Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	ASSESSMENT OF A MINIMALLY INVASIVE ESOPHAGEAL CYTOLOGY COLLECTION SYSTEM IN PATIENTS WITH BARRETT'S ESOPHAGUS OR GERD SYMPTOMS (CASE II)
Clinical Investigation Plan Identifier	COVB2710467
Study Product Name	Cytosponge™ Cell Collection Device
Sponsor/Local Sponsor	Medtronic MITG RGI Gastrointestinal & Hepatology 540 Oakmead Parkway, Sunnyvale, CA 94085 [redacted]
Document Version	G, 01-DEC-2017
Lead Principal Investigator(s)	Nicholas J. Shaheen, MD, MPH Professor of Medicine and Epidemiology Chief, Division of Gastroenterology & Hepatology University of North Carolina School of Medicine Chapel Hill, NC

1. Investigator Statement

Study product Name	Cytosponge™ Cell Collection Device
Sponsor	Medtronic MITG RGI Gastrointestinal & Hepatology 540 Oakmead Parkway, Sunnyvale, CA 94085 [redacted]
Clinical Investigation Plan Identifier	COVB2710467
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I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with International Conference on Harmonization Guidelines on Good Clinical Practice, ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects-GCP), United States Food and Drug Administration regulations, and any regional or national regulations, as appropriate. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Term	Definition
AE	Adverse event
BE	Barrett's esophagus
C1	One circumferential centimeter of BE
eCRF	Electronic case report form
EAC	Esophageal adenocarcinoma
GERD	Gastroesophageal reflux disease
H&E	Hematoxylin and eosin
HGD	High-grade dysplasia
HIPAA	Health Insurance Portability and Accountability
IRB	Institutional review board
LGD	Low-grade dysplasia
M3	A total BE segment length of at least three centimeters
MedDRA	Medical dictionary for regulatory activities
PDT	Photodynamic therapy
PHI	Protected health information
RFA	Radiofrequency ablation
TFF3	Trefoil factor 3
VAS	Visual analog scale

3. Synopsis

Title	ASSESSMENT OF A MINIMALLY INVASIVE ESOPHAGEAL CYTOLOGY COLLECTION SYSTEM IN PATIENTS WITH BARRETT'S ESOPHAGUS OR GERD SYMPTOMS (CASE II)
Clinical Study Type	U.S. Pilot Study
Product Name	Cytosponge™ Cell Collection Device
Sponsor	Medtronic MITG RGI Gastrointestinal & Hepatology 540 Oakmead Parkway, Sunnyvale, CA 94085 [redacted]
Indication under investigation	Post-market approval
Investigation Purpose	To assess the utility of the Cytosponge device as a non-endoscopic method for collecting surface cells from the esophagus in patients with BE and GERD
Product Status	510(k) clearance
Primary Objective(s)	• To assess the acceptability of a novel, minimally invasive esophageal mucosal sampling technique, the Cytosponge 1) in subjects undergoing surveillance of BE who have had at least a C1 or M3 segment confirmed (or medically suspected), and 2) in subjects with GERD undergoing screening for BE Patients who are undergoing ablative therapy on the day of Cytosponge testing will have their acceptability data analyzed separately. Based on previous data, we hypothesize that the sponge-based sampling technique will be associated with low levels of subject distress, and will be preferred by subjects, when compared to standard sedated upper endoscopy, for surveillance of their esophageal mucosa. *1)* To assess the adequacy of cytology samples obtained by Cytosponge in this population after 1 sampling, or after 2 samplings if first sample is inadequate. Based on previous data, we hypothesize that the Cytosponge will harvest adequate amounts of esophageal cells to perform centrifugation, pelleting, sectioning and staining for trefoil factor 3, a reliable biomarker of intestinal metaplasia.
Secondary Objective(s)	1) To assess the operating characteristics of this technique against a gold standard of upper endoscopy with biopsies for endoscopic surveillance in subjects with BE who demonstrate an adequate sample on Cytosponge assessment.

	2) To assess the operating characteristics of Cytosponge against the worst ever histology documented in the subject. Patients who are undergoing ablative therapy on the day of Cytosponge testing must have biopsies within 2 months prior to surgery. *Because Cytosponge provides a "field" sampling of esophageal tissue, it may provide a more comprehensive assessment of minute fields of dysplasia. If this is so, the Cytosponge may avoid sampling error associated with random clinical samples as currently performed.* 3) To assess the operating characteristics of Cytosponge on the basis of baseline histology. *To date, no data is available regarding the accuracy of Cytosponge in subjects with BE and more advanced disease (low-grade dysplasia and high-grade dysplasia). These subjects are at greatest risk for progression to cancer. We plan to collect pilot data on operating characteristics of the assay by degree of baseline dysplasia. We hypothesize that Cytosponge will perform with similar operating characteristics in this group compared to non-dysplastic BE.* 4) To assess the degree of mucosal abrasion following Cytosponge administration, using a standardized scale. *Based on previous data, we hypothesize that mucosal damage due to abrasion by the Cytosponge will be minor. Further, the distal extent of the abrasion will correlate with the presence of columnar cells in the sample.* 5) To collect and analyze safety measures of Cytosponge use in the target population. *The Cytosponge has been found to be safe and well-tolerated when administered in a primary care setting. We will continue collecting safety data as part of this project. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).*
Study Design	Multicenter, cross-sectional clinical trial
Sample Size	Up to 275 subjects with an enrollment ratio of at least ≥50% BE and ≥25% GERD
Inclusion/Exclusion Criteria	Inclusion Criteria: 1) Male or female subjects, age 18 and above. 2) Able to read, comprehend, and complete the consent form. 3) Clinically fit for an endoscopy.

	4) a) Previous confirmed diagnosis of Barrett's esophagus with intestinal metaplasia, and Prague classification of at least one circumferential centimeter of BE or a total BE segment length of at least 3 centimeters (C1+ or CXM3+) (BE arm) . OR b) If the subject does not have documented Prague Classification prior to screening, but the PI is convinced that the subject will meet the inclusion criteria based on previous documentation (for instance, mention of "long-segment BE," they may enroll the subject in the study at their discretion. The study upper endoscopy must confirm that the subject has C1+ or CXM3+ (BE arm). If (C1+ or CXM3+) is not observed at the time of study endoscopy, the subject may still be enrolled but not included in the data analysis with the BE cohort. The data may be analyzed in a separate cohort. OR c) Self-reported heartburn or regurgitation on at least a monthly basis for at least 6 months (GERD arm). Exclusion Criteria: 1) Individuals with a diagnosis of an oropharynx, esophageal or gastro-esophageal tumor, or symptoms of dysphagia. 2) Any history of esophageal varices, stricture, or prior dilation of the esophagus. 3) Current use of anti-thrombotics (anti-coagulants and anti-platelet drugs) that cannot be safely discontinued for the appropriate drug-specific interval in the peri-administration period. Depending on the particular agent or reason for the anti-thrombotic therapy, it may not be necessary to discontinue anti-thrombotic agents. There could be circumstances where the drug may not need to be discontinued if the risk of bleeding is considered negligible (e.g. daily aspirin therapy). Physicians should use their clinical judgement and should consult guidelines such as those provided by the ASGE. 4) Known bleeding disorder. 5) Individuals who have had a myocardial infarction or any cardiac event < 6 months prior to enrollment. 6) Individuals who have had a cerebrovascular event < 6 months prior to enrollment in which swallowing was affected. 7) Prior ablative or resection therapy of the esophagus including radiofrequency ablation (RFA), photodynamic therapy (PDT), spray cryotherapy, endoscopic mucosal resection, and other ablation therapies. 8) Any history of esophageal surgery, except for uncomplicated

	fundoplication. 9) Do not need upper endoscopy as part of patient management. 10) Pregnancy
Study Procedures and Assessments	This is a cross-sectional study of subjects with Barrett's esophagus (BE) to assess the utility of the Cytosponge device as a non-endoscopic method for collecting surface cells from the esophagus. This study will enroll 2 groups of subjects: 1) Subjects presenting for routine endoscopic BE surveillance examinations or planned ablation 2) Subjects with gastroesophageal reflux disease (GERD) symptoms undergoing upper endoscopy for screening for BE. After informed consent, and on the same day as the endoscopic procedure, the subject will undergo administration of the Cytosponge device and complete a questionnaire and a visual analog pain scale (VASThe subject will then undergo routine upper endoscopy, with assessment of BE (where applicable), and routine care biopsies will be taken per accepted surveillance or screening recommendations by performing physician. Photographs of the distal esophagus are encouraged to be taken. For subjects presenting for GERD, a single set of 4 quadrant biopsies (4 pieces of tissue total) of the gastric cardia (TGF+1) will be collected during the endoscopy procedure. The Cytosponge will be placed in fixative and shipped to an accredited pathology laboratory for embedding in paraffin and hematoxylin and eosin (H&E) staining to assess the adequacy of the specimen. Further evaluation of the specimen will be performed using trefoil factor 3 (TFF3). If the Cytosponge tissue specimen is inadequate, the subject will be recalled for a repeat sponge procedure. All study-specific gastric cardia biopsies, as well as any routine care tissue biopsies will undergo standard processing and H&E staining at the home institution, with assessment by gastrointestinal pathologists. Subjects will be contacted via phone 7 days (+/-3 days) after Cytosponge administration to complete additional questionnaire and assess adverse events.
Safety Assessments	Adverse events will be reported by number, severity, and relationship to the study procedures and devices. The Medical Monitor will adjudicate all serious adverse events, unanticipated adverse device effects, and events determined by the reporting investigators to be related to the device (possible, probable, definite and unable to be determined).

Statistics	For the first primary objective, to assess the acceptability of the Cytosponge in subjects with BE, we will assess the distribution of Impact of Event Scale scores, and the intrusiveness and avoidance subscales. We will generate measures of central tendency and distribution of these data. Bivariate analysis will be performed to assess predictors of low tolerance of Cytosponge surveillance, and a logistic regression model will be created to assess these factors while controlling for potential confounders. Data will be compared to population norms in published literature[1] using parametric statistics. Visual analog scale (VAS) scores will be calculated, and measures of central tendency and distribution reported. Subjects' preferences for Cytosponge versus endoscopic surveillance, as well as willingness to undergo the procedure again, will be measured as proportions, with bivariate and multivariate analyses for predictors of preference performed. Subjects who undergo same day ablative therapy will Impact of Event Scale scores evaluated separately. For the second primary objective, to assess the adequacy of samples, sample adequacy will be treated as a dichotomous variable. For purposes of this investigation, an adequate sample will be one in which at least 1 columnar cell is present. Sample adequacy will be presented as a proportion of subjects who fulfill this definition after up to 2 total administrations of the Cytosponge, as noted in the methods. For the first three secondary objectives, to assess the operating characteristics of Cytosponge against various gold standards, initially 2x2 tables will be constructed demonstrating Cytosponge and the gold standard findings (Y/N for BE). Both endoscopic evidence of BE of C1 or CXM3 or greater length and pathological confirmation of specialized IM (intestinal metaplasia with goblet cells) will be used in the final diagnosis of BE. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy will be calculated. Because Cytosponge positivity may vary based on the burden of BE, we will perform sensitivity analyses, defining "positive" cases as those with BE of ≥2 cm in length, and then ≥3 cm in length, to assess impact of disease burden on operating characteristics. Multivariate models controlling for age, sex, burden of disease, and other potential confounders will be constructed, to assess the impact of these factors

	on test accuracy. Although we do not expect to see an association between the degree of dysplasia and Cytosponge positivity, exploratory analyses will be performed using degree of dysplasia as a predictor variable, and Cytosponge positivity as the outcome variable. For the fourth secondary objective, to assess the degree of mucosal abrasion following Cytosponge, endoscopic abrasion scores will be correlated with the presence of columnar cells on the H&E slide made from the Cytosponge samples. To assess safety (fifth secondary objective), the number and percentage of subjects with adverse events related to Cytosponge administration will be summarized by MedDRA system organ class and preferred term overall, and by severity.

4. Introduction

4.1. Background

Barrett's esophagus (BE) is a premalignant condition associated with the development of esophageal adenocarcinoma (EAC). BE is the replacement of the normal (squamous) lining of the lower esophagus with a glandular lining which more closely resembles the intestine. BE is a relatively common condition, affecting 1-2% of the general adult population. In the majority of such patients, the condition will be indolent and EAC will not develop. However, in <5% of these patients, BE will progress to EAC. Progression to BE is thought to occur through worsening degrees of dysplasia: from no dysplasia, to low-grade dysplasia (LGD), to high-grade dysplasia (HGD), to EAC. The prognosis of EAC is dismal, with a five-year survival <15%. For that reason, endoscopic surveillance is suggested in patients with BE to monitor development and progression of dysplasia.

Traditional screening and surveillance endoscopy is not optimal due to cost issues, inter-observer variability in histology interpretation, and biopsy sampling error. In addition, surveillance endoscopies expose the patient to recurrent risks associated with sedation and upper endoscopy, the inconvenience of these exams, as well as the associated financial burden.

Cytosponge is a minimally invasive, sponge-based technique for sampling the esophageal mucosa. [redacted]

[redacted]

This is a comparative effectiveness study to assess the utility of the Cytosponge in endoscopic surveillance or treatment of patients with BE, as well as screening of patients with gastroesophageal reflux disease (GERD) symptoms. The central hypothesis of this study is that this novel surveillance tool could supplant upper endoscopy in patients with BE, providing less invasive and more cost-effective surveillance of this large and growing patient population.

4.2. Purpose

EAC is a lethal cancer with a rapidly increasing incidence. In stark contrast to recent progress in treating other solid tumors, incidence and death rates from EAC continue to rise rapidly in the U.S. There has been a 500% increase in the incidence of EAC from the 1970s to the 1990s,[3] and a near-parallel increase in mortality (**Figure 1**), underscoring the need for more effective prevention and treatment for this lethal cancer. Esophageal adenocarcinoma is thought to develop through a series of metaplastic, then dysplastic, changes of the mucosa.[4] GERD precipitates a metaplastic change from the normal squamous epithelium, to a more acid-resistant columnar histology.[5] When this columnar epithelium contains goblet cells, it is termed specialized or intestinalized metaplasia. When endoscopically evident, columnar metaplasia with goblet cells in the esophagus is termed BE.

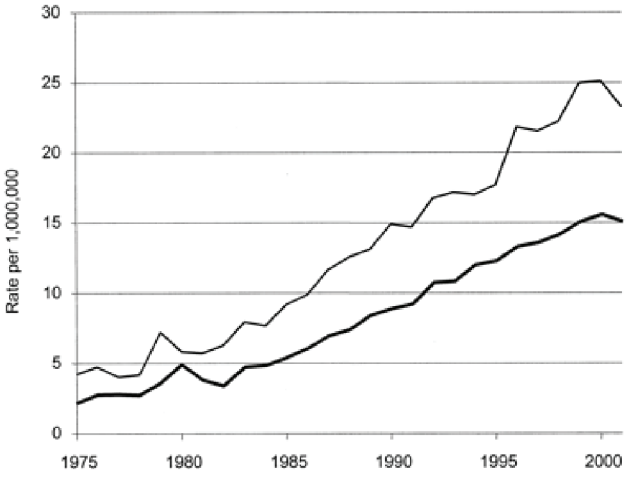

Figure 1 Incidence (top curve) and associated mortality (lower) of EAC[25]

BE is the strongest risk factor for EAC. BE is associated with a risk of EAC that is 40-120 times that of the general population.[8,9] Furthermore, BE is an extremely common condition, present in approximately 10% of patients with chronic GERD[10] and in 1-2% of the general population.[11] Since 10-20% of adult Americans have at least weekly symptoms of GERD,[12,13] the number of cases of BE in the U.S. is thought to be >2 million. BE does not generally spontaneously regress; barring an intervention, the patient will have BE for life. Most patients harboring BE will not progress to EAC. However, in a proportion (0.2-0.5%/year,)[14] the metaplastic tissue will progress from LGD to HGD, culminating in EAC.[15,16] Given the poor prognosis of cancer diagnosed symptomatically,[17,18] current effort is directed toward early detection and treatment. Current strategies for prevention of EAC focus on endoscopic screening and surveillance.[19] In the approach most commonly used in the U.S., patients with chronic heartburn are

offered a screening endoscopy to assess for BE. Patients found to have BE are then enrolled in endoscopic surveillance, consisting of periodic endoscopy at intervals governed by the presence of dysplasia.[6] In current American College of Gastroenterology guidelines,[6] patients with nondysplastic BE should undergo endoscopic surveillance no more frequently than every 3–5 years. Patients with BE and LGD are to undergo endoscopic eradication therapy, or, as an alternative, have surveillance endoscopy yearly. Patients with BE and HGD are effectively managed with endoscopic therapy.[20]. Endoscopic exams for GERD and BE are common and costly, with over 330,000 exams/year in Medicare patients alone,[21] and an average total cost in ambulatory care centers of >$2,000/exam, making for $660M in endoscopy costs in the Medicare population alone annually.[22]

A novel non-endoscopic technique as a potential surveillance tool for patients with BE. Given the large number of patients with chronic GERD and BE, and the expense and inconvenience of endoscopic examinations for BE, investigators have sought less expensive, non-endoscopic modalities of assessing patients for BE. Early attempts using a non-endoscopic balloon demonstrated inadequate sensitivity, in part due to inadequate cytological samples.23

Figure 2 Cytosponge™ (left) and Cytosponge I (right) for comparison

Medtronic Gastrointestinal and Hepatology (formerly Medtronic GI Solutions), has developed a more refined version of the Cytosponge I (referred hereafter as the CytospongeTM or “Cytosponge”). The Cytosponge was developed from the Cytosponge I specification and design, with the additional priority of a more reproducible manufacturing process, standardization of dimensions, and other quality related features (Figure 2). Because we seek to assess a tool for widespread clinical usage, this study will use the Cytosponge provided by Medtronic GIH Solutions.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The following 2 primary objectives will be assessed:

1. To assess the acceptability of a novel, minimally invasive esophageal mucosal sampling technique, the Cytosponge, in subjects undergoing surveillance of BE who have had at least a C1 or M3 segment confirmed, and 2) in subjects with GERD undergoing screening for BE. Based on previous data, we hypothesize that the sponge-based sampling technique will be associated with low levels of subject distress, and will be preferred by subjects, when compared to standard sedated upper endoscopy, for surveillance of their esophageal mucosa.

2. To assess the adequacy of cytology samples obtained by Cytosponge in this population after 1 sampling, and after 2 samplings if first sample inadequate. Based on previous data, we hypothesize that the Cytosponge will harvest adequate amounts of esophageal cells to perform centrifugation, pelleting, sectioning and staining for TFF3, a reliable biomarker of intestinal metaplasia.

5.1.2. Secondary Objective(s)

The following 5 secondary objectives will be assessed:

- To assess the operating characteristics of this technique against a gold standard of upper endoscopy with biopsies for endoscopic surveillance in subjects with BE who demonstrate an adequate sample on Cytosponge assessment.

- To assess the operating characteristics of Cytosponge against the worst ever histology documented in the subject. Because Cytosponge provides a “field” sampling of esophageal tissue, it may provide a more comprehensive assessment of minute fields of dysplasia. If this is so, the Cytosponge may avoid sampling error associated with random clinical samples as currently performed. Patients who are undergoing ablative therapy on the day of Cytosponge testing must have biopsies within 2 months prior to treatment.

- To assess the operating characteristics of Cytosponge as a function of baseline histology. To date, no data are available regarding the yield of Cytosponge in subjects with BE and more advanced disease (low-grade dysplasia and high-grade dysplasia). These subjects are at greatest risk for progression to cancer. We plan to collect pilot data on operating characteristics of the assay by degree of baseline dysplasia. We hypothesize that Cytosponge will perform with similar operating characteristics in this group compared to non-dysplastic BE.

- To assess the degree of mucosal abrasion following Cytosponge administration, using a standardized scale. Based on previous data, we hypothesize that mucosal damage due to abrasion by the Cytosponge will be minor. Further, the distal extent of the abrasion will correlate with the presence of columnar cells in the sample.

- To collect and analyze ongoing safety measures of Cytosponge use in the target population. The Cytosponge has been found to be safe and well-tolerated when administered in a primary care setting. We will continue collecting safety data as part of this project. All AEs will be coded using MedDRA.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint variables will be acceptability of the Cytosponge as demonstrated on the Impact of Event Scale, a visual analog scale, as well as the subject's willingness to undergo repeat Cytosponge administration if it were offered to him/her. Additionally, we will assess the adequacy of the sample, as defined above.

5.2.2 Secondary Endpoint(s)

Secondary endpoints include the sensitivity, specificity, positive predictive value and negative predictive value of Cytosponge both overall, and stratified by baseline histology and length of BE. The presence of BE will be defined as per ACG guidelines, with histology interpreted by the home institution. Additional secondary outcomes include degree of mucosal abrasion and safety data.

6. Study Design

This is a cross-sectional study of subjects with BE to assess the utility of the Cytosponge device as a non-endoscopic method for sampling surface cells from the esophagus. Patients presenting for routine endoscopic BE surveillance examinations, planned ablation or examinations investigating chronic GERD symptoms will be offered enrollment in the study. After informed consent, and on the same day as the planned standard of care endoscopic procedure, the subject will undergo administration of the

Cytosponge device and then complete questionnaires. The subject will then undergo standard of care upper endoscopy with or without biopsy. The biopsy protocol will be performed according to accepted recommendations. For subjects presenting for GERD, a single set of 4 quadrant biopsies (4 pieces of tissue total) of the gastric cardia (TGF+1) will be collected during the endoscopy procedure. If for some reason a biopsy is not taken, the subject will still count toward enrollment and their data will be used in the final data set. It is encouraged for Investigators to take photos of the gastroesophageal junction (GEJ) during the endoscopy procedure.

The Cytosponge will be placed in fixative and shipped to an accredited pathology laboratory for processing [redacted] will provide results on each sample. Cardia biopsies and routine care tissue biopsies will undergo standard processing and hematoxylin and eosin (H&E) staining at the home institutions, with assessment by expert pathologists. Subjects will be contacted via phone 7 days (+/-3days) after Cytosponge administration to complete an additional questionnaire and assess adverse events. For quality assurance, Cytosponge samples may be sent to the [redacted] to be processed and read, as needed to optimize training at the central lab. These results will be compared to those reported by [redacted]. If the results are conflicting, [redacted] training may be revisited and consensus read will be used.

If the initial administration of the Cytosponge demonstrates an inadequate sample, defined as a sample that does not demonstrate at least one columnar cell on H&E staining, repeat Cytosponge administration will be performed.

Subject recruitment will be from consecutive eligible patients presenting for surveillance endoscopy for BE or planned ablative or upper endoscopy for investigation of chronic GERD symptoms, either medicated or un-medicated with acid-suppressive therapy. Potentially eligible patients will be contacted by telephone in advance of their procedure and their interest in study participation assessed. Patients interested in participating will be asked to present to the endoscopy unit at least two hours (may vary by site) prior to their scheduled procedure. At that time, inclusion and exclusion criteria will be reviewed, and eligible patients will give informed consent. Subjects will then undergo Cytosponge administration. Following Cytosponge administration, subjects will complete a questionnaire and pain scale. Subjects will then attend their scheduled endoscopy session. Upper endoscopy will be performed and biopsies are required to be taken as part of routine care. For subjects presenting for GERD, a single set of 4 quadrant biopsies (4 pieces of tissue total) of the cardia will be collected during the endoscopy procedure and will be specific to this research study. The research-specific gastric cardia biopsies will be taken in addition to any routine care biopsies, if applicable, and will still be obtained even if routine care biopsies are not taken during the procedure. The Sponsor will pay for any charges related to collection and pathology of the research specific gastric cardia biopsies. It is encouraged for Investigators to take photos of the gastroesophageal junction (GEJ) during the endoscopy procedure.

All study-specific gastric cardia biopsies, as well as any routine care tissue biopsies will undergo standard processing and H&E staining at the home institution, with assessment by expert gastrointestinal pathologists. The Sponsor will pay for any charges incurred for collection and pathology assessment of the study-specific gastric cardia biopsies.

Enrolled subjects will be administered the Cytosponge one time, on the date of an endoscopy scheduled for routine care, prior to the endoscopy. Subjects can only participate one time. The only exception is for subjects who have an inadequate sample on the initial Cytosponge. These subjects will be asked to return for repeat Cytosponge administration after the initial administration.

All subjects taking part in the study will be undergoing an endoscopy as part of standard of care, the risks of the study are all linked with the administration of the Cytosponge, and are extremely low as no Cytosponge I related serious adverse events have been reported in subjects from the BEST1 study (n=504) and/or BEST2 (to date n= 1500)[2].

The results from this study will not be used to influence patient management or follow-up.

6.1. Duration

Participation in the study may last about4-10 days after the procedure. Subjects will be contacted 7 days (+/- 3 days) following the Cytosponge and upper endoscopy procedures. During this phone call, adverse events will be assessed and subjects will complete final questionnaire. Participation in the study is complete when subjects have completed the follow-up phone call.

If the Cytosponge tissue specimen is reported as inadequate by the central pathologist, the subject will be asked to return for repeat Cytosponge administration. Only the Cytosponge™ Cell Collection capsule administration will be repeated. Questionnaires and the endoscopy procedure will not be repeated.

The study is expected to last a total of 24 months (2 years).

6.2. Rationale

A simple, non-endoscopic device, termed the Cytosponge I, has been developed for endoscopic screening of patients at risk for BE by investigators at the University of Cambridge in the U.K. The Cytosponge I is an ingestible gelatin capsule enclosing a compressed spherical mesh 3 cm in diameter, the center of which is attached to a string (Figure 3). The capsule and string are swallowed with water. The string is held at the mouth without tension, allowing the capsule to move into the stomach. After 7-10 minutes (during which the gelatin capsule dissolves and the sponge is liberated), the sponge is withdrawn by gentle traction on the string. The sponge is placed in fixative for 48 hours, then the cells are pelleted, and processed into paraffin blocks. The pellets are immunostained with an antibody for trefoil factor 3 (TFF3), which is present within goblet cells thus defining the presence of specialized

intestinal metaplasia. TFF3 is interpreted in a binary fashion, i.e., either positive or negative. In a recent study of 504 subjects with chronic GERD symptoms in the U.K. who underwent both Cytosponge analysis and upper endoscopy, the Cytosponge demonstrated a sensitivity of 90% and a specificity of 94% for the detection of BE (Prague classification C2 or more).[2] Follow-up work with an additional 334 subjects (186 controls, 148 BE) demonstrated similar results, with a sensitivity of 84% and a specificity of 92% (data courtesy of Rebecca Fitzgerald, MA (Cantab) MD). These results suggest the Cytosponge may be suitable to serve as a surveillance tool in patients with BE, as well as a screening tool in patients with chronic reflux symptoms.

Dr. Fitzgerald and colleagues administered the Cytosponge I to 504 subjects in a primary care setting and found it to be safe and well-tolerated. Of these subjects, 501 (99%) were able to successfully swallow the capsule. Unsurprisingly, given pill-swallowing difficulty in the general population, 3 subjects were unable to swallow the pill, feeling it was too large. No adverse events were noted, and subjects demonstrated a low level of anxiety associated with the test.[2] A second study published by the same investigators, BEST2, administered the Cytosponge I to an additional 831 subjects in a multicenter, prospective design. An interim data analysis demonstrated a similarly excellent safety and tolerance profile, with no serious adverse events reported.[24] Overall, to date, there have been 1,335 documented administrations of the sponge, with few adverse events reported. Several hundred additional uses of the device have occurred in Cambridge, U.K., without significant adverse events (personal communication, Dr. Fitzgerald), but have not yet been reported in the peer-reviewed literature.

7. Product Description

7.1. General

The Cytosponge™ Cell Collection Device (Cytosponge) is intended to collect surface cells from the esophagus. The device consists of a swallowable capsule, which dissolves in the body cavity, releasing a self-expandable sponge. The sponge is then retrieved from the esophagus using an attached string. During the retrieval process, the sponge collects cells from the most superficial layer of the esophageal mucosa. Once removed from the patient, the sponge and cells are retained for investigation and/or testing.

The Cytosponge™ Cell Collection Device (Cytosponge) received 510(k) clearance from the FDA on November 26, 2014 (K142695). The Cytosponge ™ Cell Collection device is a Class II product under 21 CFR 874.4710 esophagoscope (flexible or rigid) and accessories. The sponsor has determined clinical study COVB2710467 entitled - Assessment Of A Minimally Invasive Esophageal Cytology Collection System In Patients With Barrett's Esophagus Or GERD Symptoms is a Non-Significant Risk (NSR) Device study based on "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors – Significant Risk and Non-significant Risk Medical Device Studies" published by the FDA (January 2006).

7.2 Dosage Form and Route of Administration

Figure 2: Cytosponge with planned packaging and retrieval cord

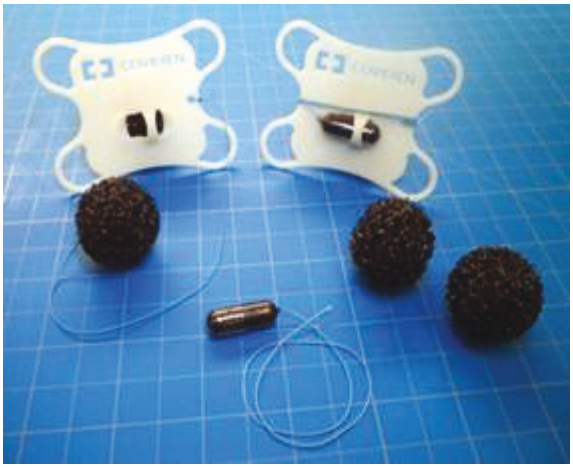

Figure 3: Cytosponge I

The Cytosponge™ device (referred to hereafter as the "Cytosponge") will be supplied by Medtronic to the participating sites. Study sites will be responsible for storage and accountability of the device. 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).[redacted]

[redacted]

Cytosponge administration will occur after an overnight fast to minimize the possibility of aspiration of any gastric contents. Every administered sponge will be assessed post-procedure for signs of fracture or incomplete retrieval of the sponge. 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]) until shipped. Samples will be

shipped to an accredited pathology laboratory for processing. [redacted]

In the unlikely case of incomplete retrieval or sponge detachment, the sponge will be retrieved with a Roth net at the standard of care endoscopy which will routinely immediately follow the administration of the sponge per the study protocol. Any bleeding noted, either clinically following the sponge administration or due to blood on the sponge itself, will be similarly investigated, and, as necessary, treated during the subsequent endoscopy. Because study inclusion/exclusion criteria are designed to exclude those at highest risk for a bleeding complication, the risk of bleeding in this study should be extremely low.

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 two times before they are classified as “Cytosponge swallowing failure” and discontinued by the investigator.

7.3 Manufacturer

The product is manufactured at a Medtronic facility located in Sunnyvale, California.

7.4. Packaging

The subject device the Cytosponge™ Cell Collection Device is a sterile single-use device. The Cytosponge™ Cell Collection Device consists of a clear, size 00 vegetable-material-derived capsule, which holds a 30mm spherical sponge inside of the capsule. The capsule containing the sponge is attached to silicone-coated braided polyester suture. The suture is attached and secured to a retainer card via an ABS plug. These materials are packaged inside a foil and polyethylene pouch. The product label is applied to the pouch and provides text containing the manufacturing lot and expiration date.

7.5. Intended Population

The intended population consists of people who are having an endoscopic exam to examine their esophagus, stomach, and first part of the small bowel and because the subject has suffered from GERD symptoms at least on a monthly basis for at least 6 months or patients who have been diagnosed with Barrett’s esophagus.

7.6. Equipment

N/A

7.7. Product Use

Refer to CytoKit IFU_717-0075-01(A) for product use information.

7.8. Product Training Requirements

Each Investigator participating in the clinical trial and the associated clinical study staff will receive training on the clinical protocol, as well as hands-on training in the use of Cytosponge™ Cell Collection Device and training on Visual Analog Scale. The CASE II Clinical Study Training Plan describes in detail study training requirements.

Sites are required to receive standardized training on Cytosponge administration before enrolling their first study subject. This will require recruiting and enrolling a cohort of healthy volunteers for training purposes. Participants enrolled for training purposes will not count toward enrollment on the study but should be approved by the site's IRBs. Prior to the recruitment of healthy volunteers, sites must receive explicit permission from the sponsor. See Appendix III: Sample Healthy Volunteer ICF.

7.9. Product Receipt and Tracking

Product information will be recorded in the packing slip, Kit Receiving and Disposition Log, and Device Accountability Log. These documents will be kept at the site and a copy will be sent to the sponsor to save in Trial Master Files.

The packing slip will contain the kit and capsule lot numbers, kit and capsule expiration dates, date of order, and date of receipt. The site will confirm sponsor to confirm receipt of the product.

7.10. Product Storage

The device will be labeled CytoKit-R (Research Use Only) and should be stored in a secure (locked) area under the appropriate storage conditions. Access should be limited to designated study staff only. Refer to CytoKit IFU_717-0075-01(A) for appropriate storage condition information.

7.11. Product Return

For all product returns not pertaining to a complaint, a Return Form is to be completed and the product is to be returned to the sponsor. For products being returned due to a complaint, Post-Market Vigilance

will provide a complaint number that will be included in the Return Form and shipping label. Expired products can either disposed of or returned to the study sponsor.

7.12. Product Accountability

The Kit Receiving and Disposition Log includes all information within the packing slip, as well as device condition, subject number, and the date the device was used. A copy of this log will be sent to the sponsor after every monitoring visit.

A Device Accountability Log will be sent to the sponsor after a device is used or after the next monitoring visit. It will include the date of the procedure, the device and capsule lot numbers, and the subject number.

8. Selection of Subjects

8.1. Study Population

The study population includes patients with:

- Previous confirmed diagnosis of BE with intestinal metaplasia
- Self-reported heartburn or regurgitation on at least a monthly basis for at least 6 months (GERD arm)
- Prague classification of at least one circumferential centimeter of BE or a total BE segment length of at least 3 centimeters (C1 or CXM3+) (BE arm) (refer to section 9.3)

8.2. Subject Enrollment

Potential subjects will be identified during their GI clinic or procedure visits at their treating institutions. All subjects will be screened and enrolled using ethics committee (EC) / Institutional Review Board (IRB)-approved and HIPAA compliant methods.

An investigator, study coordinator, or other qualified personnel will obtain 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 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 historical information from the subject pertaining to history of BE and GERD.

The consent process will be documented by the coordinator in the subject's study file.

8.3. Inclusion Criteria

1) Male or female subjects, age 18 and above.
2) Able to read, comprehend, and complete the consent form.
3) Clinically fit for an endoscopy.
4) One of the following options:
    b) Previous confirmed diagnosis of Barrett's esophagus with intestinal metaplasia, and Prague classification of at least one circumferential centimeter of BE or a total BE segment length of at least 3 centimeters (C1+ or CXM3+) (BE arm) . OR
    c) If the subject does not have documented Prague Classification prior to screening, but the PI is convinced that the subject will meet the inclusion criteria based on previous documentation (for instance, mention of "long-segment BE," they may enroll the subject in the study at their discretion. The study upper endoscopy must confirm that the subject has C1+ or CXM3+ (BE arm). If (C1+ or CXM3+) is not observed at the time of study endoscopy, the subject may still be enrolled but not included in the data analysis with the BE cohort. The data may be analyzed in a separate cohort. OR
    d) Self-reported heartburn or regurgitation on at least a monthly basis for at least 6 months (GERD arm).

8.4. Exclusion Criteria

1) Individuals with a diagnosis of an oropharynx, esophageal, or gastro-esophageal tumor, or ongoing symptoms of dysphagia.
2) Any history of esophageal varices, or active stricture.
3) Current use of anti-thrombotics (anti-coagulants and anti-platelet drugs) that cannot be safely discontinued for the appropriate drug-specific interval in the peri-administration period. Depending on the particular agent or reason for the anti-thrombotic therapy, it may not be necessary to discontinue anti-thrombotic agents. There could be circumstances where the drug may not need to be discontinued if the risk of bleeding is considered negligible (e.g. daily aspirin therapy). Physicians should use their clinical judgement and should consult relevant guidelines such as those provided by the ASGE.
4) Known bleeding disorder.
5) Individuals who have had a myocardial infarction or any cardiac event < 6 months prior to enrollment.
6) Individuals who have had a cerebrovascular event < 6 months prior to enrollment in which swallowing was affected.
7) Prior ablative or resection therapy of the esophagus including radiofrequency ablation (RFA), photodynamic therapy (PDT), spray cryotherapy, endoscopic mucosal resection, and other ablation therapies.
8) Any history of esophageal surgery, except for uncomplicated fundoplication.
9) Do not need upper endoscopy as part of patient management.

10) Pregnancy

9. Study Procedures

9.1. Schedule of Events

Assessment	Screening/Enrollment Visit	Follow-Up Phone Call (7 days +/- 3 days after Enrollment)	Repeat Cytosponge
Informed Consent Form	X		
Demographics	X		
Medical History	X		
Inclusion/Exclusion Criteria	X		
Cytosponge Administration	X		X[1]
Visual Analog Scale	X[2]		
Routine Care Endoscopy with Biopsy	X[3,4]		
Impact of Event Scale		X	
Procedure Preference and Acceptability Questionnaire		X	
Adverse Events[5]	X	X	X

[1]If the initial Cytosponge sample is inadequate, sites will be notified and subjects will be asked to return for repeat Cytosponge administration. Only the Cytosponge administration will be repeated. Questionnaires and the endoscopy procedure will not be repeated on these patients.

[2]VAS should be administered immediately following completion of the Cytosponge and prior to the upper endoscopy.

[3]Routine care biopsies should be taken during the endoscopy following the Cytosponge as this is considered standard of care for the target population.

[4]For subjects presenting for GERD, a single set of 4 quadrant biopsies (4 pieces of tissue total) of the gastric cardia (TGF+1) should be taken for this research study. The research specific biopsies will be taken in addition to any routine care biopsies taken during the procedure and will still be obtained even if routine care biopsies are not taken. The Sponsor will pay for any charges related to collection and pathology of the research specific gastric cardia biopsies.

It is encouraged for Investigators to take photos of the gastroesophageal junction (GEJ) during the endoscopy procedure.

[5]Every adverse event must be reported to the sponsor and recorded in the electronic case report form. Sites are responsible for following local IRB guidelines for reporting adverse events to their local IRB.

9.2. Subject Screening

During screening/enrollment, eligibility is assessed and those eligible and interested in participating are consented on the study. Once consent is obtained, subjects will undergo administration of the Cytosponge, complete a questionnaire, and proceed with routine care upper endoscopy immediately following completion of the Cytosponge in which biopsies are taken for clinical purposes and sent to pathology.

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

- Eligibility review
- Informed consent
- Cytosponge administration
- Visual Analog Scale
- Routine care upper endoscopy with biopsy
- Adverse event assessment
- Enrollment case report form (CRF): This captures demographics including race, ethnicity, gender, and year of birth, relevant BE and GERD medical history including documentation of endoscopic procedures received to date as well as pathology findings and endoscopic history related to current diagnosis.

9.3. Visual Analog Scale Administration

Immediately following administration of the initial Cytosponge and retrieval, subjects will be administered a Visual Analog Scale (VAS). The VAS will not be administered during the repeat Cytosponge for subjects requiring a repeat Cytosponge.

9.4. Subject Consent

If a patient is screened eligible and interested in the study, the patient will be consented on the study prior to any study procedure. Written informed consent will be obtained by qualified study personnel. Documentation of the consent process will be maintained in the subject's research record.

Patients will be given ample time to review the consent document and ask any questions they may have. A copy of the written consent form will be provided to the subject and the original maintained in the subject's research record.

If patients meet all inclusion and none of the exclusion criteria and consent to the study, they will be enrolled in the study. Subjects will be assigned a unique subject code.

9.5. Cytosponge Abrasion Scale

Cytosponge abrasions will be carefully assessed during the endoscopy and graded using a standardized abrasion scale (see Appendix I: Cytosponge Abrasion Scale). Physicians performing the endoscopy will be trained on use of the scale.

9.6. Adverse Event Assessment

Subjects should be assessed for any adverse events occurring before, during, or after Cytosponge administration. All adverse events occurring during the research study must be reported to the sponsor. Sites are responsible for following local IRB guidelines for reporting adverse events to their local IRB.

9.7. Prior and Concomitant Medications

Current use of anti-thrombotics (anti-coagulants and anti-platelet drugs) including but not limited to warfarin, clopidogrel, heparin and/or low molecular weight heparinmay be discontinued as per discretion of the principal investigator. Reference Exclusion criteria #3.

9.8. Assessment of Safety

9.8.1 Methods and Timing of Assessing Safety Parameters

To monitor safety, subjects will be asked at each visit and during telephone contacts about changes in their medical conditions. Subjects will be able to contact the investigator at any time during the study if they note any change in their medical condition

9.8.2 Documenting Preexisting Conditions(s)

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

9.8.3 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

9.9. Recording Data

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

This study will utilize electronic case report forms (eCRFs). The study eCRF is the primary data collection instrument for the study. All data requested on the eCRF must be recorded. All missing data must be explained. If a space on the eCRF is left blank because the procedure was not done or the question was not asked, this should be documented in the comments field.

Along with the data collected during screening/enrollment, a follow-up phone call will be made and the following data will be collected:

- Impact of Event Scale
- Procedure Preference and Acceptability Questionnaire
- Adverse event assessment
- Follow-up electronic case report form (eCRF): This captures relevant information for questionnaire completion and assessment of adverse events.

9.9.1. Impact of Event Scale

The impact of event scale will be completed with the subject during the follow-up phone call and measures subjective distress related to administration of the Cytosponge. See **Appendix II: Impact of Event Scale**.

9.9.2. 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 or traditional upper endoscopy as well as willingness to undergo the procedure again.

9.9.3. Follow-up Phone Call Adverse Event Assessment

During the follow-up phone call, subjects should be assessed for any adverse events that have occurred since administration of the Cytosponge. Only those events potentially related to participation in this research study must be reported to the sponsor. Sites are responsible for following local IRB guidelines for reporting adverse events to their local IRB.

9.10. Deviation Handling

The investigator must notify Medtronic and the reviewing IRB of any deviation from the protocol when specific to the protection of the life or physical well-being of a subject in an emergency. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency has occurred. Except in such an emergency, prior written approval by Medtronic is required for changes in or deviations from the plan. If these changes or deviations affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects the IRB will also be notified. All other deviations will be reported per the site's IRB deviation policy. Should any deviations from the protocol occur, these will be reviewed by Medtronic for their clinical significance.

Protocol deviations identified by the Monitor during a monitoring visit should be discussed with the Principal Investigator/ Study staff involved at the time of discovery. Protocol non-compliance will be documented accordingly and communicated again in writing to the site within the follow-up letter. Monitors will also escalate the deviations significant in nature to the study manager (or designee), as soon as possible.

9.11. Subject Withdrawal or Discontinuation

Subjects will be considered to have completed the study after completion of the last study visit (follow-up phone call). Subjects may be withdrawn prior to this for any of the following reasons:

- Death, or
- Lost to follow-up, or
- Withdrawal of consent, or
- Discontinuation by the investigator.

Documentation must be maintained at the site for any subject withdrawals. Subjects unable to complete Cytosponge administration will be withdrawn from the study (discontinued by investigator). Three attempts at contact using two different methods are required prior to determining the subject is lost to follow-up. Attempts at contact must be with certified letters OR documented telephone contact. If a subject is withdrawn prior to completion of the study, the site should complete the Study Exit e-CRF.

10. Risks and Benefits

10.1. Potential Risks

There are several possible risks that could occur when swallowing the Cytosponge capsule which include but are not limited to:

- Aspiration (accidentally inhaling material from the stomach into the lungs) and/or airway obstruction are possibilities but these risks are expected to be minimal.
- Although the sponge is soft, possible risks include, bleeding, pain, vomiting, sore/irritated throat, and burning sensation from any mucosal surfaces of the mouth, stomach or esophagus (swallowing tube) which comes in contact with the sponge.
- Laceration of any mucosal surface coming into contact with the sponge is possible, including mucosal surfaces of the stomach, esophagus, throat or mouth. Although very unlikely, perforation of the stomach or esophagus is also possible which could require secondary intervention.
- Although the risk has been found to be 2%, sponge detachment from the suture could also occur. Should this occur, the sponge will be retrieved during the planned endoscopy that follows administration of the sponge. Although not observed in previous Cytosponge studies the risk of infection or intestinal obstruction is a possibility.

The current study has been designed to minimize occurrence of these potential risks by use of the exclusion criteria. Most subjects enrolled in this study will have previously received an upper endoscopy, which will document the absence of esophageal varices and strictures. During administration of the sponge, the patient is not sedated and the device does not render the upper esophageal sphincter incompetent. These elements further reduce the overall risk for serious adverse events.

All serious adverse events, which, based on the investigator's judgment, are considered to be device related, should be reported to Medtronic-GI Solutions within 24 hours after the investigator is made aware of the event.

10.2. Potential Benefits

The study may allow Medtronic and the study doctors to assess whether this procedure can be an acceptable method of collecting a sample of cells from the lining of the esophagus.
This study will help in gathering information on the outcomes associated with the Cytosponge ™ Cell Collection Device and therefore might inform future decisions regarding this product and its indicated uses.

10.3. Risk-Benefit Rationale

Risk analysis for Cytosponge™ Cell Collection Device was conducted in compliance with ISO14971. The overall evaluation of the residual system risks found no unacceptable hazards of significant impact to the safety and reliability of the Cytosponge™ Cell Collection Device. The residual risks of the Cytosponge™ Cell Collection Device, design, and process hazards were rated as BAR (Broadly Acceptable Region) or ALAP (As Low as Possible) in accordance with the risk acceptability criteria as documented in Risk Management Report [redacted].

- Based on the risk analyses per the SHA [redacted], the dFMEA [redacted], and the pFMEA [redacted], we conclude that the current risk controls with respect to design and processes of the sterile Cytosponge™ Cell Collection Device (CYTO-101) have been reduced to acceptable level.
- Risks related to Secondary Intervention, Mucosal Laceration, Pre-Procedural Delay, Intra-Procedural Delay, Airway Obstruction, Unable to use sample for diagnosis, Infection, Minor Bleeding, Reaction due to non-Biocompatibility, Aspiration, Intestinal Obstruction and Dysphagia have been reduced to an acceptable level in BAR and/or ALAP-B risk regions for the Cytosponge™ Cell Collection Device (CYTO-101).
- Future updates to design and/or process pertaining to these risks will be captured with the inclusion of updated risk controls as applicable.
- None of the risks fall in the intolerable region and the current risks are reduced and/or continually controlled via existing measures; the residual risks from current risks are deemed acceptable based on the implementation of existing risk controls.
- This report is applicable only to sterile and non-sterile Cytosponge™ Cell Collection Device (CYTO-101) samples for intended use; performance/functionality testing was performed on e-beam sterilized samples since sterilization presents worst case processing/conditions as mentioned in [redacted] performance testing for equivalency of non-sterile samples with sterile samples.
- Within this clinical trial, the benefits of using the Cytosponge™ Cell Collection Device (CYTO-101) for the intended use outweigh the risks.

11. Adverse Events and Device Deficiencies.

11.1. Definitions/Classifications

Adverse event: any unwanted medical occurrence in a subject. An event is a sign, symptom, illness, abnormal laboratory value, or other medical event occurring to a subject that appears or worsens during a clinical study. Adverse events will be collected and documented after the subject has signed the

Informed Consent form, until the completion of the final Cytosponge administration post-procedure 7-day phone call is completed; which will be considered to be the end of the study.

All adverse events will be graded 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, may interfere with usual activity.

Severe: Sign or symptom that is intense or debilitating and that interferes with usual activities. Recovery is usually aided by therapeutic measures and the discontinuation of the study device may be required.

The relationship of the adverse event to the study is defined as follows:

No Relationship: An adverse event has no temporal relationship to study device or has a much more likely alternative etiology.

Possible: An adverse event has a minimal temporal relationship to the study device and/or a more likely alternative etiology exists.

Probable: An adverse event has a strong temporal relationship to study device, and an alternative etiology is unlikely or significantly less likely compared to the potential relationship to study device.

Definite: An adverse event was shown to be related to the study device.

Device Deficiency: Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance such as a malfunction, misuse or use error or inadequate labeling.

Unknown: The relationship of the adverse event to the study device is inconclusive.

Adverse Event will be reported to Medtronic-GI Solutions utilizing the electronic case report (Adverse Event CRF eForm)

Adverse device effects: device related adverse events caused wholly or partly by the use of the device. A causal relationship between an observed adverse event and the use of the trial device may exist with various degrees of probability, on the basis of statistical probability, or of plausible medical data and considerations.

In the case of adverse device effect with the Cytosponge™ Cell Collection Device, the Cytosponge capsule should be postponed until adverse device effect is resolved and per physician discretion.

Serious adverse event is any adverse event that:

- Led to death
- Resulted in a life-threatening illness or injury
- Led to persistent or significant disability or incapacity
- Required inpatient hospitalization or prolongation of existing hospitalization
- Led to fetal distress, fetal death, congenital anomaly/birth defect.
- Resulted in medical or surgical intervention to prevent life threatening illness or permanent impairment to body structure or body function.
- Other significant medical event.

Some important medical events, although they may not result in death, be life-threatening, or require hospitalization may still be considered serious adverse events when, based upon appropriate medical

judgment, they are felt to jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Life threatening means that the subject was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. This does not include an adverse event that, if more severe, might have caused death.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Serious Adverse Event will be reported to Medtronic-GI Solutions utilizing the electronic case report (Serious Adverse Event CRF eForm) within 24 hours of the investigator's awareness and reported to IRB within 10 working days.

An unanticipated adverse event is any serious, device related adverse event, if that event was not previously identified in the risk analysis and consent form in:

a. nature
b. severity or
c. frequency
d. Unreasonable risk is not defined. It shall be determined by management on a case-by case basis through evaluation of serious and unanticipated adverse events.

11.2. Reporting of Adverse Events

It is the responsibility of the sponsor to notify all participating investigators of any adverse event associated with the study that is serious or unexpected.

Every adverse event should be recorded in the electronic case report form. Any safety or device deficiency issues which may occur during training with healthy volunteers shall be reported using the Field and Technical report (FTR, form-0021).

The following data must be documented:

- Type of event
- Subject number
- Time of occurrence: date, time
- Time of resolution: date, time
- Severity degree: mild / moderate / severe /
- Relationship to study device: no relationship/possible/probable/definite/unknown
- Measures taken
- Outcome of event: unchanged / worsened / improved / resolved / unknown / death

If timely completion of the electronic CRF is not possible, a paper copy can be completed and sent via fax or email GI Solutions at Medtronic (408) 328-7338 or clinical3@covidien.com. If for any reason the form cannot be completed within 24 hours, a phone call should be made to the sponsor to meet the reporting timeline. In the case of a telephone or faxed/emailed report, sites must still complete the electronic reportable event eCRF at the earliest possible opportunity, and no later than 72 hours following learning of the event.

All other reportable events should be reported within **15 days** of learning of the event. Any safety or device deficiency issues which may occur during training with healthy volunteers shall be reported using the Field and Technical report (FTR, form-0021).

12. Data Review Committees

Data Monitoring Committee (DMC) or Clinical Events Committee (CEC) will not be used for this study.

13. Statistical Design and Methods

For the primary objectives, to assess the acceptability of the Cytosponge in subjects with BE, we will assess the distribution of Impact of Event Scale scores, and the intrusiveness and avoidance subscales. We will generate measures of central tendency and distribution of these data. Bivariate analysis will be performed to assess for predictors of low tolerance of Cytosponge surveillance, and a logistic regression model created to assess these factors while controlling for potential confounders. Data will be compared to population norms in published literature[1] using parametric statistics. VAS scores will be calculated, and measures of central tendency and distribution reported.

Subjects' preferences for Cytosponge versus endoscopic surveillance, as well as willingness to undergo the procedure again, will be measured as proportions, with bivariate and multivariate analyses for predictors of preference performed.

For the second primary objective, to assess the adequacy of samples, sample adequacy will be treated as a dichotomous variable. For purposes of this investigation, an adequate sample will be one in which at least one columnar cell is present. Sample adequacy will be presented as a proportion of subjects who fulfill this definition after up to two total administrations of the Cytosponge, as noted in the methods.

For the first three secondary objectives, to assess the operating characteristics of Cytosponge against various gold standards, initially 2x2 tables will be constructed demonstrating Cytosponge and the gold

standard findings (Y/N for BE via endoscopy and Y/N for Intestinal Metaplasia (IM) via biopsies). Both endoscopic evidence of BE and pathological confirmation of specialized IM (intestinal metaplasia with goblet cells) will be used in the final diagnosis of BE. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy will be calculated. Because Cytosponge positivity may vary based on the burden of BE, we will perform sensitivity analyses, defining "positive" cases as those with BE of ≥2 cm in length, and then ≥3 cm in length, to assess impact of disease burden on operating characteristics. Multivariate models controlling for age, sex, burden of disease, and other potential confounders will be constructed, to assess the impact of these factors on test accuracy. Although we do not expect to see an association between the degree of dysplasia and Cytosponge positivity, exploratory analyses will be performed using degree of dysplasia as a predictor variable, and Cytosponge positivity as the outcome variable. For the fourth secondary objective, to assess the degree of mucosal abrasion following Cytosponge, endoscopic abrasion scores will be correlated with the presence of columnar cells on the H&E slide made from the Cytosponge samples.

While the operating characteristics of Cytosponge in our patient population are unknown, the numbers for this post-market study were selected for several reasons. Approximately 50% of the patient population at the involved tertiary care centers have dysplastic BE (25% low-grade dysplasia, 25% high-grade dysplasia), so assessment of 275 patients (with an enrollment ratio of at least ≥50% BE and ≥25% GERD) should allow an adequate number of subjects with dysplastic disease to assess performance characteristics with reasonable accuracy. Ten percent of patients with chronic GERD symptoms can be expected to harbor BE, leaving us 75 patients with which to assess specificity, as well as to assess acceptability in patients without disease. For the safety perspective, a sample size of 50 will have greater than 90% probability of detecting a rare event that occurs at a rate of 5%. Results of this study will be used to provide more accurate parameters for power of subsequent studies.

All individuals offered the Cytosponge will be included in analyses of acceptability and adequacy of sampling. All individuals with adequate Cytosponge samples and endoscopy (within 48 hours of Cytosponge) will be included to determine the sensitivity for diagnosis of BE from the TFF3 data (95% confidence intervals will be used).

In an effort to understand the sensitivity and specificity of the test, an interim analysis of the data, based on the statistical methodology outlined above, may be performed after approximately half the study subjects have primary outcomes.

To assess safety (fifth secondary objective), the number and percentage of subjects with adverse events related to Cytosponge administration will be summarized by MedDRA system organ class and preferred term overall, and by severity.

14. Ethics

14.1. Statement(s) of Compliance

This clinical investigation will be conducted in accordance with the US and international standards of Good Clinical Practice (FDA Title 21 and International Conference on Harmonization guidelines), applicable government regulations, Institutional research policies and procedures, ethical principles that have their origin in the Declaration of Helsinki, ICH-GCP, and any regional or national regulations, as appropriate.

The clinical investigation will not begin until all necessary approvals/favorable opinions are obtained from the appropriate IRBs or regulatory authority, as appropriate. Should an IRB or regulatory authority impose any additional requirements, they will be followed. Information regarding the study and study data will be made available via publication on clintrials.gov. Additionally, the results of this study will be submitted for publication in an appropriate journal.

This protocol and any amendments will be submitted to a properly constituted independent IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and that provides sufficient information for subjects to make an informed decision about their participation in this study. Sample consent forms will be provided by the lead site. These consent forms include a consent for the study as well as a consent for storage of samples for future use. All consent forms will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent forms must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

15. Study Administration

15.1. Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, the lead site, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan, if required. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

15.2. Data Management

This study will utilize an electronic database and eCRF or paper CRFs. All data requested on the eCRF are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified. The Principal Investigator must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate eCRFs. The Investigator's electronic signature for specific eCRFs will be documented in compliance with local regulations. Changes to data previously submitted to the sponsor will require a new electronic signature by the Investigator to acknowledge/approve the changes.

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Oracle remote data capture (RDC) system and will be issued to the site for appropriate response. The site staff will be responsible for resolving all queries in the database.

The investigator must agree to the inspection of study-related records by the Regulatory Authority/Sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/Sponsor representatives.

15.3. Direct Access to Source Data/Documents

The investigator must agree to the inspection of study-related records by the Regulatory Authority/Sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/Sponsor representatives

15.4. Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. the subject is alive) at the end of their scheduled study period.

15.5. Liability

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB.

15.6. CIP Amendments

No changes to the protocol will be permitted without the written approval from Medtronic and the IRB/EC (at the discretion of the PI and the IRB). It is the responsibility of the sponsor to notify all participating investigators of any revisions to the protocol.

15.7. Record Retention

The investigator will maintain the records of the study including all pertinent correspondence, the study protocol with any/all amendments, all correspondence with and approval from the IRB/EC, the clinical trial agreement, the Investigator Agreement, investigational device accountability records, individual subject records, and signed ICFs. Subject files and other source data must be kept for a period of not less than 2 years after the latter of the following two dates: the date on which this investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket application. Records may need to be maintained by the Principal Investigator for a longer duration if national regulations require or if agreed to in writing with the Sponsor. All data and documents should be made available if requested by relevant authorities.

15.8. Publication and Use of Information

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the lead investigator, Dr. Nicholas Shaheen. Any investigator involved with this study is obligated to provide the lead investigator with complete test results and all data derived from the study. The results from this study will not be used to influence patient management or follow-up.

The Medtronic Publication and Authorship Policy is aligned with the International Committee of Medical Journal Editors (ICMJE) recommendations (www.icmje.org). Medtronic will seek to publish, in appropriate peer-reviewed journals and scientific conferences, results of clinical studies where human subjects are involved, regardless of outcome. While study results are owned by Medtronic, all data on which a publication is based will be made available to all authors as required for their participation in the publication process. Furthermore, data may be published or used by study investigators provided that such publication or use is in accordance with this this protocol, the Medtronic Publication and Authorship Policy, and the Clinical Investigation Agreement. Investigators must submit a copy of all manuscripts and/or abstracts to Medtronic for review and comment 30 days prior to planned submission. Medtronic acknowledges that its right to review and comment shall relate solely to the proprietary, licensing, and/or confidential rights Medtronic may have in such proposed publication, rather than whether such results and/or opinions are favorable to Medtronic.

The publication of sub-studies, post-hoc analyses, regional results, or single-center experiences based on multicenter clinical studies should not precede that of the primary multicenter publication, and should cite the primary publication whenever possible, as required by specific journal and scientific meeting guidelines.

Medtronic involvement in a publication (e.g., funding of the study; sponsor of the study; collection, analysis, and interpretation of data; professional writing assistance) must be disclosed according to journal-specific policies, submission requirements, and prevailing editorial standards, in addition to

those specified by the International Committee of Medical Journal Editors. Authors must ensure that an acknowledgement/disclosure statement is included in the body of the manuscript for Medtronic to review for accuracy. All authors must also disclose financial or personal affiliations that could be considered conflicts of interest as per journal/conference requirements.

To enable health care providers, payers, and patients access to the wealth of Medtronic's research, Medtronic will report its scientific data in accordance with the principles outlined in the Guidance Document on Registration and Reporting Results of Company-Sponsored Clinical Trials Under FDAAA 2007 (Title VIII).

15.9. Suspension or Early Termination

The Sponsor reserves the right to suspend or discontinue the study at any stage, with suitable written notice to all investigators, all reviewing institutional review boards (IRBs) or ethic committees (ECs). Similarly, investigators may withdraw from the study at any time, subject to providing written notification to the Sponsor 30 days prior to the date they intend to withdraw. However, the Sponsor and investigators will be bound by their obligation to complete the follow-up of subjects already participating in the study. The subjects must be followed according to the clinical protocol, and information obtained during subject follow-up shall be reported to the Sponsor on the appropriate eCRF.

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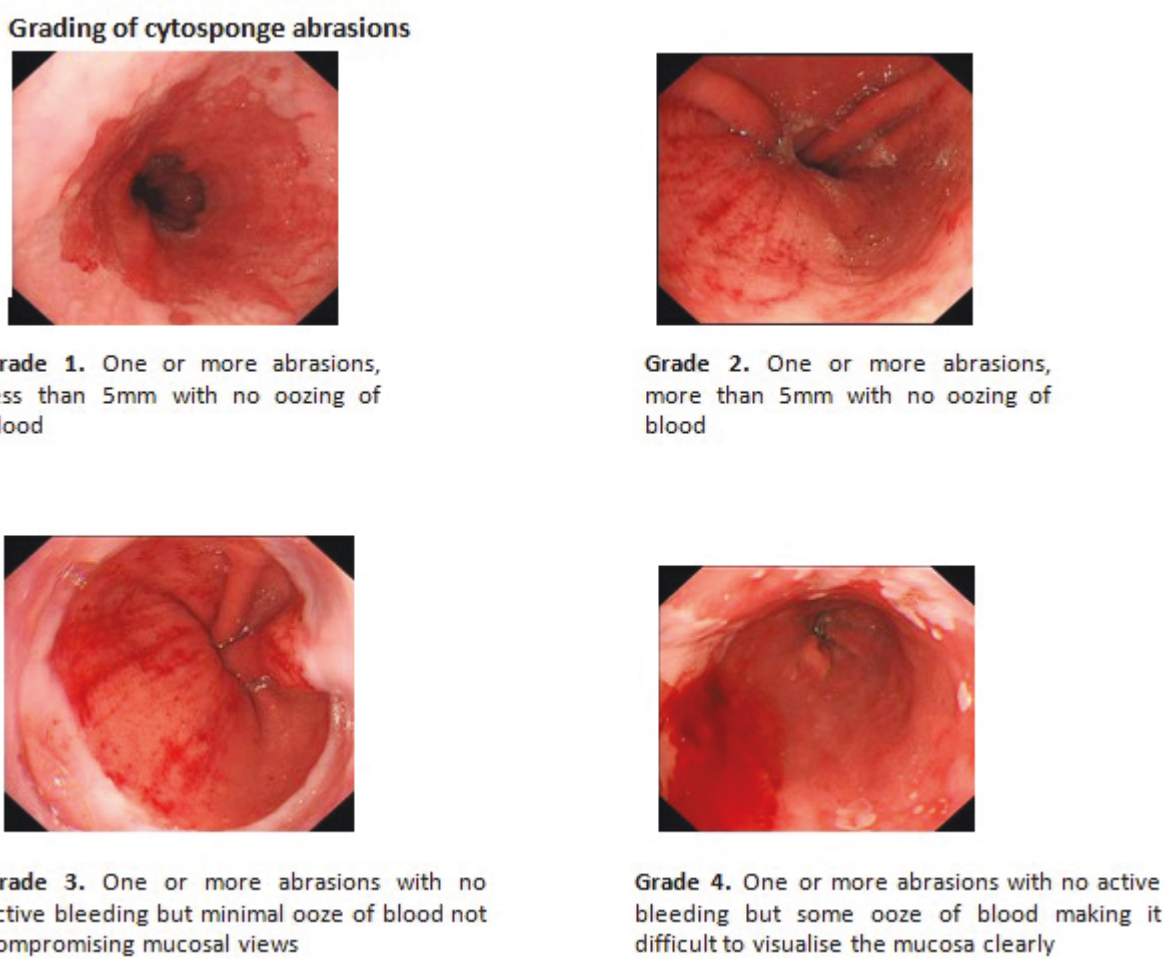
17. Appendices

Appendix I: Cytosponge Abrasion Scale

Grading of Cytosponge abrasions for US Pilot Cytosponge Study

The most distal level (depth of insertion of endoscopy from teeth) of the Cytosponge abrasions should be recorded; this is best seen on initial intubation of the esophagus and stomach. The grading of Cytosponge abrasion is shown below:



Grade 5. One or more abrasions resulting in active bleeding requiring endoscopic or surgical intervention.

Grade 5 abrasions should be considered serious adverse events and reported to the sponsor immediately per the protocol. All other abrasions should be considered adverse events and

reported per the protocol.

Sponsor contacts: [redacted]

Appendix II: Impact of Event Scale

Below is a list of comments made by people in connection with their screening test for Barrett's esophagus. Please check each item, indicating how frequently these comments were true for you. If they did not occur during that time, please mark the 'not at all' column.

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

15. My feelings about it were kind of numb.				

Horowitz, M., Wilner, N., & Alvarez, W. (1979). Impact of Event Scale: A Measure of Subjective Stress. *Psychosomatic Medicine*, *41*(3), 209–218.

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18. Version History

Version	Summary of Changes	Author(s)/Title
A	• Initial version	[redacted] Director, Clinical Affairs
B	• Added risks: There is the possibility of aspiration or airway obstruction whenever instrumentation of the esophagus or stomach is performed by access through the mouth. In the setting of aspiration, infection is also a risk. Because the patient is not sedated and the device does not render the upper esophageal sphincter incompetent, these risks are expected to be minimal. Additionally, although the sponge is soft, patients could experience abrasions or a laceration of any of the mucosal surfaces of the mouth, stomach or esophagus which come in contact with the sponge; this could result in bleeding from any of the aforementioned mucosal surfaces • Updated exclusion criteria: Are unable to discontinue anti-thrombotics including but not limited to warfarin, clopidogrel, heparin and/or low molecular weight heparin for 7 days prior and 7 days after procedure. • Added exclusion criteria: Pregnancy • Revised Assessment of Safety Section	[redacted] Clinical Program Manager
C	• Revised Assessment of Safety Section: The relationship of adverse event to the study, serious adverse events, anticipated adverse event reactions associated with Cytosponge cell collection device. • Revised protocol compliance and deviation reporting	[redacted] Clinical Program Manager
D	• Added general design: All biopsies are per routine care and are at the discretion of the physician performing the procedure. No biopsies will be taken specific to this study. Biopsies not taken at the physician's discretion is not a protocol deviation. Endoscopy without biopsies taken will still count toward enrollment and their data will be used in the final data set.	[redacted] Clinical Program Manager
E	• Cardia Biopsies: For subjects presenting for GERD, a single set of 4 quadrant biopsies (4 pieces of tissue total) of the gastric cardia (TGF+3) will be collected during the endoscopy procedure. All research-specific gastric cardia biopsies, as well as any routine care tissue biopsies will undergo standard processing and H&E staining at the home institution, with assessment by expert gastrointestinal pathologists. The sponsor will pay for any charges related to collection and pathology of the research-specific gastric cardia biopsies. • Removed from ***3.1 General Design***: "Biopsies not taken at the physician's	[redacted] Clinical Program Manager

	discretion is not a protocol deviation." • Photos of the gastroesophageal junction (GEJ): It is encouraged for investigators to take photos of the GEJ during the endoscopy procedure. • Interim Analysis: In an effort to understand the sensitivity and specificity of the test, an interim analysis of the data, based on the statistical methodology outlined above, may be performed after approximately half the study subjects have primary outcomes. • Quality Assurance of Cytosponge Samples: For quality assurance, Cytosponge samples may be sent to the University of Cambridge to be processed and read, as needed to optimize training at the central lab. These results will be compared to those reported by Miraca. • Update to ***3.5 Protocol Map***: Map updated to include collection of gastric cardia biopsy in subjects presenting for GERD. • Adverse Event (AE) Reporting Clarification: Updated wording from, "*Only those events potentially related to participation in this research study*…" to "*Every adverse event* must be reported to the sponsor *and recorded in the electronic case report form*. See section 7.2 for definition of a reportable adverse event *and documentation guidance*." Removed "*theoretical*" and added "*and/or irritation of*" to section ***7.2.4 Anticipated adverse events reactions associated with Cytosponge™ Cell Collection Device*** • Updated Revision to Rev. E and Revision date to 15.December.2015	
F	• Update to inclusion criteria 4a to include protocol amendment memo, "If the subject does not have documented Prague Classification prior to screening, and the PI is convinced that the subject will meet the inclusion criteria based on previous documentation, they may enroll the subject in the study at their discretion. The study upper endoscopy must confirm that the subject has C1+ or CXM3+ (BE arm). If (C1+ or CXM3+) is not determined at the time of study endoscopy, the subject may still be enrolled but not included in the data analysis with this cohort. The data may be analyzed in a separate cohort. • Added clarification to Safety Assessment noting all serious adverse events will be adjudicated. Updated risk section 11.1 There are several possible risks that could occur when swallowing the Cytosponge capsule which include but are not limited to: • Aspiration (accidentally inhaling material from the stomach into the lungs) and/or airway obstruction are possibilities but these risks are expected to be minimal. • Although the sponge is soft, possible risks include, bleeding, pain, vomiting, sore/irritated throat, and burning sensation from any mucosal	[redacted] Director, Global Clinical Affairs [redacted] Sr. Clinical Project Specialist [redacted] Clinical Research Associate [redacted] Sr. Clinical Project Specialist

	surfaces of the mouth, stomach or esophagus (swallowing tube) which comes in contact with the sponge. • Laceration of any mucosal surface coming into contact with the sponge is possible, including mucosal surfaces of the stomach, esophagus, throat or mouth. Although very unlikely, perforation of the stomach or esophagus is also possible which could require secondary intervention. • Although the risk has been found to be 2%, sponge detachment from the suture could also occur. Should this occur, the sponge will be retrieved during the planned endoscopy that follows administration of the sponge. • Although not observed in previous Cytosponge studies the risk of infection or intestinal obstruction is a possibility. The current study has been designed to minimize occurrence of these potential risks by use of the exclusion criteria. Most subjects enrolled in this study will have previously received an upper endoscopy, which will document the absence of esophageal varices and strictures. During administration of the sponge, the patient is not sedated and the device does not render the upper esophageal sphincter incompetent. These elements further reduce the overall risk for serious adverse events • BE arm biopsies are required during standard upper endoscopy • Although the risk has been found to be 2%, sponge detachment from the suture could also occur. Updated Revision to Rev. F and Revision date to 23.Sept.2016	
G	• Investigation Purpose: ADD GERD: To assess the utility of the Cytosponge device as a non-endoscopic method for collecting surface cells from the esophagus in patients with BE and GERD • Primary Objective(s): Remove "within the last 5 years": To assess the acceptability of a novel, minimally invasive esophageal mucosal sampling technique, the Cytosponge 1) in subjects undergoing surveillance of BE who have had at least a C1 or M3 segment confirmed (or medically suspected), ~~within the last 5 years,~~ and 2) in subjects with GERD undergoing screening for BE. • Sample Size: Increase the sample size by 100 subjects: ~~120~~ 275 subjects (Enrollment ratio of at least ≥50% BE and ≥25% GERD) _~~with BE (at least C1 or M3 confirmed at Cytosponge endoscopy, and 75 55 subjects with GERD symptoms undergoing screening for BE.~~ • Inclusion Criteria: 4)a) Remove "in last 5 years" Previous confirmed diagnosis of Barrett's esophagus with intestinal metaplasia, and Prague classification of at least one circumferential centimeter of BE or a total BE segment length of at least 3 centimeters	[redacted] Sr. Clinical Project Specialist [redacted] Clinical Research Specialist

	(C1+ or CXM3+) (BE arm) ~~in last 5 years.~~ OR • Updated Exclusion #3: Current use of anti-thrombotics (anti-coagulants and anti-platelet drugs) that cannot be safely discontinued for the appropriate drug-specific interval in the peri-administration period. Depending on the particular agent or reason for the anti-thrombotic therapy, it may not be necessary to discontinue anti-thrombotic agents. There could also be circumstances where the drug may not need to be discontinued if the risk of bleeding is considered negligible (e.g. daily aspirin therapy). Physicians should use their clinical judgment and should consult relevant guidelines such as those provided by the ASGE. • Repeat sponge procedure: Remove ~~30 days later (+/- 10 days).~~ • Subjects will be contacted via phone 7 Days Change 2 days to 3 days: (+/- ~~2~~ 3 days). • Lab processing – remove time of lab processing: Samples will be shipped to an accredited pathology laboratory for processing ~~before the end of the next business day~~. • Add Appendix III: Healthy Volunteer ICF • Remove Exclusion criteria #9: ~~Planned ablation or resection therapy (including endoscopic mucosal resection and submucosal dissection) within 3 days after Cytosponge administration.~~ • Subjects who undergo same day ablative therapy (as Cytosponge testing) will Impact of Event Scale scores evaluated separately as opposed to the BE surveillance group. • Secondary Objectives 2) Add: Patients who are undergoing ablative therapy on the day of Cytosponge testing must have biopsies within 2 months prior to surgery.	