Advanced a/LCI Systems for Improved Clinical Utility: An Optical Coherence Tomography (OCT) Pilot Study (OCT Pilot)

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Version Number: 4.0

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Summary of Changes

The table below summarizes changes from protocol version 3.0, 10Oct2019.

Description of Change	**Section(s) Impacted**	**Brief Rationale**
Added dual modality a/LCI-OCT probe	Entire document	Addition of a/LCI engine aids in detection of dysplasia by measuring nuclei within the epithelium.
Added "Cohort B" defined as the cohort who will be administered the dual modality a/LCI-OCT probe	Entire document	To allow for a combined modality a/LCI-OCT probe to be studied in parallel with the current probe.
Increased study duaration to 24 months	Section 1.1	To allow for phase II/Cohort B.
Added collection of research-specific biopsies for Cohort B only and associated risks	Sections 1.2, 1.3, 2.3, 2.3.1, 2.3.3, 8, 8.1.2.1, 8.1.2.3, 10.2	Conconcurrent biopsies at imaging site to validate imaging with current standard of detecting dysplasia.
Added Inclusion criteria specific to Cohort B: Current dysplastic or non-dysplastic Barrett's Esophagus of any length OR, History of dysplastic or non-dysplastic Barrett's Esophagus after treatment with endoscopic eradication therapy (EET) OR, Normal asymptomatic controls without any history of dysplastic Barrett's Esophagus	Section 5.1	To specify inclusion criteria for Cohort B.
Modified Inclusion criterion 2.1.3 for Cohort A to clarify subjects previously ablated with current neosquamous tissue are allowable	Section 5.1	Clarification.
Added Exclusion criteria specific to Cohort B: Uncontrolled coagulopathy	Section 5.2	To specify exclusion criteria for Cohort B.
Modified section title from "Optical Probe" to "OCT Optical Probe"	Section 6.1.1	To clarify section is referencing OCT optical probe
Added A/LCI Engine Section	Section 6.1.3	To provide specifications on the a/LCI engine probe components.
Added A/LCI Optical Probe Section	Section 6.1.4	To provide specifications on the a/LCI optical probe components.
Added A/LCI-OCT Engine Section	Section 6.1.5	To provide specifications on the dual modality a/LCI-OCT probe.
Added section referencing use of clincial pathology reports and slide acquisition from clinical biopsies in this study	8.1.2.3	To aid in evaluation of device performance.
Amended statistics section to increase sample size	Section 9.2, 9.3, 9.4	Statistics amended for larger sample size required to accommodate Cohort B.
Administrative changes to table of contents, protocol version date, and number	Entire document	Administrative.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Cancer Institute Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

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

Principal Investigator:

_____
Print/Type Name

Signed:

_____ Date: _____
Signature

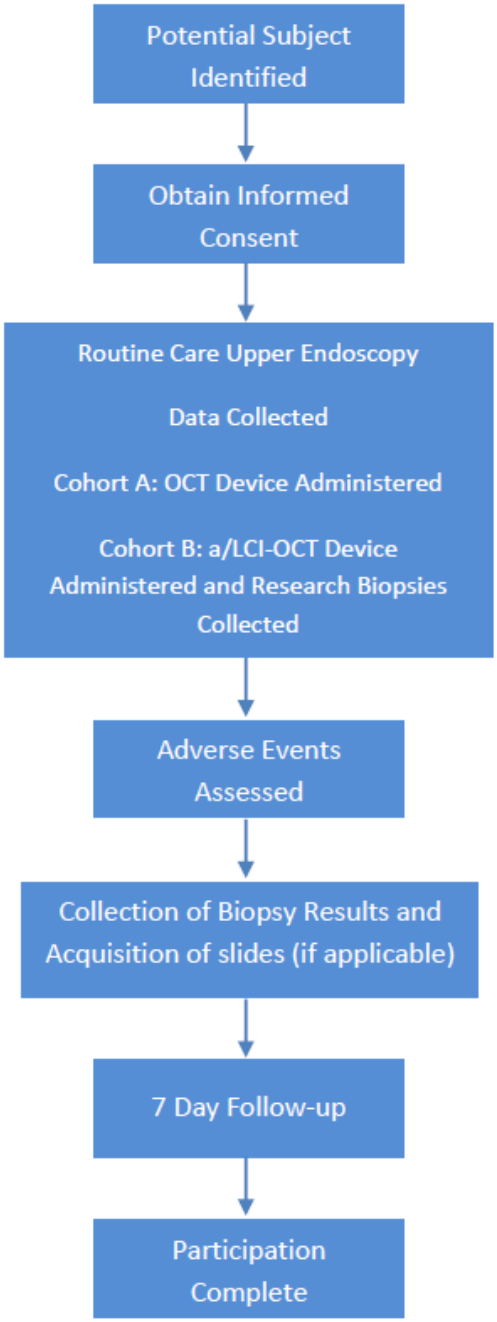
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Advanced a/LCI Systems for Improved Clinical Utility: An Optical Coherence Tomography (OCT) Pilot Study (OCT Pilot)
Study Description:	This is a pilot study to test the operating characteristics of a newly developed dual modality probe including optical coherence tomography (OCT) and angle-resolved low-coherence interferometry (a/LCI) in human subjects, and to collect data for further optimization of the a/LCI-OCT device. Phase I will incorporate the single modality OCT probe. Phase II will consist of a dual modality probe to include both OCT and a/LCI components. Potential subjects will be presenting to a UNC Endoscopy unit for routine upper endoscopy (EGD) for clinical signs or symptoms. If eligible, informed consent will be obtained prior to undergoing this routine care upper endoscopy. During the endoscopy, and prior to taking any biopsies, the probe will be attached to the end of the endoscope and passed with the endoscope into the esophagus. The probe will make contact with the epithelium of the esophagus, and data will be collected as part of this research study to identify operating characteristics of the new OCT device and the a/LCI-OCT combined device. Esophageal images and pictures will be obtained during the procedure and will be used in this study. If biopsies are taken for routine care (clinical biopsies), then results from those biopsies will be used in this study. For a subset of subjects, participating in the combined-modality probe, study-specific biopsies will be taken at the same location the probe is deployed, to allow comparison of data from the imaging modalities to "gold-standard" biopsy data. Additionally, slides may be requested from clinical biopsies for use in this study after they have yielded their results for routine care.
Objectives:	To test a newly developed imaging device in human subjects to determine 1) whether adequate tissue contact can be attained to acquire high quality images, and 2) to identify if these images can discern whether the imaged tissue is squamous or Barrett's Esophagus (BE) epithelium.
Endpoints:	None
Study Population:	Patients of UNC Healthcare undergoing routine care endoscopy with or without Barrett's Esophagus. Target enrollment includes two cohorts, with an approximate enrollment of up to 82 subjects. Cohort A will consist of 14 subjects in each of 3 groups; normal asymptomatic controls, non-dysplastic Barrett's Esophagus, and

	history of or current dysplastic Barrett's Esophagus (High Grade Dysplasia (HGD) or Low Grade Dysplasia (LGD)). Cohort B will consist of 20 patients in each of the two groups; current dysplastic Barrett's Esophagus of either High Grade Dysplasia (HGD) or Low Grade Dysplasia (LGD)) and normal controls (with or without history of previous successful esophageal ablation). Classification of patients will occur based on medical history and clinical pathology obtained during the EGD.
Description of Sites/Facilities Enrolling Participants:	UNC Chapel Hill (Enrolling Site) Duke University (Device Manufacture)
Description of Study Intervention:	The purpose of this instrument is to obtain optical measurements from the esophageal mucosa via an endoscopic probe. The modalities used by this probe are angle-resolved low-coherence interferometry (a/LCI) and Optical Coherence Tomography (OCT); depth-resolved optical imaging technology. These optical readings provide indications of subsurface tissue architecture and will assist in the detection and diagnosis of metaplastic and dysplastic conditions such as Barrett's esophagus. The probe is designed to be used in conjunction with the visual guidance provided by a commercial endoscope. The probe has mechanical features similar to a radiofrequency ablation (RFA) "paddle", which is externally attached to an endoscope to provide ablative therapy under visual guidance of the endoscope. Once inserted into a patient's esophagus and placed against the tissue surface, the probe will acquire 2D OCT images of the tissue surface at operator-selected locations. Some of the optical data received will be displayed in real-time. All optical data will also be stored on a computer for post hoc analysis. During Phase I the OCT instrument will be used alone. The components of the OCT device are grouped into the following modules: 1) Optical probe, 2) OCT engine, 3) computer system and 4) physical enclosure. Phase II of the study will consist of a dual modality a/LCI - OCT combined probe. The combined probe will consist of the following modules: 1) Optical probe, 2) OCT engine, 3) a/LCI engine, 4) computer system and 4) physical enclosure. See section 6.1 for detailed device descriptions.
Study Duration:	24 Months
Participant Duration:	7 days

1.2 SCHEMA


Potential Subject Identified
Obtain Informed Consent
Routine Care Upper Endoscopy
Data Collected
Cohort A: OCT Device Administered
Cohort B: a/LCI-OCT Device Administered and Research Biopsies Collected
Adverse Events Assessed
Collection of Biopsy Results and Acquisition of slides (if applicable)
7 Day Follow-up
Participation Complete

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures[7]	Screening[1]	Enrollment[1]	Post-EGD	7 Day Follow-Up (+/-3 days)
Informed consent	X			
Eligibility Assessment	X	X		
Demographics	X			
Medical history	X			
Urine Pregnancy Test		X[2]		
Routine Care EGD		X[3]		
Esophageal Images		X		
Research Biopsies		X[6]		
Administer Probe		X[5]		
Collection of Pathology Results			X[4]	
Adverse event review and evaluation	X	X		X
Complete Case Report Forms (CRFs)	X	X	X	X

[1]Screening and enrollment can occur on the same day
[2]Urine pregnancy tests will be performed on females with reproductive potential.
[3]EGD is performed as part of routine care. Subjects would be receiving this EGD regardless of participation in the study.
[4]Only if biopsies are taken for routine clinical care during the procedure. If biopsies are taken for routine clinical care during this procedure, then pathology results will be collected as part of this study, and slides may be requested from clinical biopsies for use in this study after they have yielded their results for routine care.
[5] Probe utilized can be either the OCT probe (Cohort A) or the combined a/LCI-OCT probe (Cohort B), based on Investigator discretion at time of enrollment.
[6] Research biopsies may be taken for participants in Cohort B, per discretion of principal investigator.
[7] Both cohorts (A and B) will follow the same schedule of activities, unless specifically mentioned otherwise.

2 INTRODUCTION

2.1 BACKGROUND

Barrett's esophagus (BE) is a metaplastic change where the normal squamous epithelium of the esophagus is replaced by intestinal columnar epithelium, typically in response to chronic gastro esophageal reflux.[1, 2] BE is a known risk factor for esophageal adenocarcinoma (EAC)[3], a cancer with a high mortality rate and rapidly increasing incidence in developed countries.[4, 5] The increased risk of cancer in BE patients leads to a need for surveillance, via endoscopy with random biopsies scattered across the affected tissue, using a biopsy pattern termed the "Seattle protocol".[6] However, this pattern samples <5% of BE tissue, leading to substantial sampling error. In spite of evidence that endoscopic surveillance does not substantially impact cancer mortality,[7] it is still the recommended management tool for in BE patients, due to a lack of proven alternatives.[8]

Because of this problem with sampling error, many optical techniques have been proposed for improving detection of pre-cancerous, dysplastic BE tissues but none have yet been widely adopted for routine use,[8] due primarily to limited performance. While high resolution methods, such as confocal microscopy, have shown good sensitivity and specificity, the need to manually move a point probe to scan large areas of epithelium limits clinical utility. In comparison, wide area imaging approaches, such as autofluorescence imaging, view more tissue area but offer lower sensitivity and specificity. Recently, Thekkek and Richards-Kortum advocated a multi-modality approach for optimal cervical screening.[9] Similar approaches have been suggested for BE screening as well.[10] The Investigators seek to create a novel imaging platform embodying this approach. This platform combines wide area imaging, using optical coherence tomography (OCT) to visualize esophageal epithelial regions, with high resolution, depth-resolved measurements of nuclear morphology, using angle-resolved LCI (a/LCI) to provide highly sensitive and specific detection of dysplasia.

The Investigators seek to implement and test advanced optical systems for detection of dysplastic tissue in BE patients. The a/LCI technique is based on examining the angular distribution of light scattering to determine structural features in a biological sample.[11] The approach can be used as a diagnostic of early pre-cancerous changes (dysplasia) by measuring the size of cell nuclei in the basal layer of the epithelium.[12] In a preliminary in vivo study, a/LCI nuclear morphology measurements were shown to be an effective biomarker for detecting dysplastic tissues in BE patients,[13] achieving 87.8% accuracy. Significantly, this biomarker has 100% negative predictive value (NPV), a strong justification for clinical use. The Investigators seek to improve the clinical utility of a/LCI by covering wider tissue areas and incorporating the visual guidance of OCT.

Angle-resolved LCI (a/LCI) and OCT are two imaging technologies that will be integrated into one probe. The purpose of the first phase of this pilot study is to utilize optical coherence tomography (OCT) technology alone. In the second phase of the study, the optical coherence tomography (OCT) technology will be combined with the angle-resolved LCI (a/LCI) into a multimodal device developed by investigators on a small population of patients in an effort to gather information necessary for continuing development as a screening tool described above.

2.2 STUDY RATIONALE

Esophageal adenocarcinoma (EAC) is a deadly disease which has been rapidly increasing in incidence.[14] The rate of mortality from this cancer has remained above 80%,[14] even as mortality and incidence of other types of gastrointestinal cancers, such as colon cancer[15], have been decreased through improved screening programs.[16] The leading risk factor for EAC is Barrett's esophagus (BE), a very common metaplastic tissue condition arising from gastroesophageal reflux disease (GERD)[3] which is thought to be the precursor to this cancer. BE can progress to EAC through dysplastic changes,[17] transitioning from non-dysplastic BE to low grade dysplasia (LGD), high grade dysplasia (HGD), and eventually EAC.[18] The increased risk of EAC in BE patients justifies periodic surveillance via endoscopy with biopsy[3]. The difficulty of accurate identification of dysplasia in the epithelium requires clinical guidelines to recommend frequent surveillance endoscopy[8]. However, the endoscopic surveillance protocol is laborious,[8] and nearly half of surveillance procedures do not adhere to guidelines.[19] The net result is that current surveillance approaches are not particularly effective at preventing mortality.[7] The need for more effective tools for preventing esophageal cancer in the setting of BE is urgent, especially given that 2-3 million Americans harbor this lesion.

Investigators seek to create a multimodal screening tool that combines in situ measurements of nuclear morphology, a proven biomarker of dysplastic progression[20], with an imaging modality that gives visual representation of the architecture of BE tissues.[21-24] Angle-resolved LCI (a/LCI) obtains accurate, high resolution nuclear morphology measurements using depth-gated light scattering measurements[11,25]. Investigators have shown that a/LCI nuclear morphology measurements can detect dysplastic lesions in vivo in the esophagus[26] and ex vivo in other types of epithelia such as colon[27] and trachea[28] with high sensitivity and specificity. As a standalone modality, a/LCI is somewhat limited for clinical screening of BE tissues in that it has only been implemented as a point modality to date. To address this limitation, investigators propose to expand a/LCI to cover more tissue area with each measurement and to incorporate image guidance using optical coherence tomography (OCT), as a "red flag" to help target abnormal tissue for closer interrogation. OCT provides micron scale, cross-sectional tissue images. It can discriminate BE tissues from typical squamous epithelium but has lesser accuracy in detecting dysplasia compared to a/LCI.[21-24] By combining these two imaging modalities, investigators seek to provide a more incisive, clinically useful tool to aid physicians in diagnosis and monitoring of BE patients.

Angle-resolved LCI (a/LCI) and OCT are two imaging technologies that will be integrated into one probe. The purpose of this pilot study is to first utilize optical coherence tomography (OCT) technology alone, delivering it in a form factor that is conducive to upper endoscopy. In the second phase of the study, the optical coherence tomography (OCT) technology will be combined with the angle-resolved LCI (a/LCI) into a multimodal device developed by investigators on a small population of patients in an effort to gather information necessary for continuing development as a screening tool described above.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There are no known complications due to application of either a/LCI or OCT imaging techniques. Similar approaches have been previously approved by the UNC and Duke IRBs as non-significant risk device studies, and there were no safety issues in that study (UNC IRB# 07-1860).

Although the technique is not invasive, the probe itself will come in contact with esophageal tissue. For the dual modaility probe (a/LCI-OCT) a small invagination in the surface of the instrument will mark the mucosa of the eosphagus applied at the same location images are taken. This will aid in co-localization of research biopsies, to allow comparison of optical and histological diagnoses. We have used similar methodology in a previous study[26], with no adverse events noted. However, there is a theoretical risk of infection. To guard against this, the probe will be cleaned per current clinically approved methods for disinfecting endoscopy equipment which will utilize Cidex and/or Revital-Ox. Disinfection methods for this study have been reviewed and approved by the UNC Hospitals outpatient care and instrument reprocessing group. Refer to study standard operating procedures for additional information.

To date, there have been no adverse effects reported from exposure to the spectrum of light used in this device. Additionally, the device does not generate thermal injury, and because it is placed on the epithelial surface, and does not penetrate the tissue, no epithelial trauma is experienced. There is no risk of radiation from this device because the device uses only light waves.

Because the device is administered in conjunction with an upper endoscopy, there are a number of potential risks associated with the endoscopy that will be reviewed with subjects as part of their clinical care. There are also adverse events subjects may experience as a result of the endoscopy in which the contribution of the device may not be able to be ruled out. However, these events will be considered expected unless the nature, severity, or frequency implies the event is possibly related to the device itself (>50% likelihood that the event is related to the device or study procedures). These events include but are not limited to: throat irritation including scratchy or sore throat, esophageal pain, bloating, bleeding or tearing (perforation) of tissue in the esophagus, allergic reaction to the medication used for the endoscopy procedure (nausea, vomiting, fever, hypoxia (reduction in oxygen to tissues), pneumonia, adverse drug reactions, urine retention, clumsiness, drowsiness, blurred vision, and death), or aspiration of contents into the lungs. This may require the use of antibiotics, hospitalization and sometimes a surgery to repair.

The number of biopsies taken for this study is within the spectrum of routine clinical practice for esophageal diseases and Barrett's Esophagus in particular. Nevertheless, there is a very small risk of perforation or significant bleeding that would require a blood transfusion or other measures to stop the bleeding. To minimize this risk, subjects will be monitored for any bleeding during the biopsy portion of the procedure, and if bleeding is heavy, clinically indicated actions to stop the bleeding will be performed, and further biopsy procurement will be stopped. In the performance of esophageal research biopsies in greater than 5,000 patients previously, the investigators have not either had to perform endoscopic therapy to halt bleeding, nor has any patient experienced esophageal perforation.

2.3.2 KNOWN POTENTIAL BENEFITS

This study will not likely result in immediate direct benefit to its participants. Because standard-of-care endoscopy will be performed regardless of imaging results, and because the imaging results from this trial will not be clinically actionable, immediate benefit in participation is not anticipated. However, should these imaging approaches be found to be an accurate, safe, and well-tolerated means of monitoring this patient population, several potential benefits would accrue to both study participants and others who undergo upper endoscopy. These individuals would have the option of a more efficient surveillance method.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

There are no known complications due to application of the a/LCI or OCT imaging techniques, with similar approaches having been previously approved by the UNC and Duke IRBs as a non-significant risk device. The new instruments will again be evaluated by the IRB for application in this study.

The endoscopy referenced in this pilot study is performed as routine clinical care for patients and not specific to participation in this study, meaning subjects would undergo this procedure regardless of participation in this study.

Serious risk of endoscopic biopsies is very uncommon in subjects without known bleeding disorders and in those who do not regularly take blood thinning medications (such as aspirin, nonsteroidal anti-inflammatory medications, Coumadin (warfarin), Plavix, Lovenox, heparin, and low molecular weight

heparin). This is because the biopsies are very small (2-3 mm) and are obtained with blunt tipped forceps under direct vision of the physician performing the endoscopy. Possible serious complications include excess bleeding from the biopsy sites causing the blood pressure to drop and/or the need for blood transfusion or esophageal perforation (tear) due to trauma.

More common, but not serious, is minor bleeding which requires no treatment or responds to treatment with oral antacids. The risk of bleeding secondary to endoscopic biopsies is less than 1/1,000 and there is an even smaller risk of perforation or infection. When bleeding does occur, adequate medical staff and equipment are on hand to abate any long-term damage that could result from this risk. These participants will often already be undergoing biopsies as part of their standard of care so the incremental risk is expected to be minimal. The additional time necessary to complete biopsies for this study will be less than 2 minutes.

The Seattle biopsy protocol is used for standard of care (SOC) which includes taking 4 quadrant biopsies every one to two centimeters throughout the area of interest. Because we generally take these biopsies every two centimeters, up to 10 research biopsies in addition to SOC biopsies would generally be within the total number of biopsies advocated as the standard of care (give our mean BE segment length of 4-5 cm). It should also be noted that no higher incidence of complications has been documented by taking biopsies by the more aggressive biopsy protocol (4 biopsies every one cm) than the less aggressive (4 biopsies every two cm) protocol.

Given the excellent safety profile of these imaging techniques, the risks and costs inherent in the current standard of care, the potential benefits of this investigation outweigh the risks.

3 OBJECTIVES AND OUTCOMES

The purpose of this pilot study is to use the angle-resolved Low-Coherence Interferometry (a/LCI) and optical coherence tomography (OCT) technologies, developed by investigators on a small population of patients in an effort to gather information necessary for continuing development as a screening tool described above. Specifically, the study is designed to test the newly developed a/LCI-OCT device in human subjects to determine 1) whether adequate tissue contact can be attained to acquire high quality images, and 2) to identify if these images can discern whether the imaged tissue is squamous or BE epithelium.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a pilot study to test the operating characteristics of a newly developed optical coherence tomography (OCT) device in human subjects, and to collect data for further optimization of the OCT device.
Phase II of the study will consist of a combined probe consisting of angle-resolved Low-Coherence Interferometry (a/LCI) with developed optical coherence tomography (OCT).

Potential subjects will be presenting to a UNC Endoscopy unit for routine care endoscopy for clinical signs or symptoms. If eligible, informed consent will be obtained prior to undergoing routine care upper endoscopy. During the endoscopy, and prior to taking any routine care biopsies, the probe will be attached to the end of the endoscope and passed with the endoscope into the esophagus. The probe will make contact with the epithelium of the esophagus, and data will be collected as part of this research study to identify operating characteristics of the new device. Esophageal images and pictures will be obtained during the procedure and will be used in this study.

In Cohort A, if biopsies are taken for routine care, then results from those biopsies will be used in this study. Slides may be requested from clinical biopsies for use in this study, after they have yielded their results for routine care.

In Cohort B, co-localized research biopsies may be taken at the same location the probe is deployed. The indentation on the surface of the probe leaves a transient raised area of mucosa, which will aid in endoscopic identification of the site and allow for targeted concurrent biopsies.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a pilot study to test the operating characteristics of a newly developed optical coherence tomography (OCT) and angle-resolved Low-Coherence Interferometry (a/LCI) imaging technologies in human subjects.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Subjects must meet all of the following criteria to be eligible for this study:

1. Presenting to UNC for routine care upper endoscopy
2. Meet one of the following criteria:
   2.1. Cohort A
      2.1.1. Presenting to UNC for upper endoscopy of GI conditions without esophageal symptomology with no history of gastroesophageal reflux disease (GERD) or other esophageal condition affecting the epithelium (asymptomatic controls). Esophageal

symptomology includes, but is not limited to, heartburn, globus, chest pain, dysphagia, and odonophagia OR,

2.1.2. Current dysplastic or non-dysplastic Barrett's Esophagus of any length OR,

2.1.3. History of dysplastic or non-dysplastic Barrett's Esophagus after treatment with endoscopic eradication therapy (EET)

OR

2.2. Cohort B

2.2.1. Current dysplastic or non-dysplastic Barrett's Esophagus of any length OR,

2.2.2. History of dysplastic or non-dysplastic Barrett's Esophagus after treatment with endoscopic eradication therapy (EET) OR,

2.2.3. Normal asymptomatic controls without any history of dysplastic Barrett's Esophagus

AND

3. Aged 18 to 80
4. Able to read, comprehend, and understand the informed consent document.

5.2 EXCLUSION CRITERIA

Subjects meeting any of the exclusion criteria below will not be eligible for this study:

1. Prior esophageal surgery (uncomplicated nissen fundoplication OK)
2. Pregnant women
3. Unable to provide written informed consent
4. History of esophageal stricture or prior esophageal dilation

Additionally, subjects meeting any of the exclusion criteria below will not be eligible for Cohort B of this study:

5. Uncontrolled coagulopathy

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

6 STUDY INTERVENTION

6.1 DEVICE DESCRIPTION

The purpose of this instrument is to obtain optical measurements from the esophageal mucosa via an endoscopic probe. The imaging modalities used by this probe are angle-resolved Low-Coherence Interferometry (a/LCI), a technology that measures the depth- and angle-dependent scattering of light by tissue and Optical Coherence Tomography (OCT), a depth-resolved optical imaging technology. These optical readings provide indications of subsurface tissue architecture and will assist in the detection and diagnosis of metaplastic and dysplastic conditions such as Barrett's esophagus.

The probe is designed to be used in conjunction with the visual guidance provided by a commercial endoscope. The probe has mechanical features similar to a radiofrequency ablation (RFA) "paddle",

which is externally attached to an endoscope to provide ablative therapy under visual guidance of the endoscope. This form is advantageous because it is known to be well-tolerated and easily passed when mounted on the endoscope. It will also eventually allow the development of a single paddle that could both image and treat diseased mucosa.

Once inserted into a patient's esophagus and placed against the tissue surface, the probe will acquire 2D OCT images of the tissue surface at operator-selected locations. Some of the optical data received will be displayed in real-time. All optical data will also be stored on a computer for post hoc analysis.

The components of the combined probe system a/LCI-OCT instrument are grouped into the following modules: 1) Optical probe, 2) OCT engine, 3) a/LCI engine, 4) computer system, and 5) physical enclosure.

6.1.1 aCI/OCT OPTICAL PROBE

The optical probe is similar in form to a RFA "paddle," with a length of approximately 23 mm, width of 14 mm, and a thickness of 4 mm. The paddle housing is fabricated by a 3D printing process known as stereolithography (SLA). A miniature optical assembly for both a/LCI and OCT imaging is contained within the paddle, composed of silica and borosilicate glass, optical fiber, and optical adhesives. These components are fully enclosed within the paddle, except for the optical fiber, which extends from the paddle through a hollow sheath to the optical engine. The paddle and sheath are sealed against air and moisture to isolate the internal optical components from the patient environment. A transparent region of the paddle housing allows the beam to exit the paddle. Figure 1 below illustrates the general concept of the paddle probe attachment to the endoscope. Figure 2 depicts the probe layout within the paddle. (This figure is schematic and not to scale.)

The OCT modality components will rotate on command to sweep a beam across the tissue surface to generate 2D images, as well as translate longitudinally on command to generate 3D volumes. The speed of OCT rotation will be 40 rotations per second (2,400 rotations per minute) or less. The speed of OCT translation will be 2 mm per second or less.

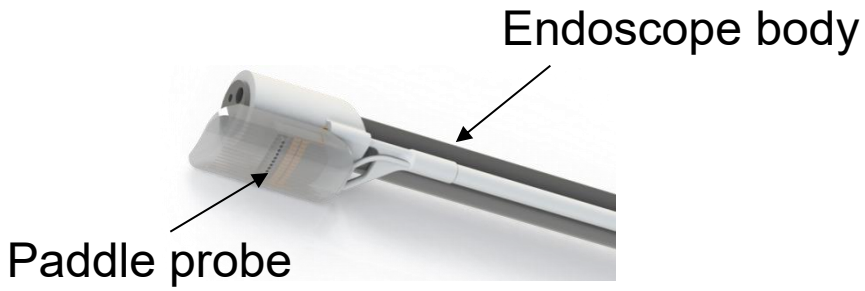
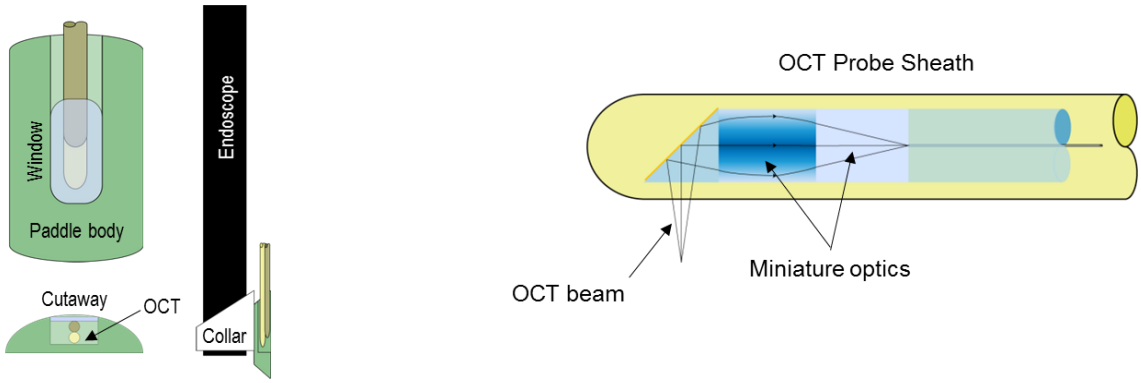


Figure 1: 3D concept rendering of probe paddle attached to endoscope

Figure 2: Schematic for placement of optical probe components within paddle. Right, schematic of OCT optical component layout within OCT probe



To transduce its linear and rotational motion, a wound steel torque coil encloses the OCT optical fiber, which transmits force from motors mounted on the OCT engine to the OCT optical components within the paddle.

A flexible tether containing the OCT driveshaft and optical fiber protrudes from the proximal end of the probe, runs alongside the endoscope until it exits the body where it is connected to the OCT engine. The probe contains no electrical components or wires.

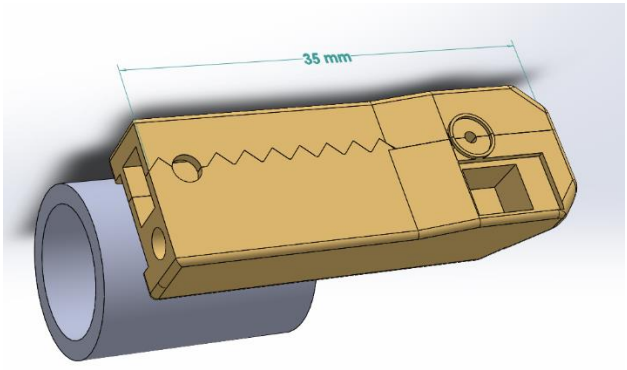


Figure 3: 3D drawing of paddle probe housing. This housing will contain miniature optics and will be attached to the tip of an upper GI endoscope via a silicone cuff (gray cylinder).

6.1.2 OCT ENGINE

The OCT engine contains the optical, electrical, and mechanical components related to the acquisition of OCT images from the esophagus.

The OCT system includes a light source (superluminescent diode, Exalos AG) emitting at approximately 1300 nm, a spectrometer composed of lenses and a diffraction grating, a sensor (linear array camera, Sensors Unlimited Inc.), a rotary motor system including a motor driver and belt assembly, a fiber-optic rotary junction (FORJ, Princetel), a translational motor system including a motor driver and translating stage, and various optical fibers, connectors, and controllers.

In brief, the OCT light source transmits light that is simultaneously divided among two paths: a static reflector within the OCT engine ("reference" light) and a path directed towards the patient tissue via the probe ("sample" light). The FORJ allows the probe fiber to rotate relative to the stationary fiber while remaining optically connected. The light from both sample and reference paths are recombined by a fiber coupler, resulting in an interference pattern that encodes the depth of reflective objects and surfaces in the sample. This interference is detected by a spectrometer, which divides the interference signal into its constituent wavelengths that are individually detected by pixels of a linear camera. Figure 4 below depicts the block diagram of the OCT engine.

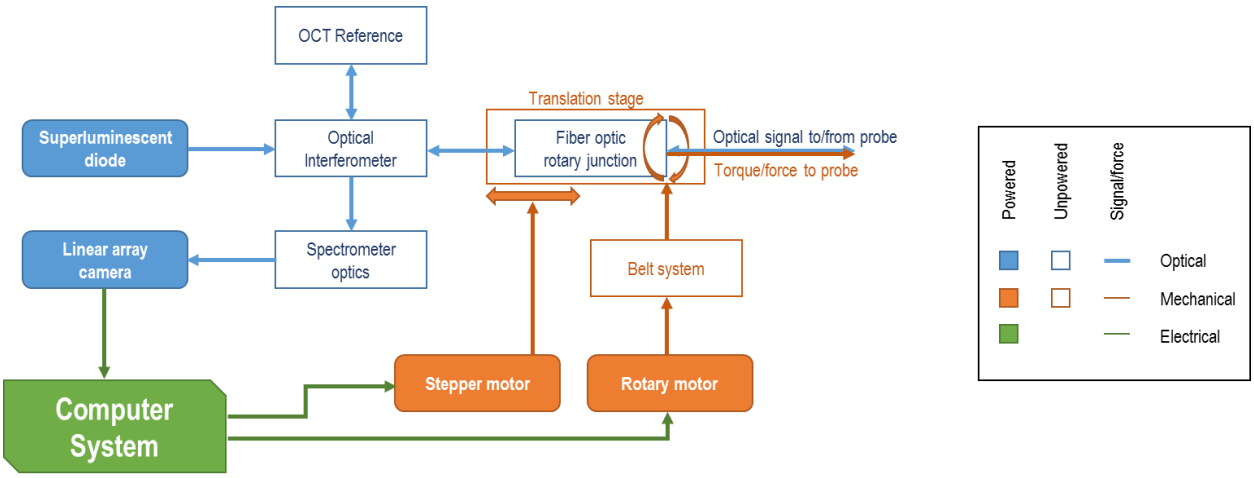


Figure 4: Block diagram of OCT engine components

Each such measurement produces a column of data, or "A-scan," which represents the depth-resolved reflectance profile of the tissue where the OCT beam intersects it. To produce 2D OCT images, the miniature optics in the probe are rotated by the rotary motor and FORJ system, which are mechanically linked by a belt system and the wound-steel torque coil within the probe sheath. To produce 3D OCT images, a stage is translated by a stepper motor such that the entire fiber optic assembly moves longitudinally during its rotation, resulting in a spiral scan.

The maximum permissible exposure (MPE) for exposures greater than 10 seconds on skin is 1.0 W/cm^2 at the principal OCT wavelength of 1300 nm and a defined limiting aperture of 3.5 mm diameter (ANSI Z136.1). The OCT beam focus falls entirely within the 3.5 mm (0.35 cm) aperture, and thus is the power limit is 1.0 W/cm^2 * 3.14 * (0.175 cm)^2 = 96.2 mW. The total power of OCT beam on the tissue is less than 20 mW.

6.1.3 A/LCI ENGINE

The a/LCI engine contains the optical, electrical, and mechanical components related to the acquisition of a/LCI images from the esophagus. a/LCI, uses the pattern of scattered light to measure the size of nuclei within the epithelium, which is a known biomarker for dysplasia.

The a/LCI engine is very similar to the OCT engine in terms of the diagrammatic modules that compose the system, operating in parallel with the OCT engine.

The a/LCI engine includes a light source (superluminescent diode, Superlum) emitting at approximately 830 nm, a spectrometer composed of lenses and a diffraction grating, a sensor (area camera, FLIR Imaging), and various optics that compose the interferometer. The interferometer sends light to the probe via an optical fiber, collects the scattered light returning from the probe's optical fiber bundle, and combines that sample light with reference light to be detected on the camera.

The maximum permissible exposure (MPE) for exposures greater than 10 seconds on skin is 3.6 mW/mm2 at our principal wavelength of 830 nm (ANSI Z136.1). Our imaging region in the tissue is approximately 100 µm, smaller than the minimum limiting aperture given in ANSI Z136.1 of 3.5 mm. Our total permissible power is thus 3.6 mW/mm2 x 3.14 x (1.75 mm)2 = 34.6 mW. Our maximum power of 10 mW is much lower than the ANSI MPE.

6.1.4 A/LCI OPTICAL PROBE

The optical probe is similar in form to a RFA "paddle," with a length of approximately 23 mm, width of 14 mm, and a thickness of 4 mm. The paddle housing is fabricated by a 3D printing process known as stereolithography (SLA). Miniature optical assembly for a/LCI is contained within the paddle, composed of silica and borosilicate glass, optical fibers, and optical adhesives. These components are fully enclosed within the paddle, except for the optical fibers, which extend from the paddle through a hollow sheath to the a/LCI optical engine. The paddle and sheath are sealed against air and moisture to isolate the internal optical components from the patient environment. Transparent window regions of the paddle housing allow the a/LCI beam to exit the paddle.

Upon identification of an area of interest on the esophagus, based on video endoscopy and/or the OCT images, an a/LCI acquisition will be initiated. This component does not entail moving parts in the probe, but engages a series of optical acquisitions lasting less than 10 seconds while the probe is held in place. A flexible tube containing the OCT driveshaft and optical fiber protrudes from the proximal end of the probe, runs alongside the endoscope until it exits the body where it is connected to the OCT engine. A second tube containing the a/LCI illumination and detection fibers runs parallel to the first. Both tubes are tethered together in a single outer tubing, composed of polyolefin. The probe contains no electrical components or wires.

6.1.5 A/LCI-OCT ENGINE

The combined a/LCI-OCT engine will operate both systems in tandem. Individual components have been previously described in Section 6.1.2 and 6.1.3. Figure 5 below depicts the block diagram of combined a/LCI-OCT engine.

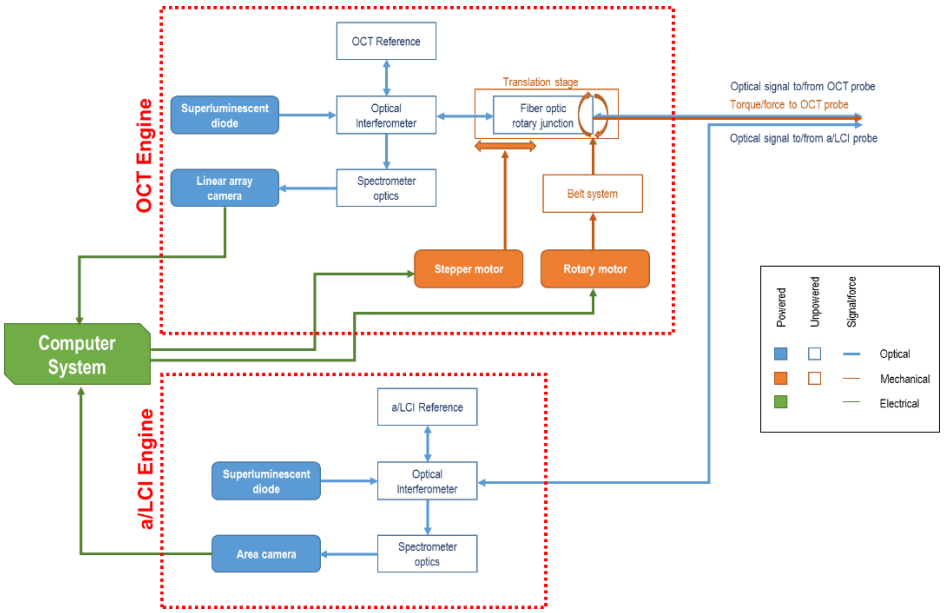


Figure 5: Block diagram of combined a/LCI and OCT engine components.

6.1.6 COMPUTER

A computer workstation performs the data acquisition and control through a custom application. Software control of the data acquisition sequence is provided. Real-time display of the OCT and a/LCI data is shown on a monitor. Raw and/or processed OCT image data and a/LCI data are saved to the hard drive. Storage of patient data on the computer is protected by encryption (Bitlocker).

6.1.7 PHYSICAL ENCLOSURE AND POWER BUS

The a/LCI and OCT engine and computer are contained within a painted and grounded aluminum enclosure. An isolated 120V power bus is connected through a medical isolation transformer, which provides power to all electrical components.

6.2 NON-SIGNIFICANT RISK (NSR)

6.2.1 NSR JUSTIFICATION

The FDA defines an NSR device as one which does not meet the definition of a significant risk (SR) device. Per 21 CFR 812.3(m), a Significant Risk Device is an investigational device that:

a. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

b. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
c. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
d. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

This device is (a) not intended as an implant, (b) is not used to support or sustain life, (c) is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; and (d) does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

In fact, the FDA guidance document titled "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies," specifically cites gastroenterology and urology endoscopes and accessories as examples of non-significant risk devices (Section X, subpart A, page 8).

6.2.2 NSR COMPLIANCE

The device used in this study may be deemed a non-significant risk (NSR) device by the IRB or FDA. If deemed an NSR, this means the device qualifies for an abbreviated investigational device exemption (IDE). To qualify as an NSR, the FDA or IRB must determine the device does not pose a serious risk to the health, safety or welfare of a subject and does not otherwise meet the definition of a significant risk device according to 21 CFR 812.3(m). If deemed non-significant risk (NSR); the sponsor and investigator must comply with "abbreviated IDE requirements" described in 21CFR812.

Subpart A--General Provisions
§ 812.1 **- Scope.**
§ 812.2 **- Applicability.**
§ 812.3 **- Definitions.**
§ 812.5 **- Labeling of investigational devices.**
§ 812.7 **- Prohibition of promotion and other practices.**
§ 812.10 **- Waivers.**
§ 812.18 **- Import and export requirements.**
§ 812.19 **- Address for IDE correspondence.**
Subpart B--Application and Administrative Action
§ 812.20 **- Application.**
§ 812.25 **- Investigational plan.**
§ 812.27 **- Report of prior investigations.**
§ 812.30 **- FDA action on applications.**
§ 812.35 **- Supplemental applications.**
§ 812.36 **- Treatment use of an investigational device.**
§ 812.38 **- Confidentiality of data and information.**
Subpart C--Responsibilities of Sponsors
§ 812.40 **- General responsibilities of sponsors.**

§ 812.42 - FDA and IRB approval.
§ 812.43 - Selecting investigators and monitors.
§ 812.45 - Informing investigators.
§ 812.46 - Monitoring investigations.
§ 812.47 - Emergency research under 50.24 of this chapter.
Subpart D--IRB Review and Approval
§ 812.60 - IRB composition, duties, and functions.
§ 812.62 - IRB approval.
§ 812.64 - IRB's continuing review.
§ 812.65 - [Reserved]
§ 812.66 - Significant risk device determinations.
Subpart E--Responsibilities of Investigators
§ 812.100 - General responsibilities of investigators.
§ 812.110 - Specific responsibilities of investigators.
§ 812.119 - Disqualification of a clinical investigator.
Subpart F [Reserved]
Subpart G--Records and Reports
§ 812.140 - Records.
§ 812.145 - Inspections.
§ 812.150 - Reports.

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812

6.3 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.3.1 ACQUISITION AND ACCOUNTABILITY

The devices listed in this protocol will be manufactured by the co-PI, Dr. Adam Wax, at Duke University and provided to UNC Chapel Hill for use in this pilot study. Accountability logs will be maintained by both Duke University and UNC Chapel Hill.

6.3.2 DEVICE LABELING

The device will be labeled with a serial number, and in accordance with 21CFR812.5 (below):

(a) Contents. An investigational device or its immediate package shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with §801.1), the quantity of contents, if appropriate, and the following statement: “CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use.” The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

(b) Prohibitions. The labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

(c) Animal research. An investigational device shipped solely for research on or with laboratory animals shall bear on its label the following statement: "CAUTION—Device for investigational use in laboratory animals or other tests that do not involve human subjects."

(d) The appropriate FDA Center Director, according to the procedures set forth in §801.128 or §809.11 of this chapter, may grant an exception or alternative to the provisions in paragraphs (a) and (c) of this section, to the extent that these provisions are not explicitly required by statute, for specified lots, batches, or other units of a device that are or will be included in the Strategic National Stockpile.

6.3.3 DEVICE STORAGE

The device(s) will be stored in a secure location with access limited to research personnel.

6.3.4 PREPARATION

Prior to each use, the device will be cleaned per current clinically approved methods for disinfecting endoscopy equipment which will utilize Cidex and/or Revital-Ox. Disinfection methods for this study have been reviewed and approved by the UNC Hospitals outpatient care and instrument reprocessing group. Refer to study standard operating procedures for additional information.

6.4 CONCOMITANT THERAPY

There are no medication restrictions to participate in this study other than the standard of care medication discontinuation instructions patients receive in preparation for an upper endoscopy.

6.4.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 STRATEGIES FOR RECRUITMENT AND RETENTION

All participants will be screened and enrolled using IRB-approved and HIPAA compliant methods. IRB approved site personnel will obtain consent prior to completion of 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. After the subject signs the consent, a copy of the signed consent will be provided to the subject. The consent process will be documented.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

This is a pilot study involving one-time collection of data during a routine care endoscopy. Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study if the participant is deemed ineligible based on findings from the endoscopy, or other reason.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are withdrawn may be replaced.

Withdrawn or terminated subjects will be excluded from the study. If data were collected, then they will not be used.

7.3 LOST TO FOLLOW-UP

This pilot study involves a one-time visit with data collection. However, if for some reason a subject needs to be contacted for follow-up, then a participant will be considered lost to follow-up if he or she fails to return for a scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening[1]	Enrollment[1]	Post-EGD	7 Day Follow-Up (+/-3 days)
Informed consent	X			
Eligibility Assessment	X	X		
Demographics	X			
Medical history	X			
Urine Pregnancy Test		X[2]		
Routine Care EGD		X[3]		
Esophageal Images		X		
Research biopsies		X[6]		
Administer Probe[5]		X		
Collection of Pathology Results			X[4]	
Adverse event review and evaluation	X	X		X
Complete Case Report Forms (CRFs)	X	X	X	X

[1]Screening and enrollment can occur on the same day
[2]Urine pregnancy tests will be performed on females with reproductive potential.
[3]EGD is performed as part of routine care. Subjects would be receiving this EGD regardless of participation in the study.
[4]Only if biopsies are taken for routine clinical care during the procedure. If biopsies are taken for routine clinical care during this procedure, then pathology results will be collected as part of this study, and slides may be requested from clinical biopsies for use in this study after they have yielded their results for routine care.
[5] Probe utilized can be either the OCT probe (Cohort A) or the combined a/LCI-OCT probe (Cohort B), based on Investigator discretion at time of enrollment.
[6] Research biopsies may be taken for participants in Cohort B.

8.1.1 SCREENING

The following procedures will be performed during the screening visit:

1) Identification of potential subjects via IRB approved methods
2) Informed consent (see section 10.1.1 for details regarding the informed consent process)
3) Collection of data including demographics and medical history
4) Complete CRFs and data entry

8.1.2 ENROLLMENT

The following procedures will be performed during the enrollment visit:

1) Re-assess eligibility

2) Completion of urine pregnancy test on women with reproductive potential
3) Administration of OCT-probe for Cohort A or combined a/LCI-OCT probe for Cohort B and completion of esophageal images during routine care upper endoscopy
4) Collection of data from endoscopy
5) Collection of co-localized research biopsies (Cohort B)
6) Adverse event assessment
7) Complete CRFs and data entry

For this study, an enrolled subject is defined as a subject who was successfully administered the OCT device and for whom we have evaluable data.

***Screening and enrollment can occur on the same day.

8.1.2.1 PROBE ADMINISTRATION, ESOPHAGEAL IMAGES, AND RESEARCH BIOPSIES

Subjects will proceed with routine care EGD, during which esophageal landmarks will be identified, and the OCT or a/LCI-OCT device administered. In brief, the probe will be affixed to the end of the endoscopy using a plastic band, in a manner similar to that used to deliver other devices into the esophagus. The device and endoscope tip will be passed through the posterior pharynx and the upper esophageal sphincter under direct endoscopic visualization. Areas of normal squamous epithelium can be easily identified endoscopically, as can areas of columnar mucosa in the esophagus, based on the endoscopic appearance. The OCT or a/LCI-OCT combined device will be apposed to both normal and columnar (Barrett's) tissue, by deflection of the endoscope tip. Images will be acquired by the device, as detailed below, and subjects enrolled in cohort B will also receive research-specific biopsies as detailed below. The indentation on the tip of the probe will create a transient tissue bump that is visible endoscopically to allow for concurrent research biopsies after images are taken.After acquisition of these images and research biopsies (as applicable), the remainder of the study will be performed as per the standard of care.

Erosions, erosive disease, and areas of inflammation will be avoided when placing the paddle for probe administration. Adequacy of device-to-epithelium contact will be measured based on the quality of the OCT image. In images with poor contact, esophageal mucosal layers are poorly defined. In this situation, the probe will be repositioned in an effort to improve image quality. A good image is that in which esophageal mucosal layers are clearly defined in the OCT image.

COHORT A:
During the procedure, the OCT device will be administered, and at least one white light image and at least one narrow band image will be taken from the following locations of the esophagus:

1) 3 centimeters above the top of the gastric folds (TGF-3)
2) 5 centimeters above the top of the gastric folds (TGF-5)
3) Any planned clinical biopsy locations

COHORT B:
During the procedure, the a/LCI-OCT device will be administered, and at least one white light image and at least one narrow band image will be taken from the following locations of the esophagus:

1) 3 centimeters above the top of the gastric folds (TGF-3)
2) 5 centimeters above the top of the gastric folds (TGF-5)

3) Co-localized research-specific biopsies will be taken at the imaging location
4) Any planned clinical biopsy locations

Variations to the imaging protocol (location and number of images obtained) are allowable and are not considered protocol deviations.

Device images will not be used to diagnose or categorize participants. Participants will be categorized based on endoscopy, clinical pathology and medical history, as per usual clinical practice. If no biopsies are taken for clinical care, and the subject is presenting for upper endoscopy for GI conditions without esophageal symptomatology, then the epithelium will be assumed to be normal squamous epithelium per the endoscopic imaging.

8.1.2.2 PATHOLOGY REPORTS AND SLIDES ACQUISITION

If clinical biopsies are obtained during the enrollment upper endoscopy, then results from those clinical biopsies will be obtained for this research study after they have yielded their results for routine care.

Slides may be requested from clinical biopsies and used as part of this research study.

8.1.2.3 RESEARCH BIOPSY COLLECTION AND ANALYSIS

For participants enrolled in cohort B, research biopsies will be obtained from the location of device imaging. Research biopsies are taken only if the additional biopsies do not significantly increase the patient's risk or interfere with routine care procedures. The research biopsy protocol may be modified by the physician performing the procedure if necessary. During the procedure up to 10 research biopsies may be taken for use in this study. The total number of research biopsies may vary based on presence/absence of nodularity but will not exceed 10 research-specific biopsies. This number of esophageal biopsies is within the standard of care for biopsying the esophagus. Biopsies will be immediately placed in formalin for processing and histopathological analysis by Dr. Goldblum.

Variations to the biopsy protocol (location and number of specimens obtained) are allowable and are not considered protocol deviations.

8.1.3 7 DAY FOLLOW-UP

Enrolled subjects will be contacted 7 days (+/-3 days) after administration of the device via phone or other IRB approved method. Subjects who do not meet the definition of enrolled will not be contacted. During the 7 day follow-up, the following procedures will be performed:

1) Assess for adverse events
2) Complete eCRF and data entry

No additional follow-up is anticipated.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

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

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

1) Death,
2) A life-threatening adverse event,
3) Inpatient hospitalization or prolongation of existing hospitalization,
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
5) A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.3 UNANTICIPATED ADVERSE DEVICE EFFECT

According to 21 CFR 812.3(s), an “unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.”

8.2.4 CLASSIFICATION OF AN ADVERSE EVENT

8.2.4.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Grade 1 (Mild)** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.

- **Grade 2 (Moderate)** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 (Severe)** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."
- **Grade 4 (Life-Threatening) -** Life-threatening consequences; urgent intervention indicated.
- **Grade 5 (Death) -** Death related to AE.

8.2.4.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by an investigator who evaluates the event based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

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

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.2.4.3 EXPECTEDNESS

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

8.2.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

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

All AEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study device (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

Research staff will record all adverse events with start dates occurring any time after informed consent is obtained until completion of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All new or worsening adverse events (AEs) will be collected for all subjects from the time of subject enrollment through completion or termination of the clinical investigation. This includes AEs that are not device or procedure related.

8.2.6 ADVERSE EVENT REPORTING

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

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

8.2.7 OTHER SAFETY REPORTING

Sites may have additional safety reporting requirements or reporting requirements that differ from those outlined in this protocol. Sites are responsible for complying with requirements outlined in this protocol, as well as any local reporting requirements and definitions.

8.2.8 REPORTING EVENTS TO PARTICIPANTS

Not applicable. Participation involves a one-time visit. Safety information will be reviewed as part of the initial consent process, and consent will be obtained with new safety information as applicable.

8.2.9 EVENTS OF SPECIAL INTEREST

Not applicable.

8.2.10 REPORTING OF PREGNANCY

Not applicable.

8.3 UNANTICIPATED PROBLEMS

8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP) AND UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research, reasonable possibility means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures); and

- Serious or suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

According to 21 CFR 812.3(s), an unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.3.2 UNANTICIPATED PROBLEM (UP) REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and other study investigators. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

Unanticipated problems must be reported to participating investigators within **48 hours** of learning of the event, and to local IRBs per local IRB reporting policies.

Participating sites are responsible for ensuring compliance with local IRB policies and procedures on safety reporting, which may differ from those outlined in this protocol.

8.3.3 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE) REPORTING

Unanticipated adverse device effects (UADEs) must be reported to participating investigators within **48 hours** of learning of the event, and to local IRBs per local IRB reporting policies.

Per 21 CFR 812.46, a sponsor shall immediately conduct an evaluation of any unanticipated device effects. A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.

A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators

within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests 21 CFR 812.150(b)(1)).

Participating sites are responsible for ensuring compliance with local IRB policies and procedures on safety reporting, which may differ from those outlined in this protocol.

8.3.4 REPORTING UNANTICIPATED PROBLEMS (UPS) AND UNANTICIPATED ADVERSE DEVICE EFFECTS (UADES) TO PARTICIPANTS

Not applicable. Participation involves a one-time visit. Safety information will be reviewed as part of the initial consent process, and the consent will be obtained with new safety information as applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No hypothesis tests will be performed. All statistical estimates (e.g., proportions, incidence rates, sensitivity, specificity, means, correlations, etc.) will be tabulated with 95% confidence intervals (CIs).

9.2 SAMPLE SIZE DETERMINATION

Cohort A will be imaged with OCT. Previous data on OCT demonstrate that established systems are sensitive with respect to detecting Barrett's mucosa. For instance, Poneros et al (2001) found a 97% sensitivity rate using OCT in 38 patients[29]. At this stage of development, if we can achieve at least 70% sensitivity, then the device will pass initial testing. If optimal sensitivity is 95%, and the lowest acceptable sensitivity is 70%, then we will require at least 14 patients with evaluable data in each group (42 total in Cohort A) to assess whether the device adequately meets this threshold with 85% power.

Cohort B will be imaged with a/LCI. Our group previously conducted and published a study in 2011 using single-point a/LCI to measure nuclear diameter as an indicator of dysplasia in the esophagus.[13] The primary differentiating characteristic between dysplastic and normal tissue was nuclear diameter (measured by a/LCI). For dysplastic tissue, the mean nuclear diameter and standard deviation was 13.0 ± 1.1 µm, and for normal tissue, the same respective values were 10.3 ± 1.7 µm. This difference was highly statistically significant, and we rejected the null hypothesis (no difference between normal and dysplastic nuclear diameters) with a p-value of 0.0001.

To determine the number of targeted patient enrollments in Cohort B, we conducted a statistical power analysis based on our previous results. For a sample size of 20 patients with dysplasia and 20 patients with normal esophageal tissue, and targeting the same p-value of 0.0001, we expect a robust statistical power of 97% when conducting a two-sample t-test for nuclear diameter distributions matching our observations from the 2011 study. We would therefore expect a 97% chance of validating our previous observations at the same level of significance for a sample size of 20. Comparatively, for a sample size

of 10 patients in each category, our power would be only 36%, far too low; for a sample size of 30 patients in each category, our power would be greater than 99.9%, which is unnecessarily high. Therefore, for Cohort B, we will target 20 patients with dysplasia and 20 normal patients to achieve a strong statistical power without an undue excess in patient enrollment.

To accommodate Cohort B, which will be receiving the dual modality a/LCI-OCT probe, we have therefore changed the sample size to be a total of 82 (42 in Cohort A, and 40 in Cohort B).

9.3 POPULATIONS FOR ANALYSES

All subjects who were administered the probe, regardless of enrolling cohort, will have data included for optimization unless withdrawn per section 7.2. For this study, an enrolled subject is defined as a subject who was successfully administered the device and for whom we have evaluable data.

9.4 STATISTICAL ANALYSES

This is a pilot study collecting data for OCT and a/LCI-OCT device optimization. This study will provide initial images for the investigational device, and depending on the device's accuracy in discerning tissue, these data will help form the basis for further investigations. Data analysis will consist of simple bivariate analysis, with endoscopy results being compared to a/LCI-OCT image results. Specifically, 2 x 2 tables of OCT, a/LCI-OCT, and endoscopy results will be constructed, with each imaging site being categorized as columnar versus squamous. Sensitivity will be defined as the proportion of sites correctly categorized by OCT, or a/LCI-OCT, using endoscopy results as the gold standard. Measures of variability of sensitivity results will be generated using non-parametric statistics.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

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

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator or designee will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigators, funding agency, the Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension.

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

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

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

This is a pilot study with very low risk, therefore it is not anticipated the study will be terminated or suspended. However, the data safety monitor (DSM) will monitor the trial for unanticipated adverse events on regular (3 month) intervals, as well as performing interim assessments of the performance characteristics of the imaging devices, which may merit consideration of premature termination of the study should the device prove inadequately accurate for clinical use, or conversely be so highly accurate that further enrollment would not be likely to change the results of the trial.

10.1.3 CONFIDENTIALITY AND PRIVACY

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

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

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of North Carolina at Chapel Hill and Duke University. This will not include the participant's contact or identifying information other than date of birth and procedure dates (limited data set). Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the University of North Carolina at Chapel Hill and Duke University will be secured and password protected. At the end of the study, all study databases will be coded and archived at the University of North Carolina at Chapel Hill and Duke University. One master list linking subjects to their code will be maintained securely by the PI, and separate from the research data.

10.1.4 FUTURE USE OF DATA

Data collected for this study will be analyzed and stored at the University of North Carolina at Chapel Hill and Duke University. After the study is completed, the coded, archived data will be stored at the University of North Carolina at Chapel Hill and Duke University, for use by other researchers including those outside of the study.

When the study is completed, access to study data and/or samples will be provided through investigators at the University of North Carolina at Chapel Hill and Duke University.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Principal Investigator and IDE Sponsor**	**Data Safety Monitor**
Nicholas J Shaheen, MD, MPH Professor of Medicine and Epidemiology Director Chief, Division of Gastroenterology & Hepatology	Adam P Wax. PHD Professor and Director of Graduate Studies Department of Biomedical Engineering	Evan Dellon, MD, MPH Associate Professor of Medicine, Gastroenterology
UNC Chapel Hill	Duke University	UNC Chapel Hill
130 Mason Farm Road, Ste. 4150 Chapel Hill, NC 27599-7080	2571 CIEMAS, Box 90281 Durham, NC 27708-0281	130 Mason Farm Road, Ste. 4140 Chapel Hill, NC 27599-7080
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Nicholas_shaheen@med.unc.edu	a.wax@duke.edu	Evan_dellon@med.unc.edu

Dr. Wax is responsible for programming and computations for data management.
Dr. Shaheen is responsible for statistical computations for analyses of the data.

10.1.6 SAFETY OVERSIGHT

Monitoring for the trial will occur at several levels. On a daily basis, the clinical study PI will monitor any adverse events in subjects enrolled in the trial. In addition to performing the endoscopies, and, in conjunction with other study personnel, the clinical study PI will supervise other study-related activities and be well-positioned to evaluate the safety of the intervention. Additionally, the study will comply with all monitoring regulations of UNC and Duke's IRBs. The study will also have a formal Independent Safety Monitor (ISM), Evan Dellon, MD, MPH. Dr. Dellon is a faculty member at UNC who has extensive experience in the care of subjects with Barrett's esophagus, and no connection to the trial. Dr. Dellon will perform review of any reported adverse event within a week of occurrence or within a week of the study team's knowledge of the event, whichever is applicable. As events occur, the monitor will characterize each event in terms of relatedness, expectedness, severity, and seriousness. These AEs will be reported to the IRB and the NIH according to their specified reporting time frames.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP).

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

Hardcopies of study visit worksheets may be used as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. If source documentation is maintained in an electronic medical record, then electronic source is allowable as long as the system is 21 CFR 11 compliant, and access is provided to the monitor for clinical monitoring.

Clinical data (including adverse events (AEs)) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by UNC Chapel Hill. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Data collected directly from the OCT device will be stored on the OCT's computer. Data will stored and transmitted between UNC and Duke using secure IRB-approved methods.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the

formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

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

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion by contacting Duke University.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single

nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

a/LCI	Angle-resolved Low Coherence Interferometry
AE	Adverse Event
BE	Barrett's Esophagus
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DHHS	Department of Health and Human Services
EAC	Esophageal Adenocarcinoma
eCRF	Electronic Case Report Forms
EET	Endoscopic Eradication Therapy
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HGD	High Grade Dysplasia
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IRB	Institutional Review Board

ISM	Independent Safety Monitor
ISO	International Organization for Standardization
LGD	Low Grade Dysplasia
MOP	Manual of Procedures
NCI	National Cancer Institute
NCT	National Clinical Trial
NIH	National Institutes of Health
NSE	Neosquamous Tissue
OCT	An Optical Coherence Tomography
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
UP	Unanticipated Problem
US	United States

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