse Events
MCC-T	Tethered-MCC
VCE	Video Capsule Endoscopy
WHO	World Health Organization

STUDY SYNOPSIS

Study Title	A prospective single blinded, pilot study, comparing a magnetically controlled capsule with or without a tether (MCC or MCC-T) with conventional upper endoscopy for the diagnosis of patients with upper abdominal symptoms
Device Name	NaviCam Upper GI Capsule FDA approved May 2020
Sponsor	AnX Robotica Corp.
Principal Investigator	David Cave MD PhD
Study Site	University of Massachusetts Medical School; Worcester, MA
Device Indication	The NaviCam Upper GI Capsule (MCC and MCC-T) is intended for visualization of the esophagus and stomach. The system can be used in clinics and/or hospitals.
Study Rationale	<p>In the United States patients commonly undergo esophagogastroduodenoscopy (EGD) for upper abdominal symptoms to try to resolve whether they have gastroesophageal reflux disease or functional dyspepsia, if they are older than the age of 60 with symptoms, or have alarm symptoms such as unexplained weight loss, persistent nausea and vomiting or if they have symptoms that are refractory to acid suppression therapy. Given the increasing burden of digestive disease in the United States, the use of EGD is increasing in volume nationwide. EGD usually requires either conscious sedation or monitored anesthesia sedation, which has put an additional cost burden on the healthcare system. Since MCC or MCC-T does not require sedation, it offers an attractive option for both patients and clinicians alike.</p> <p>The aim of this study is to compare in the same patient the accuracy of the MCC and MCC-T and EGD in patients presenting with upper abdominal symptoms.</p>
Objectives	<p><u>Primary:</u></p> <ol style="list-style-type: none"> 1. To demonstrate the effectiveness of the MCC and MCC-T compared to EGD in identifying lesions in patients presenting with upper abdominal symptoms. 2. To evaluate rates of adverse events and overall safety of MCC and MCC-T as compared to EGD. <p><u>Secondary:</u></p>

	<ol style="list-style-type: none"> 1. To compare rates of complete examination of the foregut by MCC and MCC-T and EGD in patients presenting with upper abdominal symptoms using sets of predetermined still images. 2. To assess patient satisfaction for patients undergoing MCC or MCC-T or EGD.
Study Design	Prospective, single center, tandem study.
Study Duration	<p>Total duration of the study for each patient will be 7-14 days including follow-up 24 hrs. after the final study related procedure.</p> <p>Total anticipated study duration, including data analysis and final report, is estimated to be up to 12 months.</p>
Study Endpoints	<p>Primary</p> <p><u>Effectiveness:</u></p> <p>For both MCC, MCC-T and EGD, rates of diagnosis of clinically relevant pathology in patients with upper abdominal pain will be assessed. Detection of D2 findings (clinically relevant) will be considered positive. Sensitivity, specificity, positive predictive value, and negative predictive values will be calculated for both MCC or MCC-T and EGD. In this study the “gold standard” will be the expert group’s decision regarding the presence of a relevant finding. McNemar’s test will be used to assess for statistically significant differences between the two modalities. Sub-analyses will be performed to compare accuracies of the two modalities based on anatomic region (i.e. esophagus, stomach, duodenum) and across various lesions (i.e. ulcers, gastropathy, esophagitis, etc.).</p> <p><u>Safety:</u> Rate of device or procedure related adverse events during the procedures or in the follow-up period (24 hrs. post procedure).</p> <p>Secondary</p> <p><u>Examination completion:</u> Compare rates of complete examination of the foregut by MCC, MCC-T and EGD in patients presenting with upper abdominal complaints using sets of predetermined still images</p> <p><u>Patient Satisfaction:</u> Assess patient satisfaction for patients undergoing MCC or MCC-T and EGD.</p>
Inclusion Criteria	<ol style="list-style-type: none"> 1. Patient is 18 years up to 75 years 2. Patient is able to provide informed consent

	<ol style="list-style-type: none"> 3. Patient has appropriate indications for EGD including symptoms of, but not limited to upper abdominal pain, acid reflux, heartburn, iron deficiency anemia, weight loss, bloating, belching, nausea, vomiting and atypical chest pain. 4. Patients are COVID-19 negative by PCR testing 1-3 days prior to EGD or fully vaccinated against SARS-CoV-2 (at least two weeks after final dose of authorized or approved vaccine) and completion of a symptom screening questionnaire before participating in the study.
Exclusion Criteria	<ol style="list-style-type: none"> 1. Patient with dysphagia. 2. Patient with previous intestinal surgery. 3. Patient with Crohn's disease or other potential obstructive conditions, unless there is a recent CTE, MRE or patency capsule performed to exclude an obstructive lesion that may retain the capsule. 4. Female patient who is pregnant. 5. Patient with implanted medical device that would be potentially affected by magnets or radiofrequency emissions (e.g., pacemakers, implanted cardiac defibrillators). 6. COVID-19+ or with symptoms consistent with the infection. Fever, new cough, myalgias, and chills
Study Population and Sample Size	Since there is no predicate data in the USA, we plan a pilot study with 100 patients and 10 volunteers to help optimize the use of the MCC and MCC-T

1 RATIONALE FOR CONDUCTING THE INVESTIGATION

Since its introduction in 2001, video capsule endoscopy (VCE) has developed an increasing role in the management of luminal gastrointestinal disease. New guidelines supported by the American College of Gastroenterology and the American Society of Gastrointestinal Endoscopy recommend that VCE be considered the gold standard test for the assessment of most small bowel diseases. Capsules have also been developed to image the esophagus, stomach, and colon and to measure intestinal physiological parameters. Despite these advances, most of these new capsules are still passive devices, meaning that they travel through the gastrointestinal tract propelled by peristalsis. While this

has been successful for the evaluation of the small bowel, detailed examinations of the stomach and proximal duodenum require active control of the device for optimal imaging.

NaviCam is a new magnetically controlled capsule (MCC or MCC-T) that clinicians can control and more closely examine the foregut. The magnetically controlled capsule comes in two versions, either as a free-floating device or with a tether that can retard its progress down the esophagus. It then can be released from the tether to become the free-floating device for examining the stomach and duodenum. The former version has been subject to evaluation and to studies in China, these are detailed in the summary of clinical experience. Unpublished data on 25 patients with tethered device is also described below.

In the United States patients commonly undergo esophagogastroduodenoscopy (EGD) for upper abdominal symptoms to try to resolve whether they have gastroesophageal reflux disease or functional dyspepsia, if they are older than the age of 60 with symptoms, or have alarm symptoms such as unexplained weight loss, persistent nausea and vomiting or if they have symptoms that are refractory to acid suppression therapy. The burden of digestive disease in the United States, is increasing nationwide with a parallel increase in the use of EGD. Given that conventional EGD usually requires either conscious sedation or monitored anesthesia sedation, this has put an additional cost burden on the healthcare system. Since MCC does not require sedation, it offers an attractive option for both patients and clinicians alike.

Early iterations of the MCC were not ideal for examining the esophagus, due to relatively low frame rates. However, the latest version has a tether that allows for maneuvering the device within the esophagus. The tether can then be removed after the MCC has entered the stomach and the MCC can be manipulated by the magnetic field. Alternatively, by moving the magnet to the thorax it has been shown in volunteers that it is possible to slow the magnet down as it traverses the esophagus

The aim of this study is to compare in the same patient the accuracy of the MCC and MCC-T and EGD in US patients presenting with upper abdominal symptoms

2 SUMMARY OF CLINICAL EXPERIENCE

ANKON Medical Technologies, the Chinese company sister of AnX Robotica, sold about 300,000 NaviCam Capsules between 2016 to 2018. Additionally, the NaviCam Controllable System had been the subject of several articles published in scientific journals summarizing the results of clinical studies as well as real-life experience.

The Chinese FDA study was conducted to evaluate the clinical effectiveness of the NaviCam Stomach Capsule (MCC). The primary objective of the study was to compare NaviCam Stomach Capsule procedure with EGD in subjects diagnosed with gastro duodenal lesions.

The study was conducted in two centers in China all patients underwent the NaviCam Stomach Capsule procedure, followed by conventional EGD without sedation. The sensitivity, specificity, positive predictive value, and negative predictive value of detection of gastric focal lesions by MCC

were calculated, using EGD as the gold standard. One hundred subjects were enrolled in the study, but one subject refused to undergo EGD, therefore the statistical analysis was done on 99 subjects.

No adverse events were reported for any of the patients in this study. With respect to performance, the NaviCam Stomach Capsule was found to be equivalent to the EGD gold standard. All capsules were successfully expelled rectally with an average passage time of 76.1 hours.

The primary objective of the second comparative study was to compare a procedure with the MCC with gastroscopy for subjects diagnosed with gastric focal lesions. The study was conducted in 7 centers in China in which all patients underwent an MCC procedure followed by conventional gastroscopy 2 hours later without sedation. The sensitivity, specificity, positive predictive value, and negative predictive value of detection of gastric focal lesions by the MCC were calculated, using gastroscopy as the gold standard. A total of 353 subjects were enrolled in the study, but three subjects refused to undergo gastroscopy, therefore the statistical analysis was done on 350 subjects.

With respect to performance, the MCC was found to be equivalent to conventional gastroscopy in visualizing gastric mucosa. A total of 9 adverse events were reported in 5 (1.4%) of the 350 patients who completed this study. Three patients had abdominal distension and nausea, 1 patient had headache and vomiting, and 1 patient had foreign body sensations. In 4 of these 5 patients, adverse events including abdominal distension, nausea, vomiting, and headache were considered to be related to gastric preparation. All reported symptoms were resolved within 24 hours after ingestion of the capsule. Moreover, because of the noninvasiveness of the MCC procedure, more than 95% of patients preferred the MCC procedure as an initial diagnostic method.

Out of a total of 449 patients, only 5 patients reported mild adverse events which were all resolved within 24 hours. These results indicate that the MCC is safe, and any risks associated with the device and procedure are negligible when compared to the benefits of a minimally invasive procedure.

Additionally, a study utilizing the tether device was conducted in Changhai Hospital on 4 healthy volunteers and 21 patients with suspected esophageal disease. The MCC-T using the tether device was successfully carried out in all 25 participants. No adverse events were observed. Mean overall discomfort score during the procedure was 0.96 (range 0 – 3). NaviCam System diagnoses were in accordance with EGD in all 25 participants. The per-patient sensitivity of the NaviCam for esophageal disease detection was 100 %. The accuracy of the NaviCam for grading esophageal varices and reflux esophagitis were 66.7% and 100 %, respectively. (Unpublished). Additional unpublished data in volunteers has demonstrated that by moving the magnet over the chest with the patient in the prone position the MCC can be slowed down while it transits the esophagus.

On May 22, 2020 the company obtained FDA approval for the MCC device.

3 INVESTIGATIONAL PRODUCT

The NaviCam Capsule Endoscope System with NaviCam Stomach Capsule MCC-T, presented in Figure 1, is a novel endoscopic capsule imaging system intended to obtain images of the stomach. It differs from passive capsule endoscopy systems in that it uses magnetic fields to allow the position of the capsule to be controlled by an operator.



Figure 1: NaviCam Stomach System

The MCC-T includes the following key components:

1. Ingestible capsule for obtaining images
2. Data recorder for logging image data
3. Controller that allows the position of the capsule to be moved in 3D space.
4. Locator for determining the position of the capsule.
5. Tether device which connects to an ingestible capsule and allows for the visualization of the esophagus.

3.1 Capsule

The MCC (Figure 2) is an ingestible imaging device having an outer diameter of 12mm and a total length of 28mm.

The capsule captures images via a CMOS sensor. A clear top cover contains a compact objective lens in front of the CMOS. LEDs and a photoresistor are allocated around the objective lens. It consists of RF transmitter and an antenna for radio transmission. The capsule is powered by two silver oxide batteries.



Figure 2: NaviCam Stomach Capsule

The exterior of the capsule is designed with biocompatible polymer composites, polycarbonate and ethyl cyanoacrylate, which provide adequate tolerance to exposure to digestive juices and external compression. The capsule captures images at a frame rate ranging from 0.5 to 2 fps with a maximum resolution of 480x480 pixels.

3.2 Data Recorder

The NaviCam Data Recorder (Figure 3) is a portable data receiving unit powered by a built-in rechargeable lithium battery, which is placed inside an examination vest (Figure 4) worn by patient during examination. It is used to receive image data wirelessly transmitted from the capsule. The Data Recorder is charged with an included charger when not in use.

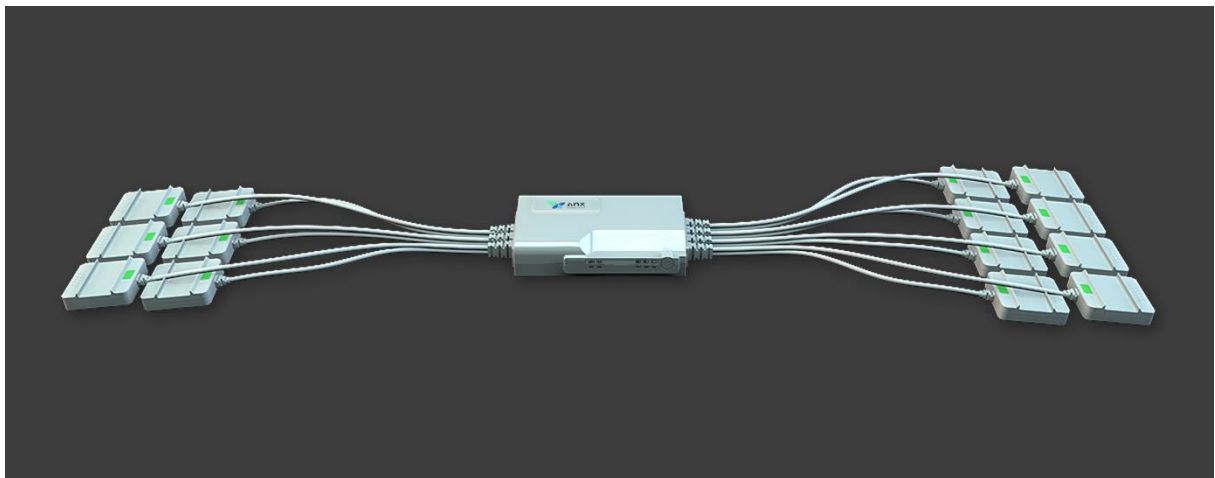


Figure 3: NaviCam Data Recorder



Figure 4: NaviCam Data Recorder in Examination Vest

3.3 Controller

The NaviCam Controller (Figure 5) is comprised of the following core components:

- Console
- Translational rotation platform
- Magnetic ball
- Examination bed



Figure 5: NaviCam Controller

During examination, the patient lies on the examination bed. The translational rotation platform with 5 degrees of freedom adjusts the movement of the magnetic ball to generate a corresponding magnetic field, and thereby to control the movement of capsule inside the patient's body.

The console is composed of a computer workstation installed with ESNavi Software, a monitor and joysticks to manually control the movement of translational rotation platform.

3.4 Locator

The NaviCam Locator (Figure 7) is a portable magnetic scanning device powered by a built-in rechargeable lithium battery. It is used to detect whether the capsule is inside the human body and probe its approximate position. This device negates the need for X-ray imaging.



Figure 7: NaviCam Locator

3.5 Tether

The Capsule Tether is an optional component which allows the visualization of the esophagus. The component is comprised of soft tubing which on one end is attached to a capsule cradle (to hold the capsule in place) and on the other end attaches to a 20ml standard syringe injection of water by the syringe detaches the capsule from the tether. (Figure 8).

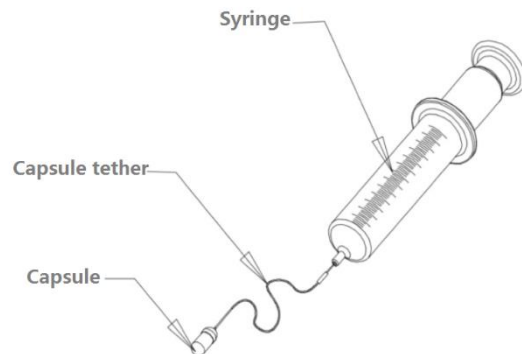


Figure 8: Capsule Tether

4 STUDY OBJECTIVES

4.1 Study Objectives

Primary:

1. To demonstrate the effectiveness of the MCC and MCC-T when compared to EGD in identifying esophageal, gastric and duodenal abnormalities in patients presenting with upper abdominal symptoms.
2. To evaluate rates of adverse events and overall safety of MCC-T as compared to EGD.

Secondary:

1. To compare rates of complete examination of the foregut by MCC, MCC-T and EGD in patients presenting with upper abdominal complaints using sets of predetermined still images
2. To assess patient satisfaction for patients undergoing MCC, MCC-T and EGD.

4.2 Study Endpoints

Primary

Effectiveness:

For both MCC, MCC-T and EGD, rates of diagnosis of clinically relevant pathology in patients with upper abdominal pain will be assessed. Detection of D2 findings will be considered positive. Sensitivity, specificity, positive predictive value, and negative predictive values will be calculated for both MCC and EGD. In this study the “gold standard” will be the expert group’s decision regarding the presence of an abnormal finding. McNemar’s test will be used to assess for statistically significant differences between the two modalities. Sub-analyses will be performed to compare accuracies of the two modalities based on anatomic region (i.e. esophagus, stomach, duodenum) and across various lesions (i.e. ulcers, gastropathy, esophagitis, etc.).

Safety: Rate of device or procedure related adverse events during the procedures or in the follow-up period (24 hrs. post procedure).

Secondary

Examination completion: Compare rates of complete examination of the foregut by MCC or MCC-T and EGD in patients presenting with upper abdominal complaints using sets of predetermined still images

Patient Satisfaction: Assess patient satisfaction for patients undergoing MCC or MCC-T and EGD.

5 INVESTIGATION DESIGN

5.1 Study Design

This study is a prospective, single center, tandem study designed to evaluate the safety and effectiveness of the MCC, MCC-T compared with EGD.

5.2 Patient Population

Approximately 400 patients a month are seen in the UMass Gastroenterology outpatient clinic or are referred for EGD with complaints of upper abdominal pain requiring an upper endoscopy. These patients will be screened for possible inclusion in the study the day prior to their visit to the clinic.

A total of up to 100 patients will be enrolled in the study, including up to 30 healthy volunteer participants for training.

5.3 Study Duration

Total duration of the study for each patient will be 7 days (+7 days) including follow-up 24-72 hrs. after the final study related procedure.

Total anticipated study duration, including data analysis and final report, is estimated to be up to 12 months.

5.4 Inclusion Criteria

The inclusion criteria for this study are:

1. Patient is 18-75 years
2. Patient is able to provide informed consent
3. Patient has appropriate indications for EGD including symptoms of, but not limited to upper abdominal pain, acid reflux, heartburn, iron deficiency anemia, weight loss, bloating, belching, nausea, vomiting and atypical chest pain.
4. Patients are COVID-19 negative by PCR testing 1-3 days prior to MCC/MCC-T and EGD or fully vaccinated against SARS-CoV-2 (at least two weeks after final dose of authorized or approved vaccine) and completion of a symptom screening questionnaire before participating in the study.

5.5 Exclusion Criteria

The exclusion criteria for this study are:

1. Patient with dysphagia.

2. Patient with previous intestinal surgery.
3. Patient with Crohn's disease or other potential obstructive conditions, unless there is a recent CTE, MRE or patency capsule performed to exclude an obstructive lesion that may retain the capsule.
4. Female patient is pregnant.
5. Patient with implanted medical device that would be potentially affected by magnets or radiofrequency emissions (e.g., pacemakers, implanted cardiac defibrillators).
6. COVID-19+ or with symptoms consistent with the infection. Fever, new cough, myalgias, and chills

5.6 Informed Consent

All potential subjects will receive a comprehensive explanation regarding the study and associated procedures. Patients meeting the eligibility criteria will receive a copy of the informed consent form and given sufficient time to determine whether they would like to participate in the study. All patients enrolled in the study must sign and date the informed consent form and receive a copy of the signed form for their records.

5.7 Patient Identification and Confidentiality

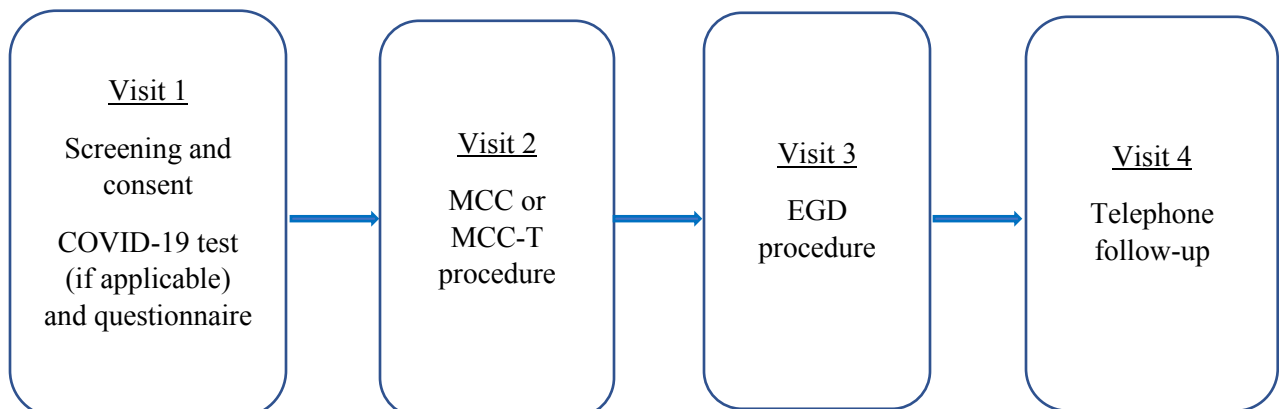
Patients will be identified on all CRFs by a unique study number. CRFs are confidential documents and will only be available to the sponsor, the Investigator, Investigators' staff, the Investigation statistician, and, if requested, to regulatory authorities. The Investigator will maintain as part of the investigation file a list identifying all patients entered into the trial.

5.8 Screening Failure

Patients who have not fulfilled all the inclusion criteria or have fulfilled one of the exclusion criteria will not be included in this study. Screening failures will be replaced by suitable candidates.

6 STUDY PROCEDURES

6.1 Diagram of Study Flow



6.2 Table of Procedure Schedule

Assessment	Pre-screening	Visit 1 Screening Enrollment	Patient data extraction	Visit 2 MCC-T Procedure	Visit 3 EGD	Visit 4 Telephone Follow-up & Termination
Recruitment and Informed Consent review	X	X				
Sign informed consent		X				
PCR for COVID-19 if not fully vaccinated				X*	X*	
Symptom screening for COVID-19		X		X	X	
Inclusion/Exclusion Criteria	X	X				
Demographic & Medical History		X	X			
Physical Examination		X				
Concomitant Medication		X				
Enrollment		X				
MCC procedure		X		X		
EGD procedure					X	
Patient satisfaction/preference questionnaire						X
Adverse events evaluation				X	X	X
Identification of relevant lesions	On a weekly basis					
Exit Form						X

*COVID testing must be completed 24-72 hours prior to the procedure if required. If, due to scheduling, the NaviCam and EGD cannot be scheduled on the same day or the next day, the COVID test may need to be repeated.

All collected parameters and comments will be documented in the CRF.

6.3 Recruitment

Approximately 400 patients a month are seen in the UMass Gastroenterology clinic or are referred for EGD with complaints of upper abdominal pain requiring an upper endoscopy. These patients will be screened for possible inclusion in the study the day prior to their visit to the clinic. This number is subject to change due to the COVID-19 epidemic.

6.4 Visit 1 – Screening and Enrolment

Patients found to be potential study candidate will be flagged and contacted by a study nurse before their visit. The study coordinator will review the study with the patient. If patients show interest in being involved in the study, a visit will be arranged at which consent will be obtained and a PCR and symptom survey will be performed. If negative, a time and date for the MCC and EGD procedures will be arranged.

The MCC or MCC-T will be performed first followed by an EGD at least 2-3 hours later, but up to 7 days later.

A member of study staff will then extract all relevant demographic data from the patients' medical record to the patient CRF. Relevant demographic data includes but is not limited to date of birth, height, weight, gender, race, past medical history, past surgical history, medications and allergies.

6.5 Visit 2 – MCC, MCC-T and EGD Procedure

Upon being checked in, the subject will be brought to the study area with the NaviCam System. A study staff member (NP/Attending/Fellow) trained in the MCC-T procedure will review the study procedure with the patient and confirm that the patient has been NPO for at least 8 hours. The patient will drink about 250ml of water prior to ingesting the capsule containing 1-2 drops of simethicone (infant formulation).

Examination of Esophagus:

The sensor array jacket will be attached to the patient. After the capsule is activated the patient will swallow the capsule (attached to a tether) in the sitting position. It will then be slowly lowered down the esophagus for a complete exam. Alternatively, the patient will be placed in the prone position with a 10° elevation of the head and ingest the capsule without the tether using sips of water. The study staff member will then record the video of the examination of the esophagus by moving the capsule down the esophagus using the magnetic field.

Images to be obtained:

1. Upper esophagus

2. Middle esophagus
3. Lower esophagus
4. Z line.
5. Any pathological lesions

Examination of Stomach:

Once the examination of the esophagus is complete and the capsule is in the stomach, the tether, if used, will be used to view the stomach as the patient drinks about 500 to 1000 cc of water with 4 drop of simethicone to ensure adequate gastric distention. The tether is then detached from the capsule by injecting air through the tether causing separation of the two components. The tether is withdrawn. Then instructed to lay down per physician instructions. The study staff member will begin controlling the device using the magnetic system. The patient will move their position in a predetermined patent to enhance complete visualization of the stomach as was done in the esophagus, a video will be recorded of the full examination. Photo documentation in accordance with a gastric mapping protocol will also be done. This includes images of the following:

- Distal Antrum
- Centered view of the pylorus
- Proximal Antrum
- Two pictures along the length of the incisura
- Distal body
- Mid/proximal body (lesser curvature)
- Mid/Proximal body (greater curvature)
- Gastric fundus
- Gastric cardia
- Any gastric pathology (e.g. gastric varices, gastric ulcers, gastropathy, polyps, etc.)

Examination of duodenum:

Once the final images have been obtained the capsule will be piloted through the pylorus and into the duodenum. Following a brief examination (with photo documentation) of the duodenal bulb the capsule will be released into the small intestine with the video still running. Once the capsule reaches the distal duodenum the video recording can then stop, and the examination is completed.

Recording of MCC procedure:

The responsible study staff member will generate a procedure report documenting his/her findings that will then be cosigned by the study staff attending. This document will be deidentified and only linked to the patient by their study ID number. The document will be placed in the patient's study file along with the video recording of the entire procedure. The patient must be blinded to the findings at this time.

EGD Procedure:

At least two hours after the MCC-T ingestion the subject will be brought to the endoscopy procedure area; study staff will confirm that the patient has been NPO for at least 2 hours after the ingestion of water for the MCC or MCC-T procedure. If practicable, both procedures may be performed on the same day. If not, the EGD will be performed within 7 days and the patient will need to fast overnight prior to the EGD appointment and have nothing by mouth for at least 2 hours prior to arrival (per standard EGD instructions).

The patient will then be sedated using conscious sedation with midazolam and fentanyl or monitored anesthesia with propofol. The upper endoscopy will be performed in the left lateral position. The same photos of the esophagus, stomach, and duodenum will be obtained as described above. The doctor performing the upper endoscopy will not have any knowledge of the findings of the MCC procedure. The patient is then allowed to recover for 30 minutes in the recovery room and discharged.

Image management

Images from the MCC-T procedure will be stored in the Navicam system.

Images of the endoscopic procedure will be stored in Provation and EPIC as per routine.

Images from the MCC, MCC-T and EGD will be printed on photographic paper for comparison by the study team.

6.6 Visit 4 – Telephone Follow-up and Termination

24 hours after all procedures are completed the study coordinator will call the patient and briefly go through a standardized form of questions. Most importantly, the study coordinator will ask the patient which procedure they preferred and would be more agreeable to having done again (Questionnaire provided in Appendix I).

6.7 Identification of relevant lesions

On a weekly basis, 2 study attendings will independently review the results of the EGDs/MCCs that were performed during the week and complete a report sheet. A per-patient analysis of any abnormal lesion/s will be performed. During this analysis, the physicians will be asked if either the MCC or MCC-T or the EGD identified a lesion that would be of high likelihood to explain the patient's symptoms. If a responsible lesion is identified, then the physicians will review both the MCC and EGD to see if the lesion(s) were identified on both exams. Findings will be graded on a three-tier scale as follows:

- **D0:** finding is unlikely to be related to patient's presenting complaint
- **D1:** finding is of a medium likelihood to be related to the patient's presenting complaint
- **D2:** finding is of a high likelihood to be related to the patient's presenting complaint.

In addition, reviewing group will be responsible to perform a per-lesion analysis to assess whether all findings identified on the MCC and/or EGD were seen on the other exam (regardless of whether the finding is relevant to the patient's complaint). The statistician will then compare the results and obtain a Kappa statistic of the three sets of observations. And perform a statistical analysis as outlined under the analysis section.

7 ETHICS

7.1 Regulatory Approval

The study will be conducted in compliance with the Declaration of Helsinki, ISO 14155:2011 standard, and 21 CFR part 812.

An IDE application was made to the FDA for the MCC tethered capsule. We received a nonsignificant risk letter from the FDA. Letter attached. The Navicam system is now FDA approved as of 5-22-2020

7.2 Investigational Review Board (IRB) Approval

The final version of the Clinical Study Protocol with the patient information and consent forms will be submitted by the Investigators to their IRBs prior to the commencement of the study.

7.3 Informed Consent

The Investigator must obtain from the patient or from his/her legal guardian a written informed consent for their inclusion in the study, after explaining its rationale and all details, including aims and objectives of the study, the risks and benefits and the extent of the patient's involvement. All patients must sign and date the informed consent.

The Investigator is responsible for ensuring that no patient is subject to any study-related examination or activity before the patient has given his/her written informed consent. After obtaining signature of the patient, duly signed informed consents will be kept and archived in the Investigator file, according to the requirements provided in 21 CFR 812.

7.4 Changes to Clinical Study Protocol or Related Procedures

Any changes to the clinical protocol or related procedures will be reported to the IRB before they are implemented.

7.5 Deviations from Clinical Study Protocol

Any deviation from the protocol shall be recorded and reported to the IRB and sponsor together with an explanation for the deviation.

Significant deviations defined as compromising or potentially compromising the safety of the patients, enrolment of non-eligible patients and any deviation which compromises significantly the outcome of the study, shall be subject to reporting to FDA and the IRB within the appropriate deadlines indicated by the regulations.

7.6 Patient Compensation

Product liability and No-Fault Clinical Trial Insurance covering the duration of the trial are in place, to enable compensation in the event of an injury to a participating patient.

Patients will be compensated for their inconvenience and travel expenses.

8 PATIENT BENEFIT AND RISKS

A risk management according to ISO 14971, has been conducted and is periodically reviewed. The risk management report is documented in NaviCam Capsule Endoscope System with NaviCam Stomach Capsule Risk Management Report (RM-NCES-ST-02). Risks have been proven minimized or eliminated through appropriate design control, confirmed by pre-clinical bench, laboratory, animal and clinical testing.

The NaviCam Stomach Capsule is MR unsafe. MRI exams should be avoided until capsule passage is confirmed.

Based on the available clinical data previously collected, the following anticipated adverse events may occur:

- Bloating
- Nausea
- Vomiting
- Headache
- Throat irritation
- Transient, two weeks retention of the capsule in the G.I. tract.

The main risk associated with the EGD procedure is perforation. Additionally, reaction to sedation may include:

- Difficulty breathing or an inability to breathe
- Low blood pressure
- Slow heartbeat
- Excessive sweating

Laryngeal spasm

Study Rationale

The safety and effectiveness of the NaviCam Stomach capsule has already been demonstrated via two clinical studies as well as in ongoing use in China and the EU. Basic usability and safety of the tether device was assessed by the company in healthy volunteers. The ability to visualize the esophagus utilizing the tether device may result in a simpler procedure that does not require sedation (when compared to EGD).

This study is designed to evaluate the safety and effectiveness of the NaviCam Stomach Capsule with Tether device for its intended use by comparing the obtained findings with those obtained via standard EGD.

9 ADVERSE EVENTS

9.1 Definition

Adverse Event (AE): Any untoward medical occurrence in a subject whether device related or not.

Serious Adverse Event (SAE): 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

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): Adverse Event caused by or involving the device that has resulted in any of the consequences characteristics of a Serious Adverse Event. A SADE may occur at any time after exposure to the study device.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational

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

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 investigational device use is defined as follows:

Probably related: Follows a reasonable temporal sequence from study device 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.

Occurrence of death, whether or not it is assessed as related to the device, must be well-documented. The information should include the date expired, cause of death, what attempts were made to treat the condition, the performance and functioning of the device prior to the event and causal relationship to the device. If device or procedure relation cannot be ruled out, an autopsy should be encouraged.

9.2 Handling and Reporting of Adverse Events and Device Deficiencies

Patients will be carefully monitored during the study for possible adverse events. Any adverse events observed will be fully investigated by the Investigator. Appropriate treatment, if needed of the patient will be initiated.

The Investigator will attempt to assess the involvement of the investigational procedure in the adverse event. All observations and clinical findings, including the nature, severity, will be documented on the CRF (Adverse Events).

The Investigator will report all serious adverse events to the IRB and sponsor by telephone or e-mail within twenty-four hours.

ANX Robotica will report the results of an evaluation of an unanticipated adverse device effect to FDA and the reviewing IRBs and investigators within 10 working days after the sponsor first receives notice of the adverse effect.

10 DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS

Study will be performed according to the protocol. The investigator will appoint a person that will be responsible to complete the Case Report Forms using the REDCap system, a secure data collection system. Source documentation will be either paper documents or the electronic medical record.

All relevant documents such as MCC images/videos, EGD images/videos, etc. will be uploaded to the EDC. Patient identification will be redacted from all data. Patients will be identified by their patient ID. The list of patient IDs will be kept in the site and will not be available for the sponsor.

The EDC system will provide streamlined communication between the study monitors, data managers and study coordinators. The system will allow the generation of queries which will need to be responded to and resolved by the relevant personnel.

De-identified color images will be used by the reader panel to compare MCC-T and endoscopy images.

10.1 Statistical Methods

All data collected will be summarized and presented. Continuous variables will be described as the mean, median, standard deviation, and range of n observations. Categorical data will be described with contingency tables including frequency and percentage. Individual patient listings of all data will be generated and presented. Sensitivity, specificity positive predictive value and negative predictive value will be calculated using EGD as the gold standard. Comparison between readers will be measured by a Kappa statistic. Statistical tests will be performed at the University of Massachusetts Medical School. Statistical descriptions and analyses will be carried out using STATA version 13.

10.2 Study Populations

The safety population will include all subjects who swallowed the NaviCam Capsule with tether and underwent upper endoscopy. All safety and efficacy analyses will be performed on the safety population.

10.3 Demographic and Baseline Parameters

Demographic and baseline parameters will be summarized. All continuous variables will be summarized by descriptive statistics. All discrete variables will be summarized by frequencies and percentages.

10.4 Safety Analysis

Analysis for the safety endpoint will be descriptive in nature.

AEs will be coded by the MedDRA (version 18.0 or later) system organ class and preferred term. AE data will be listed individually and summarized by system organ class and preferred terms within a system organ class for each indication. In addition, summary of AEs will be presented by severity and relation to study treatment.

Serious adverse events will be similarly summarized.

10.5 Efficacy Analysis

1) Clinical success – Diagnostic yield

For both MCC-T and EGD, we will be assessing rates of diagnosis of clinically relevant pathology in patients with upper abdominal pain. Detection of D2 findings will be considered positive. Sensitivity, specificity, positive predictive value, and negative predictive values will be calculated for both MCC-T and EGD. In this study the “gold standard” will be the expert group’s decision regarding the presence of a relevant finding. McNemar’s test will be used to assess for statistically significant differences between the two modalities. Sub-analyses will be performed to compare accuracies of the two modalities based on anatomic region (i.e. esophagus, stomach, duodenum) and across various lesions (i.e. ulcers, gastropathy, esophagitis, etc.).

2) Secondary Outcomes

Technical success:

- i. We will assess the ability of the -MCC-T and the EGD to photo document the esophagus, stomach, and duodenum as described in this protocol.
- ii. We will assess the ability of the MCC-T to be released upon command in the stomach once esophageal examination is complete.

Learning curves:

When training staff to use the device, we will assess how many capsules it takes to obtain “competency.” This will be defined as being able to obtain the appropriate photo documentation as described above at a 90% success level.

Patient satisfaction

Patient responses will be analyzed on a Likert scale to determine which procedure did the patients prefer.

10.6 Sample Size

Since there is no predicate data in the United States we have elected to do a pilot study involving 70 patients and up to 30 volunteers who will help the investigators optimize the technique with the MCC and MCC-T. We will allocate patients to MCC or MCC-T randomly using a randomization protocol generated by Redcap

10.7 Handling of Missing Data

Missing data will not be imputed. Analysis will be conducted on available data only.

10.8 Monitoring Plan

Monitoring functions shall be performed in compliance with Good Clinical Practice per ISO 14155:2011, and as outlined in 21CFR§821.43(d) and 21CFR§812.46.

ANX Robotica will appoint Clinical Monitors for this study. The Clinical Monitors should be qualified by training and experience to oversee the conduct of the study. The Clinical Monitor's responsibilities include maintaining regular contact with the investigational site, through telephone contact and on-site visits, to ensure that: 1) the study protocol is followed; 2) complete, timely, and accurate data are gathered; 3) problems with inconsistent and incomplete data are addressed; and 4) complications and Unanticipated Adverse Device Effects are reported to the Sponsor.

10.9 Device Accountability

ANX Robotica will provide the site with one NaviCam System as well as capsules and tethered devices sufficient to perform the required number of procedures. The system as well as its various components will be marked "for investigational use" and the investigators are responsible for storing all investigational device components in a secure place to avoid unauthorized use. Immediately upon completion of the study the system and unused items will be returned to ANX Robotica.

11 PUBLICATION POLICY

Any presentation/publication of complete/partial study data by the Investigator or any other party is stipulated by written authorization from the sponsor.

12 ADMINISTRATIVE PROCEDURES OF THE INVESTIGATION

12.1 Audit and Supervision

The investigators, the site and study documentation may be subject to Quality Assurance audits during the course of the study. In addition, inspections may be conducted by regulatory bodies at their discretion, during and after study completion.

12.2 Reporting of Results

The study results will be summarized and presented in the study report according to the ISO 14155 standard and 21 CFR 812.150.

The investigators will be able to publish and/or present the data generated from the study after mutual written agreement between the Investigator and Sponsor.

12.3 Criteria for Removal from the Study

The investigator may withdraw subjects from the study as is deemed necessary or deemed to be in the best interests of the subject, such as,

- continued noncompliance with the protocol or study visits,
- severe illness or disability during the study for non-study issues,
- pursuit of subsequent alternative treatment for the same condition, or
- development of intolerable side effects where continued follow-up becomes too burdensome.

In addition, a subject may also choose to exit the study at any time but will be strongly encouraged to participate in the follow-up telephone call for safety reasons.

13 APPLICABLE DOCUMENTS

1. 21 CFR 812, Investigational Device Exemption
2. ISO 14155:2011, Clinical investigation of medical devices for human subjects -- Good clinical practice
3. FDA guidance “Adaptive Designs for Medical Device Clinical Studies” (July 27, 2016).

14 REFERENCES

1. ZhuanLiao MD, Rui Gao MD, Can Xu MD, Dan-Feng Xu MD, Zhao-Shen Li MD; Sleeve string capsule endoscopy for real-time viewing of the esophagus: a pilot study (with video) *Gastrointestinal Endoscopy*; Volume 70, Issue 2, August 2009, Pages 201-209

2. Francisco C. Ramirez MD Rodney Akins LPN, Masud Shaukat MD. Screening of Barrett's esophagus with string-capsule endoscopy: a prospective blinded study of 100 consecutive patients using histology as the criterion standard. *Gastrointestinal Endoscopy*. Volume 68, Issue 1, July 2008, Pages 25-31
3. Liao, Zhuan, Hou, Xi, Lin-Hu, En-Qiang, Sheng, Jian-Qiu, Ge, Zhi-Zheng, Jiang, Bo, . . . Li, Zhao-Shen. (2016). Accuracy of Magnetically Controlled Capsule Endoscopy, Compared with Conventional Gastroscopy, in Detection of Gastric Diseases. *Clinical Gastroenterology and Hepatology*, 14(9), 1266-1273.e1.

15 APPENDICES

- 1. Appendix I: Patient satisfaction questionnaires**
- 2. Timeline - Appended**
- 3. NSR letter from FDA**

Appendix I: Patient Satisfaction Questionnaires

1. Please tell us on a score of 1 to 10 your preference for the magnetic capsule test or magnet on a string test, with 1 being the least liked and 10 the best:

1	2	3	4	5	6	7	8	9	10
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2. Please tell us on a score of 1 to 10 your preference for the upper endoscope, with 1 being the least liked and 10 the best:

1	2	3	4	5	6	7	8	9	10
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3. Was there anything you particularly liked about the magnetic capsule test or magnetic capsule on a string test: _____

4. Was there anything you particularly disliked about the magnetic capsule test or magnetic capsule on a string test: _____:

5. Was there anything you particularly liked about the upper endoscopy test: _____

6. Was there anything you particularly disliked about the upper endoscopy test: _____

7. Did you have any problems with the magnetic capsule or magnetic capsule on a string test at the time of the test: _____

8. Did you have any problems with the magnetic capsule or magnetic capsule on a string test after the test: _____

9. Did you have any problems with the endoscopy test at the time of the test: _____

10. Did you have any problems with the endoscopy test after the test: _____

Timeline for MCC v EGD Pilot study

