STUDY PROTOCOL

Patient Acceptance and Preference Among Screening Modalities for Detection of Barrett's Esophagus

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UNC SCHOOL OF MEDICINE

PATIENT ACCEPTANCE AND PREFERENCE AMONG SCREENING MODALITIES FOR DETECTION OF BARRETT'S ESOPHAGUS

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PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial 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 U.S. federal regulations and ICH guidelines.

_____
Investigator Name (Printed)

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Investigator Signature Date

0 Protocol Version 3.0 Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Version 4.0	16Jul2021
Version 3.0	04Mar2021
Version 2.0	02Sep2020
Version 1.0	23Sep2019
Version 0.8	19Sep2019

Version 4.0 (16Jul2021)

Overall Rationale for Version 4.0:

This summary includes changes made to Protocol AGA TNE Preference from Version 3.0 (dated 04Mar2021). The purpose of Protocol Version 4.0 is to communicate changes made to the Protocol to revise the inclusion/exclusion criteria. Updates will not impact the safety assessment of administration of Cytosponge or Transnasal Endoscopy (TNE) nor will they alter the risk-benefit ratio for study participants.

The following is a summary of context-oriented changes that were made. Strikethrough text denotes text removed, and bolded text denotes added text. Additional administrative edits were also made but not specifically noted (e.g., corrected spelling, punctuation, grammar, abbreviation, and style errors), including edits required for consistency.

Section	Description of Change	Rationale
Section 1 Protocol Synopsis, Section 6.1 Inclusion Criteria	Amended inclusion criteria to include all eligible patients undergoing upper endoscopy	To increase enrollment by including all eligible patients
Section 1 Protocol Synopsis, Section 6.2 Exclusion Criteria	6. Inability to hold use of anti-coagulation medications or non-aspirin anti-platelet agents (APAs) for the recommended clinically indicated duration ~~Current use of blood thinners, such as warfarin, clopidogrel, heparin and/or low molecular weight heparin (requires discontinuation of medication five (5) days prior to and five (5) days after esophagogastroduodenoscopy [EGD] and Cytosponge administration; aspirin use is OK)~~	To provide clarity. Discontinuation of blood thinners per standard of care is acceptable
Section 1 Protocol Synopsis, Section 6.2 Exclusion Criteria	1. Cohort B only: History of pre-existing esophageal stenosis/stricture , esophageal diverticulum or significant esophageal anatomic abnormalities (masses, obstructive lesions, etc.) **with active symptoms of dysphagia**	To clarify that patients with active symptoms of dysphagia will be excluded
Section 5.1 Study Population	We will recruit adults at least 18 years of age ~~with Barrett's esophagus (BE) or Gastroesophageal Reflux Disease (GERD)~~ who are presenting for routine clinically indicated upper endoscopy (EGD) at UNC presenting for routine outpatient upper endoscopy	To clarify that enrollment includes all eligible patients undergoing upper endoscopy

TABLE OF CONTENTS

1 PROTOCOL SYNOPSIS

Title	Patient Acceptance and Preference Among Screening Modalities for Detection of Barrett's Esophagus
Purpose	To assess patient acceptance and preference among screening modalities, Esophagogastroduodenoscopy (EGD), Transnasal Endoscopy (TNE), and Cytosponge for Barrett's esophagus (BE).
Population	Patients with Barrett's esophagus or gastroesophageal reflux disease (GERD).
Design	Single-center, prospective, single arm, non-randomized study
Sample Size	40 patients
Primary Outcome	To assess acceptability of the three modalities: traditional upper endoscopy, TNE and Cytosponge.
Secondary Outcomes	Patient preference and willingness to perform procedure again.
Inclusion Criteria	1. At least 18 years of age at time of consent 2. Able and willing to provide written informed consent 3. Able and willing to comply with required study procedures and follow-up schedule 4. Presenting to UNC Hospitals for outpatient routine care upper endoscopy
Exclusion Criteria	1. Cohort B only: History of pre-existing esophageal stenosis/ stricture, esophageal diverticulum or significant esophageal anatomic abnormalities (masses, obstructive lesions, etc.) with active symptoms of dysphagia 2. History of head and neck malignancy or anatomical abnormalities of the nasopharynx 3. Any history of Ear, Nose and Throat (ENT) surgery within three (3) months before the screening visit. Past medical history of ENT surgery altering the anatomy of the nasopharynx is exclusionary 4. History of significant epistaxis or hereditary hemorrhagic telangiectasia (HHT) 5. Sinus or pulmonary infection in the last 4 weeks 6. Inability to hold use of anti-coagulation medications or non-aspirin anti-platelet agents (APAs) for the recommended clinically indicated duration 7. Known bleeding disorder 8. Pregnancy, or planned pregnancy during the course of the study 9. Any history of esophageal varices, liver impairment of moderate or worse severity (Child's- Pugh class B & C) or evidence of varices noted on any past endoscopy 10. Any history of esophageal surgery, except for fundoplication 11. History of coagulopathy, with international normalized ratio (INR)>1.3 and/or platelet count of <75,000 12. General poor health, multiple co-morbidities placing the patient at risk, or otherwise unsuitable for trial participation

	13. Subject has any condition that, in the opinion of the investigator or sponsor, would interfere with accurate interpretation of the study objectives or preclude participation in the trial
Study Summary	Potential subjects will be identified via protocol and Institutional Review Board (IRB) methods prior to obtaining written informed consent. Once written informed consent is obtained and baseline demographic and medical history is collected, subjects will undergo administration of Cytosponge and Transnasal Endoscopy (TNE) prior to their scheduled clinically indicated upper endoscopy performed per routine standard of care. Following the procedure, a follow-up phone call will be made during which an impact of events scale related to the subjective distress of each procedure, a preference and acceptance questionnaire, and adverse events related to study participation will be collected.
Funder	American Gastroenterological Association Research Scholar Award
Principal Investigator	Swathi Eluri, MD, MSCR
Co-Investigator	Nicholas J. Shaheen, MD, MPH
NCT Number	NCT04301986

2 BACKGROUND AND JUSTIFICATION

The incidence of esophageal adenocarcinoma (EAC) is increasing in the western world. In 2017, it is estimated that there will be 16,940 new cases of esophageal cancer in the US and an estimated 15,690 people will die of this disease.[1] Survival outcomes in EAC are dramatically improved with early stage diagnosis.[2, 3] However, only 8% of EAC cases annually are diagnosed through current methods of cancer prevention (Figure 1),[4] indicating that high-risk patients are ineffectively screened. We know that gastroenterologists (GI) are highly likely to perform EGD in symptomatic or chronic GERD patients[5] with one study[6] showing trigger for EGD in 51/100 GERD episodes by GI compared to 6/100 by primary care providers (PCP), indicating that understanding and optimizing screening practices at the patient or primary care level is critical to improve EAC detection.

One strategy for early detection of EAC is identification of Barrett's esophagus (BE), a known precancerous lesion of EAC with a long latent stage, in high-risk GERD patients. BE with dysplasia can be effectively eradicated with endotherapy to prevent progression,[7,8] which can improve EAC outcomes and associated mortality.[9] Currently, nearly 70% of patients with BE go undiagnosed.[10] Considering that 3-6% of the approximately 87 million people with GERD in the US are estimated to have BE,[11,12] it is a significant public health concern, and represents an unexploited opportunity to stem the remarkable rise in deaths from EAC.

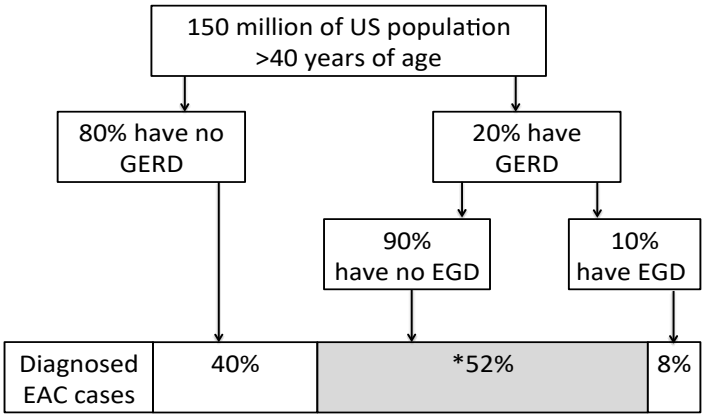

Figure 1: Proportion of EAC cases diagnosed annually in the US

We know that 60% of EACs occur in GERD patients over the age of 40 in the United States,[4] and as a result it makes sense to target this group for BE and EAC screening. Screening for BE/EAC is currently done by sedated upper endoscopy with endoscopic and histologic assessment. Most recent guidelines[13] recommend screening in men with more than 5 years of GERD or more than weekly symptoms, who have at least two other risk factors. Risk factors include age >50, Caucasian race, central obesity, smoking history, and family history of BE or EAC in first-degree relative. Additive risk factors appear to increase the risk of developing BE and EAC. For example, an obese, white, male, smoker with GERD, has more than three times the relative risk of developing EAC compared to a white male with GERD.[14]

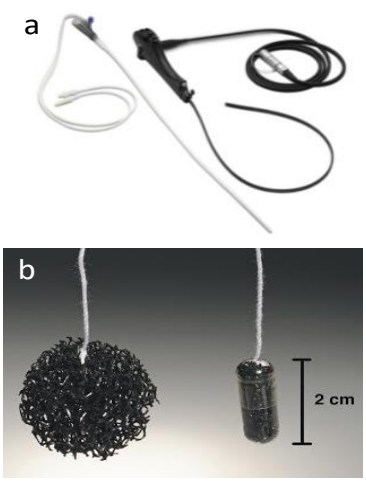

Figure 2: (a) Transnasal Endoscopy (b) Cytosponge

However, since a large proportion of the population has GERD, it is neither practical nor cost-effective to screen everyone with GERD with traditional upper endoscopy. Therefore, risk-stratification tools[18] and alternate screening methods to EGD with both endoscopic and non-endoscopic approaches have been explored (Figure 2). Of the endoscopic approaches, Transnasal Endoscopy (TNE) is as sensitive as EGD for BE diagnosis, well tolerated, and less expensive.[15-18] TNE uses a small caliber scope that is inserted into the nares after application of local anesthetic, and can be performed without sedation. Of the non-endoscopic screening techniques, the most studied is an ingestible sponge attached to a string, Cytosponge. Cytosponge is a minimally invasive, sponge-based technique for sampling the esophageal mucosa. It is an abrasive sponge encapsulated in a gelatin coating, which is attached to a string. After ingestion, the capsule dissolves upon exposure to gastric secretions. It is then withdrawn through the hiatus and distal esophagus and out of the mouth by the string, sampling cardiac and esophageal epithelium. The resulting sample is immunostained for markers, which have been sensitive and specific for the presence of BE. Cytosponge has also been shown to have good acceptability and tolerance by patients.[19,20]

These alternate screening modalities, while demonstrated to be effective, have not been implemented in clinical practice. There are prior studies comparing the clinical effectiveness and patient acceptability measures between EGD and TNE,[21,22] and more recently EGD and Cytosponge.[19] To date, however, no study has simultaneously evaluated all three available modalities. Given that we have more available screening tools, it is vital to understand patient acceptability in utilizing these new modalities. Therefore, the goal of the study is to compare patient acceptance and preference between three screening modalities for BE: traditional upper endoscopy (EGD), Transnasal Endoscopy (TNE), and Cytosponge.

3 STUDY AIMS

3.1 Primary Objective

The primary objective is to assess patient acceptance of each screening modality (Cytosponge, TNE, and EGD) using Impact of Events (IES)[23] score evaluated at approximately seven (7) days post-EGD.

3.2 Secondary Objective

The secondary objectives are:

Secondary objective 1: Assess patient comfort pertaining to each screening modality (Cytosponge, TNE, and EGD) using VAS acceptability score at baseline.

Secondary objective 2: Assess willingness to repeat each screening modality (Y, N) evaluated ~7 days post-EGD.

Secondary objective 3: Determine ranking of preferred screening modality (1,2,3) evaluated ~7 days post-EGD.

Secondary objective 4: Identify factors that influence preference rankings or preferred choices among the 3 methods.

4 SCHEDULE OF EVENTS

Study Period	Screening[2]	Follow-Up
Visit Title	**Baseline Visit[2]**	**~7 Days Post-Endoscopy**
Informed Consent	x	
Inclusion/Exclusion Criteria	x	
Pregnancy Test	x[3]	
Medical History	x	
Demographics	x	
Endoscopy *(per SOC guidelines)*	x	
Cytosponge Administration	x[1]	
Transnasal Endoscopy Administration	x	
Procedure Preference and Acceptability Questionnaire		x
Visual Analog Scale (VAS)	x	
Impact of Events Scale (IES)		x
Enrollment Case Report Form (eCRF)	x	
Adverse Event Assessment	x	x

[1] Subjects who have previously undergone Cytosponge as a part of the UNC IRB study #13-2618 will not repeat Cytosponge.

[2] Screening and baseline visits can occur on the same day or on separate days.

[3] Performed on females with reproductive potential. The urine pregnancy test does not need to be repeated if already performed as part of routine care during the visit.

5 SAMPLE SIZE

To satisfy enrollment for the primary objectives, it is estimated approximately 40 subjects will need to be enrolled into the study (please refer to section 9.1 for additional details pertaining to sample size determination).

5.1 Study Population

We will recruit adults at least 18 years of age who are presenting for routine clinically indicated upper endoscopy (EGD) at UNC. Since the primary objective is to compare patient acceptance and preference between EGD, Cytosponge, and TNE, patients will have to undergo all three procedures. The ideal study design would have subjects undergo all three procedures the same day. However, this could potentially be cumbersome to the patients. To have Cytosponge testing prior to EGD, patients need to present at their EGD appointment more than 2 hours ahead of time. This is because Cytosponge administration requires patients drinking sips of water to swallow the Cytosponge. Following this, patients must wait at least 2 hours prior to undergoing sedated EGD per standard NPO guidelines. Therefore, in an attempt to decrease individual patient burden, we primarily plan to recruit patients from a prior study conducted by our group (*IRB #13-2618) who have already undergone Cytosponge and EGD testing and are returning to have a clinically indicated EGD.* A significant proportion of these patients, given that they have a history of BE, will undergo routine EGD for BE surveillance. *Patients recruited through this pathway (Cohort A)* will be approached to only undergo TNE right before their clinically indicated EGD.

If we have difficulty recruiting patients through this path, we will plan to recruit subjects who are presenting for a clinically indicated routine endoscopy and recruit them to undergo Cytosponge and TNE prior to their EGD (Cohort B).

Cohort A: Participants from IRB# 13-2618

- Subjects will undergo: TNE, clinically indicated EGD

Cohort B: Cytosponge-naïve

- Subjects will undergo all procedures: Cytosponge, TNE, clinically indicated EGD

After administration, follow-up procedures for both cohorts are the same. Since subjects from Cohort A have already undergone Cytosponge, data from those administrations will be used for VAS, IES, and adaptability of Cytosponge procedures.

6 ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

1. At least 18 years of age at time of consent
2. Able and willing to provide written informed consent
3. Able and willing to comply with required study procedures and follow-up schedule
4. Presenting to UNC Hospitals for routine care upper endoscopy

6.2 Exclusion Criteria

1. For Cohort B only: History of pre-existing esophageal stenosis/ stricture, esophageal diverticulum or significant esophageal anatomic abnormalities (masses, obstructive lesions, etc.) with active symptoms of dysphagia
2. History of head and neck malignancy or anatomical abnormalities of the nasopharynx

3. Any history of Ear, Nose and Throat (ENT) surgery within three (3) months before the screening visit. Past medical history of ENT surgery altering the anatomy of the nasopharynx is exclusionary
4. History of significant epistaxis or hereditary hemorrhagic telangiectasia (HHT)
5. Sinus or pulmonary infection in the last 4 weeks
6. Inability to hold use of anti-coagulation medications or non-aspirin anti-platelet agents (APAs) for the recommended clinically indicated duration
7. Known bleeding disorder
8. Pregnancy, or planned pregnancy during the course of the study
9. Any history of esophageal varices, liver impairment of moderate or worse severity (Child's-Pugh class B & C) or evidence of varices noted on any past endoscopy
10. Any history of esophageal surgery, except for fundoplication
11. History of coagulopathy, with international normalized ratio (INR)>1.3 and/or platelet count of <75,000
12. General poor health, multiple co-morbidities placing the patient at risk, or otherwise unsuitable for trial participation
13. Subject has any condition that, in the opinion of the investigator or sponsor, would interfere with accurate interpretation of the study objectives or preclude participation in the trial

7 STUDY PROCEDURES

All procedures will be documented on study-specific electronic case report forms that are provided in addition to this protocol. Refer to Schedule of Events in section 4 for a summary of study procedures.

7.1 Screening and Recruitment

Patients will be screened for potential eligibility according to UNC IRB approved screening methods. Potential subjects will be approached prior to routine care endoscopy by research staff to explain the study and obtain informed consent.

Since the study population involves recruitment from the population who would be receiving EGD clinically as part of SOC, this will be the main recruitment strategy. This can include prescreening the clinic and procedure schedule for potential subjects, and referrals from UNC providers (PCP or GI).

An investigator, study coordinator, or other qualified personnel will obtain written informed consent prior to any study procedures. Potential subjects will have an opportunity to carefully review the consent form. The details of the study will be reviewed verbally, and all questions will be answered to the satisfaction of the patient. Only adults with the ability to provide consent will be eligible for enrollment in this study. After the subject signs the consent, a copy of the signed consent will be provided to the subject. Once written consent has been obtained, the coordinator will collect demographic and medical history. The consent process will be documented by the coordinator in the patient's study file.

7.2 Written Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks will be provided to the participant and written documentation of informed consent is required prior to performing any

study procedures. In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) (e.g., 45 CFR Part 46) and should adhere to International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before any study procedures are performed, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by federal regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The informed consent process will be documented by the study team. A copy of the signed and dated informed consent form will be retained by the study team and a copy of the signed and dated informed consent will be provided to the subject.

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

7.3 Baseline Visit

Potential subjects who agree to participate and provide written informed consent will be enrolled. Eligibility will be based on the inclusion and exclusion criteria.

The following will be completed during the screening/enrollment visit:

- Eligibility review
- Informed consent
- Cohort A: TNE administration only if subjects are participants of previous Cytosponge study (UNC IRB # 13-2618)
  OR
  Cohort B: Cytosponge followed by TNE administration
- Routine care upper endoscopy with biopsy
- Visual Analogue Scale (VAS) to measure pain
- Adverse event assessment
- Enrollment Case Report Form (eCRF): This captures demographics including race, ethnicity, gender, and year of birth, relevant medical history including documentation of endoscopic procedures received to date as well as pathology findings and endoscopic history related to current diagnosis. It will also capture date of TNE and Cytosponge administration and associated exam findings.

7.3.1 Cytosponge Administration

The Cytosponge will be supplied by Medtronic. The Cytosponge lifetime/use by date will be confirmed on the product packaging. The device received FDA 510(k) clearance on November 26, 2014 (K142695). The Cytosponge device consists of a spherical 3.0 cm diameter reticulated polyester foam compressed and encapsulated in a standard vegetarian capsule (size 00). An investigator, study coordinator, or other trained and qualified personnel will perform the Cytosponge administration and retrieval. Our clinical staff

will be members of the Center for Esophageal Diseases and Swallowing (CEDAS) and are all well versed in the administration and collection of the Cytosponge, due to previous studies our group has conducted *(15-0332; 13-2618).*

Subjects will undergo administration of the Cytosponge according to the IFU. Briefly, subjects will be placed in the seated position and will swallow the capsule with 150 – 250 mL of water. Additional water may be used if necessary. The sponge is attached to a length of suture material which passes out through the capsule. The suture is affixed to a retainer card, which is held by the subject or administrator to prevent inadvertent swallowing of the suture. The string is to be held without tension as peristalsis and gravity advance the capsule into the stomach.

The capsule dissolves in the stomach, allowing the sponge to expand to its full size. Seven minutes and 30 seconds to ten minutes after ingestion, the sponge is then withdrawn by gentle traction on the suture, collecting cells from the lining of the esophagus in passing. After retrieval, the string is cut and the retrieved foam sphere containing the cytological specimen is immersed in fixative and stored refrigerated (1° to 12°C [34° to 54°F]).

If a subject fails to swallow the Cytosponge, the subject will be asked to swallow again. Subjects who are willing to try again will be asked to wait 5 minutes before the Cytosponge is presented to them again. Subjects will be able to try up to three times before they are classified as “Cytosponge swallowing failure”. Subjects who are unable to swallow the Cytosponge will continue to participate in the remainder of the study.

7.3.2 TNE Administration

Prior to the scheduled upper endoscopy, Transnasal Endoscopy will be performed using the neonatal (ultrathin) endoscope (Olympus America Inc). The TNE will be performed by qualified trained investigator or sub-investigators. While it would be ideal to have one provider perform all cases, in an effort to be cognizant of the patient’s time and clinical workflow demands in the endoscopy units, it would be impractical to have the same operator perform all cases. Prior to the procedure, a combination of a topical decongestant (oxymetazoline hydrochloride, 0.05%, Afrin, Schering-Plough Healthcare Products, Inc., Memphis, Tennessee) and topical anesthesia with 4% lidocaine, or another topical anesthetic based on the discretion of the physician performing the procedure, will be used to anesthetize the nares and posterior pharynx. The exam will be performed with the participant in the upright position. The posterior pharynx, esophagus and proximal stomach will be examined with the Transnasal Endoscopy approach. No biopsies will be obtained. The scope will be withdrawn from the nares following completion of the exam.

7.3.3 Clinically Indicated Routine Care Endoscopy

After examination with both Cytosponge and TNE is completed, subjects will undergo routine care upper endoscopy, with assessment of BE or GERD, and biopsy per accepted surveillance or screening recommendations. Routine care tissue biopsies will undergo standard processing and H&E staining at the home institution, with assessment by expert gastrointestinal pathologists.

7.3.4 Visual Analog Scale

Acceptability outcomes will include a Visual Analogue Scale (VAS) of acceptability of the Cytosponge, TNE, and EGD. Also, the subject will be asked whether he/she would be willing to repeat the assay, and,

assuming similar accuracy between modalities, whether he/she would rather undergo surveillance by Cytosponge, TNE, or standard EGD with biopsies.

7.4 Follow-Up Phone Call

Subjects will be contacted approximately seven (7) days after successful administration of the device via phone or other IRB approved method. The following data will be collected from subjects during the follow-up phone call:

- Impact of Events Scale (IES)
    - Cohort A: IES for EGD and TNE only (IES data has been previously collected for Cytosponge in the prior study)
    - Cohort B: IES for EGD, TNE, and Cytosponge
- Procedure Preference and Acceptability Questionnaire
- Adverse event assessment
- Follow-Up Case Report Form (eCRF): This captures relevant information for questionnaire completion and assessment of adverse events.

7.4.1 Impact of Events Scale

The Impact of Events Scale (IES) will be completed with the subject during the follow-up phone call and measures subjective distress related to the administered procedures. Primary assessment of acceptability will be via the Impact of Events Scale. This widely used scale was developed to assess the distress associated with a specific life event. It includes measures of both the intrusiveness of the event, and any avoidance responses by the subject in response to the event. IES has been used to measure acceptability of Cytosponge in prior studies.[25,26] *In addition the previous study referenced here UNC IRB #13-2618, used the IES instrument and therefore we have utilized the same instrument in this protocol so the data is comparable.*

For Cohort A subjects, we plan to use existing IES data pertaining to Cytosponge which was collected seven (7) days after Cytosponge administration in the prior study. Since a period of time has passed since the patients in Cohort A underwent Cytosponge, using the already collected data will help minimize recall bias. Therefore, Cohort A subjects will only have IES collected for TNE procedure and EGD during this current proposed study.

7.4.2 Procedure Preference and Acceptability Questionnaire

The procedure preference and acceptability questionnaire will be completed with the subject during the follow-up phone call. This assessment collects subject preference for the Cytosponge vs. traditional upper endoscopy vs. TNE, as well as willingness to undergo the procedure again.

7.5 Study Exit

Study participation is complete when the participant has completed the follow-up phone call.

8 RISK AND BENEFIT ASSESSMENT

8.1 Assessment of Safety

All endoscopies and standard of care biopsies referenced in this protocol are consistent with current standard of care, so subjects would be receiving these endoscopies regardless of participation in the study. Therefore, risks related to endoscopy procedures should be reviewed as part of the subject's

clinical care. However, subjects should be reminded of endoscopy risks as part of the consent process for the study. The endoscopy is a well-established procedure with a very low rate of complications. Subjects may experience mild discomfort due to gagging while the tube is passed down the throat. Subjects may also experience mild sore throat, chest pain or discomfort, abdominal pain, or discomfort, or painful or difficult swallowing following the procedure. Medicines may ease these problems. Rare risks from an endoscopy include bleeding and infection. There is a very small risk (about 3 in 10,000) of esophageal perforation that could require surgery to repair and a similarly small risk (8 in 10,000) of aspiration that could cause pneumonia. If clinical biopsies are taken, there is a very small risk of perforation or significant bleeding that would require a blood transfusion or other measures to stop the bleeding. Subjects could also have an adverse reaction to the anesthetic or medication used. These reactions may require treatment. There may be inflammation of the vein through which medication is given. If subjects have asthma, they may have an increased risk for problems with the anesthesia. An adverse reaction to the medications used for the endoscopy can include difficulty breathing, respiratory depression, hypotension, bradycardia, excessive sweating, spasms in the larynx, or an allergic reaction, such as hives and itching or anaphylaxis. These risks are indicative of the procedure itself and are not added risk of participating in the study.

The Seattle biopsy protocol is used for standard of care (SOC) which includes taking four (4) quadrant biopsies every one to two centimeters throughout the area of interest.

Serious risk of endoscopic biopsies is very uncommon in subjects without bleeding disorders and in those who do not regularly take blood thinning medications (such as aspirin, nonsteroidal anti-inflammatory medications, Coumadin (warfarin), Plavix, Lovenox, heparin, and low molecular weight heparin). This is because the biopsies are very small (2-3 mm) and are obtained with blunt tipped forceps under direct vision of the doctor performing the endoscopy. Possible serious complications include excess bleeding from the biopsy sites causing the blood pressure to drop and/or the need for blood transfusion or esophageal perforation (tear) due to trauma. More common, but not serious, is minor bleeding which requires no treatment or responds to treatment with oral antacids. The risk of bleeding secondary to endoscopic biopsies is less than 1/1,000 and there is an even smaller risk of perforation or infection. When bleeding does occur, adequate medical staff and equipment are on hand to abate any long-term damage that could result from this risk. These participants will often already be undergoing biopsies as part of their standard of care, so the incremental risk is expected to be minimal. These risks are indicative of the procedure itself and are not added risk of participating in the study.

Cytosponge risks: There are several risks associated with the administration of the Cytosponge. These include risk of bleeding or aspiration. In addition, discomfort from either the string when the device is in the stomach, or when the sponge is retracted from the body, or mild soreness or irritation in the throat following the procedure which is common in patients receiving an endoscopy, but the Cytosponge may also cause soreness or irritation in the throat.

To date there have been >1,000 administrations and detachment of the sponge from the string has occurred in less than 1% of cases. Detachment of the sponge from the string could block the intestines. Should the sponge detach from the string, it will be retrieved during the routine care upper endoscopy immediately following administration.

To reduce the likelihood of these risks, Cytosponge administration will occur after an overnight fast, to minimize the possibility of aspiration of any gastric contents. Patients' throats may be sprayed with a numbing agent prior to administration of the sponge to minimize discomfort from the procedure. Every

administered sponge will be assessed post-procedure for signs of fracture or incomplete retrieval of the sponge, and in the unlikely case such incomplete retrieval occurs, the sponge will be retrieved during the routine care endoscopy which is scheduled to immediately follow administration of the sponge. If any potential bleeding is noted due to administration of the sponge, this will also be investigated, and, as necessary, treated during the routine upper endoscopy.

Transnasal Endoscopy (TNE) potential risks share the same risks as a conventional endoscopy (reported above). These include nasal discomfort; gagging (mild); discomfort during insertion; aspiration (drawing matter into the lungs along with the breath); bleeding; epistaxis (nosebleed); sinus infection; choking; nausea; retching or vomiting; anxiety; severe pain. A rare risk includes esophageal perforation (occurring in <0.1% of people, or less than 1 out of 10,000 people) which could possibly require surgery to repair.

The equipment for small-caliber endoscopy is FDA approved, and all study procedures will be carried out with trained and/or licensed qualified staff. In the case of procedural complications, the participating investigators will refer the patient for the appropriate care.

8.2 Patient Confidentiality

There is a risk that subjects' confidential medical information could be compromised because of participation in this study. Precautions will be taken to protect confidential information including assigning each subject a unique identifier for study records and restricting access to research records. In addition, study case report forms (CRFs) will collect minimal protected health information.

There may be uncommon or previously unknown risks. Study participants should be instructed to report any problems to the study team for additional reporting per protocol.

8.3 Minimization of Risk

All efforts will be made to minimize risk to subjects who participate in this clinical study.

- Investigators participating in this study are licensed, experienced, and skilled in endoscopic procedures at their institution.
- Treatment and follow-up are consistent with current medical practice.
- Patients will be closely monitored during the procedure and at regularly scheduled intervals for the duration of the study.
- The protocol clearly defines eligibility criteria to ensure that only the appropriate patients are enrolled.
- Investigators agree to maintain the highest level of confidentiality, including conducting appropriate training for site staff prior to study initiation.

8.4 Potential Benefits

It is not expected for participants to benefit directly from participating in this study. Subjects will receive standard of care (SOC) treatment regardless of study participation. There is, however, the potential for researchers and patients to benefit in the future as a direct result of what is learned from this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Plan & Sample Size Calculation

The acceptability of each screening modality will be assessed with the Impact of Events Scale (IES) scores, and the intrusiveness and avoidance subscales. We plan to recruit 40 subjects for the study.

Since the same subject will undergo treatment with each of the screening modalities, we anticipate that the scores generated will be correlated. We assume each pair of scores will have the same correlation. For the planned analysis, each IES score will be classified as low or high. High score will be defined as total IES score >38.[25] A low score will be defined as a total IES score less than or equal to 38.

To compute power, for each of the three devices we specified the proportion of high scores as well as the correlation between observations within a subject. Estimating that 1% of the subjects undergoing sedated EGD group, 5% of those undergoing Cytosponge,[25] and 20% of those undergoing TNE will experience a high IES score, using a correlation of 0.3, and a sample size of 40, we specified a trivariate Binomial distribution. Random data were generated from such a distribution and Fishers Exact Test was computed from the data. This was done 10,000 times. The percentage of the 10,000 trials in which the Fishers Exact Test p-value was less than 0.05 provided our power estimate of 80% for a sample size of 40.

We will compare the median IES score for each modality using Kruskal-Wallis testing as well comparing the proportion of subjects with high IES scores for each modality using Pearson's chi-square testing. For the secondary objectives:
- **Secondary objective 1:** Median VAS score will be compared between the three modalities using Kruskal-Wallis testing
- **Secondary objective 2:** The proportion of subjects willing to repeat each test will be computed.
- **Secondary objective 3:** Subjects' preferred screening modality ranked highest will be measured as proportions. The proportion of the highest ranked screening modality will be computed.
- **Secondary objective 4:** Bivariate and multinomial logistic regression analyses will be used to identify factors such as patient discomfort, sex, and EGD indication influencing screening preference among the three modalities.

Since we are recruiting patients from two separate pathways (described in Section 5.1), we plan to account for the differences by analyzing the two groups separately as well as the entire cohort as a whole to see if there is a statistically significant difference in results between the groups. In addition, we acknowledge that the results may be affected by carryover effect for subjects recruited via Pathway 1, but recruiting via this strategy makes this study feasible, and we will acknowledge this as one of the limitations.

All hypothesis tests that are deemed to be not statistically significant will be reported as being inconclusive.

All statistical estimates of population parameters will be tabulated along with corresponding standard errors, or confidence intervals (CI) to convey levels of precision and imprecision.

10 STUDY MANAGEMENT

10.1 Institutional Review Board (IRB) Approval

IRB approval will be obtained prior to subject recruitment and enrollment. Research staff are responsible for maintaining IRB approval throughout the duration of the study, including submission of continuing review and modifications when appropriate per local IRB reporting requirements. In addition, research staff must ensure timely submission of any protocol amendments and obtain IRB approval prior to implementation of protocol amendments.

10.2 Required Documentation

Before the study can be initiated, the following documentation must be placed on file.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study
- Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol

10.3 Data Management

The study principal investigator and study team will be responsible for study conduct and analysis. The study monitor will be responsible for source data verification.

10.4 Data Collection

Data collection is the responsibility of the study personnel at the site under the supervision of the principal investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of study visit worksheets may be used as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. If source documentation is maintained in an electronic medical record, then electronic source is allowable if the system is 21 CFR 11 compliant, and access is provided to the monitor for clinical monitoring.
Study data (including adverse events, AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by UNC Chapel Hill. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data will be entered directly from the source documents. Missing data will be noted in the database and the study team will provide reasons for missing data.

10.5 Adherence to the Protocol

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

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations in a timely manner after identification of the protocol deviation, or prior to the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the reviewing Institutional Review Board (IRB) per their policies. The principal investigator is responsible for knowing and adhering to the reviewing IRB requirements.

Any deviations from the protocol identified will be documented on case report forms.

10.6 Noncompliance

Noncompliance is defined by the UNC IRB as intentional or unintentional failure to follow applicable federal regulations, the requirements or determinations of the IRB, the IRB-approved study protocol, or University policies. Noncompliance can occur as a result of performing an act(s) that violate(s) requirements. Noncompliance can also occur as a result of failing to act when required.

10.7 Unanticipated Problems Involving Risks to Subjects or Others

10.7.1 Definition

As defined by UNC's IRB, unanticipated problems involving risks to study subjects or others (UPIRSO) refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

10.7.2 Reporting

Any UPIRSO that occurs during the conduct of this study and that meets the criteria must be reported to the UNC IRB using the IRB's web-based reporting system.

10.8 Definition of Adverse Events (AE)

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

10.9 Adverse Event Assessment

A member of the study team will be present during all in-person visits during which Cytosponge, TNE and EGD will be administered to monitor safety and adverse event assessment. Participants will be assessed for adverse events during all in-person visits. All documented AEs will be addressed and followed until resolution and their resolution documented in the participant's research record. Local IRB guidelines for reporting adverse events will be followed. Only those AEs that meet UNC IRB criteria for reporting will be reported to the UNC IRB.

10.10 Severity of Event

For adverse events (AEs) the following guidelines will be used to describe severity.

- **Grade 1 (Mild)** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Grade 2 (Moderate)** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Grade 3 (Severe)** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."
- **Grade 4 (Life-Threatening)** – Life-Threatening consequences; urgent intervention indicated.
- **Grade 5 (Death)** – Death related to AE.

10.11 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect. Only those events that are definitely related or possibly related to participation in this research study will be reported.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Possibly Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. "Possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research. Reasonable possibility means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures.
- **Somewhat Likely to be Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events), so there is a <50% likelihood that the event is related to the research procedures. Although an AE may rate only as "somewhat likely to be related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "possibly related" or "definitely related", as appropriate.
- **Unlikely to be Related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

10.12 Expectedness

The investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

10.13 Unexpected Adverse Event

An unexpected adverse event is defined by the UNC IRB as any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Only those events that are definitely related or possibly related to participation in this research study will be reported. All AEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study device (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

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

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

All new or worsening adverse events (AEs) will be collected for all subjects from the time of subject enrollment through study completion or termination of the clinical investigation.

10.14.1 Serious Adverse Event (SAE)

An SAE is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;

- Results in a persistent or significant disability/incapacity;

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event, which must be reported as an important medical event.

*Hospitalization for anticipated or standard of care specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

10.14.2 Adverse Event Documentation and Reporting

Research staff will maintain records of all adverse events and report them in a timely manner via completion of the Adverse Event Case Report Form. The form should be updated with any changes including updates to severity, relatedness, and resolution. Adverse events will be reported to the UNC IRB per UNC IRB reporting requirements.

Events will be described using the NCI Common Terminology Criteria for Adverse Events (CTCAE).

10.15 Amending the Protocol

Should amendments to the protocol be required, amendments will be originated and documented by the Principal Investigator at UNC. Changes only go into effect after it has been approved by appropriate regulatory IRB. Non-significant changes that do not impact subject safety or scientific integrity of the study may be communicated via protocol clarification memo in lieu of a formal amended protocol.

10.16 Privacy and Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their institutions. This confidentiality is extended to cover testing and storage of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, biological specimens and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

All research activities will be conducted in as private a setting as possible.

Authorized representatives of UNC Chapel Hill, representatives of the Institutional Review Board (IRB), regulatory agencies, or funding sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and other applicable study records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the University of North Carolina at Chapel Hill. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the University of North Carolina at Chapel Hill will be secured and password protected. At the end of the study, all study databases will be coded and archived at the University of North Carolina at Chapel Hill. Study participant identifiers will be documented in a master list; the master list will be maintained securely by the site investigators and kept separate from the research data.

10.17 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Council for Harmonisation (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.18 Criteria for Terminating the Study

The principal Investigator reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of subjects. Appropriate authorities including study funder and the IRB will be notified in writing in the event of termination.

10.19 Investigator Responsibilities and Compliance

The Principal Investigator is responsible for the conduct of the study at the site in accordance with ethical principles originating from the Declaration of Helsinki. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data

This study will be conducted in full accordance all applicable UNC Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the HIPAA Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance UNC IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

10.20 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the IRB-approved protocol.

10.21 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB approval/favorable opinion.

For any such emergency modification implemented, this occurrence will be reported to a UNC's IRB as required by current UNC IRB reporting procedures.

11 PUBLICATION

Authorship of publications will abide by the criteria established by the International Committee of Medical Journal Editors: Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (August 2013). Procedural details including rights of review and timing will be governed by the terms listed and agreed to by both parties in a separate clinical research agreement.

12 ASSESSMENTS

12.1 Visual Analog Scale (VAS)

Date:

☐☐☐☐-☐☐☐-☐☐

(YYYY-MMM-DD)

Please place an “X” on the line below to indicate the worst pain you felt with administration of the [Cytosponge/Transnasal Endoscopic Procedure (TNE)/Traditional Upper Endoscopy (EGD)].

No Pain ——————————————————— **Worst pain imaginable**

Internal Use Only:

VAS score: ☐☐☐mm

Verified by:

12.2 Procedure Preference and Acceptability Questionnaire

1. On a scale of 0-10, please rate your experience with the Cytosponge procedure:

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

| | |
Unacceptable, very difficult even | Tolerable as a necessary medical test | Not an issue, would take for a medical test without hesitation

2. On a scale of 0-10, please rate your experience with the transnasal endoscopic procedure (TNE):

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

| | |
Unacceptable, very difficult even | Tolerable as a necessary medical test | Not an issue, would take for a medical test without hesitation

3. On a scale of 0-10, please rate your experience with the traditional upper endoscopic procedure (EGD):

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

| | |
Unacceptable, very difficult even | Tolerable as a necessary medical test | Not an issue, would take for a medical test without hesitation

4. Would you be willing to repeat the Cytosponge procedure if your physician indicated it was medically necessary? ☐ Yes ☐ No

5. Would you be willing to repeat the transnasal procedure (TNE) if your physician indicated it was medically necessary? ☐ Yes ☐ No

6. Would you be willing to repeat the traditional upper endoscopic procedure (EGD) if your physician indicated it was medically necessary? ☐ Yes ☐ No

7. Which procedure would you prefer to undergo again if your physician indicated it was medically necessary? ☐ Traditional Upper Endoscopy (EGD) ☐ Cytosponge ☐ Transnasal Endoscopy (TNE)

8. What factors, if any, influenced your decision (select all that apply)?
☐ Discomfort/Pain ☐ Time (needed for preparation) ☐ Cost ☐ Need for Sedation
☐ Other; Describe: _____

12.3 Impact of Events Scale (IES)

Below is a list of comments made by people in connection with their [Cytosponge/TNE/EGD] screening test. Please check each item, indicating how frequently these comments were true for you during the **past seven (7) days**. If they did not occur during that time, please mark the 'not at all' column.

	Not at all	Rarely	Sometimes	Often
I thought about it when I did not mean to.				
I avoided letting myself get upset when I thought about it or was reminded of it.				
I tried to remove it from my memory.				
I had trouble falling asleep or staying asleep, because of pictures or thoughts about it that came into my mind.				
I had waves of strong feelings about it.				
I had dreams about it.				
I stayed away from reminders of it.				
I felt as if it wasn't happening to me, or wasn't real.				
I tried not to talk about it.				
Pictures about it popped into my mind.				
Other things kept making me think about it.				
I was aware that I still had a lot of feelings about it, but I didn't deal with them.				
I tried not to think about it.				
Any reminder brought back feelings about it.				

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14 ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of variance
BE	Barrett's Esophagus
Bx	Biopsy
CFR	Code of Federal Regulations
CRF	Case Report Form
Cyto	Cytosponge
EAC	Esophageal Adenocarcinoma
eCRF	Electronic Case Report Form
EGD	Esophagogastroduodenoscopy
EMR	Endoscopic Mucosal Resection
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction
GERD	Gastroesophageal Reflux disease
GI	Gastroenterologists
H&E	Hematoxylin and Eosin
ICH	International Council for Harmonisation
IES	Impact of Events Scale
IMC	Intramucosal Cancer
INR	International Normalized Ratio
IRB	Institutional Review Board
NBI	Narrow Band Imaging
NCT	National Clinical Trial Number
PCP	Primary Care Provider
SAE	Serious Adverse Event
SOC	Standard of Care
TGF	Top of Gastric Folds
TNE	Transnasal Endoscopy
Tx	Treatment
UNC	The University of North Carolina at Chapel Hill
UPIRSO	Unanticipated Problem Involving Risk to Subjects or Others
VAS	Visual Analogue Scale