COVER PAGE

Study Title: Volumetric laser endomicroscopy with intelligent real-time image segmentation (IRIS): a multi-center randomized prospective study

NCT03814824

Document Version Date: 12-Aug-2019

Northwell Health

RESEARCH PROTOCOL

Protocol Title:	Volumetric laser endomicroscopy with intelligent real-time image segmentation (IRIS): a multi-center randomized prospective study
Principal Investigator:	Arvind Trindade, MD
Primary Contact Name:	Molly Stewart
Primary Contact Phone:	516-600-1443
Primary Contact E-mail:	Mstewart8@northwell.edu
Date Revised:	12-Aug-2019
IRB Number:	18-0963

Guidelines for Preparing a Research Protocol

Instructions:

- You do not need to complete this document if you are submitting an *Application for Exemption* or *Application for a Chart Review*.
- Do not use this template if:
  - Your study involves an FDA regulated product. In this case, use the *Clinical Trial Protocol Template.*
  - Your study has a protocol from a sponsor or cooperative group. In this case, use the *Protocol Plus*.
  - Your study is a registry or repository for data and/or samples, In this case, use *Protocol Template – Registry Studies.* .
- If a section of this protocol is not applicable, please indicate such.
- Do not delete any of the text contained within this document.
- Please make sure to keep an electronic copy of this document. You will need to use it, if you make modifications in the future.
- Start by entering study information into the table above, according to these rules:
  - Protocol Title: Include the full protocol title as listed on the application.
  - Investigator: include the principal investigator's name as listed on the application form
  - Date Revised: Indicate the date at which the protocol was last revised
  - IRB Number: Indicate the assigned IRB number, when known. At initial submission, this row will be left blank.
- Once the table information in entered, proceed to page 2 and complete the rest of the form.

↓ Continue to next page to begin entering information about this study ↓

1. PREVIOUS STUDY HISTORY

Has this study ever been reviewed and rejected/disapproved by another IRB prior to submission to this IRB?

☒ No ☐ Yes – if yes, please explain:

2. BRIEF SUMMARY OF RESEARCH

- *The summary should be written in **language intelligible to a moderately educated, non-scientific layperson**.*
- *It should contain a clear statement of the rationale and hypothesis of your study, a concise description of the methodology, with an emphasis on what will happen to the subjects, and a discussion of the results.*
- *This section should be ½ page*

This is a multi-center prospective randomized clinical trial examining how IRIS (Intelligent Real-time Image Segmentation) affects biopsy patterns in VLE (Volumetric laser endomicroscopy). Patients will undergo a VLE exam with and without IRIS per the standard of care. All patients regardless of the study participation in this study would receive VLE with and without IRIS clinically. Thus randomization into a particular order will not require more procedure time. They will be randomized into VLE without IRIS first vs VLE with IRIS first. The BUDDY Randomization System provided for use by the Northwell Health Biostatistics Unit will be used for this. Randomization will occur before the procedure starts. Randomization will be stratified based on prior diagnosis of dysplasia. The order the patient is randomized to will be recorded on the case report form. There will be concealed allocation as the study coordinator performing the randomization will not know the order of the next allocation.

Both VLE and IRIS imaging are being performed as standard of care. However, randomization of the order allows for comparison of the two. Regions of interest (ROI) will be recorded using a full scan and recorded on the case report form. The time to identification of ROIs will also be recorded. Each group will then cross over such that the VLE without IRIS group will then have IRIS turned on ROI will

then be recorded for each group based on full scans. A consensus ROI will be recorded based on the two exams. Only one ROI per centimeter will be allowed to avoid overlapping of laser marks. In addition VLE without IRIS and IRIS marks within 75 frames of each other or 2 hours (on a clock face orientation) will be considered the same target.

Laser marking will then be performed. A double laser mark will be applied to all IRIS ROIs. A single laser mark will be applied to VLE ROIs. Targeted biopsies will be taken of all laser marks and placed in separate biopsy jars. Biopsies will be taken in between the laser marks for double laser marked areas. For single laser marks, biopsies will be taken on either side of the laser mark. Resection of visible lesions will then occur per standard of care (if present) followed by random biopsies of the segment. Random biopsies are pinch biopsies every 1 cm the length of the Barrett's in a 4 quadrant fashion per gastrointestinal society guidelines. There are no additional research biopsies being performed outside this study. The targeted biopsies are based on the VLE features that are suspicious for dysplasia and thus standard of care. The other biopsies being performed here are random biopsies which are also being performed for standard of care. Biopsied samples will be stored per standard of care procedures per the pathology department. They will not be stored for future research purposes.

Following each procedure, the physician will be asked a series of Likert Scale questions (see post-protcol survey in case report form) to assess the utility of IRIS in that procedure, including how it impacts their confidence in image interpretation, their ability to assimilate data more easily and quickly, and their overall perception of the technology.

Although, the VLE with IRIS and VLE without IRIS are being performed as standard of care, all adverse events will be recorded and reported to the IRB.

All data will be entered into a central encrypted REDCap database.

Expert pathologists who specialize in gastrointestinal pathology will read the histology. A second gastrointestinal pathologist will confirm any histologic diagnosis of dysplasia. This is the standard of care at Northwell Health and academic medical centers per gastrointestinal society guidelines.

All procedures (upper endoscopy, volumetric laser endomicroscopy, and IRIS enhanced VLE) will be performed as standard of care. The prospective data collection and initial randomization will be the research component. All data collected will be de-identified before being transferred into a database. This will be kept in a safe place that is only accessible to the research team.

3. INTRODUCTION/BACKGROUND MATERIAL/PRELIMINARY STUDIES AND SIGNIFICANCE

- *Describe and provide the results of previous work by yourself or others, including animal studies, laboratory studies, pilot studies, pre-clinical and/or clinical studies involving the compound or device to be studied.*
- *Include information as to why you are conducting the study and how the study differs from what has been previously researched, including what the knowledge gaps are.*
- *Describe the importance of the knowledge expected to result*

Barrett's esophagus (BE) is a change from normal esophageal squamous epithelium to specialized intestinal metaplasia.[1] It is estimated that 5.6% of adults in the United States have BE.[2] BE is a major risk factor for esophageal adenocarcinoma (EAC), the incidence of which continues to rise.[3] Interventions to impact the increasing incidence of EAC are limited due to two factors: 1) many patients with BE may remain undiagnosed until a symptomatic cancer arises;[4] and 2) traditional surveillance approaches are imperfect at identifying which BE patients will progress to cancer.[5]

Currently, cancer risk stratification in BE is based upon the detection of dysplasia in random biopsies taken ever 1-2 cm over the length of the BE.[1,6] However,

detecting and appropriately classifying dysplasia can be difficult. Dysplasia may be focal, and most biopsy techniques sample a fraction of the BE.[7] Moreover, endoscopic surveillance of patients with known BE may not improve mortality from EAC,[5] though it is associated with increased cost. Thus, current needs in the evaluation of BE include improvements in screening approaches and the ability to detect dysplasia.

Volumetric laser endomicroscopy (VLE) procedures use an advanced imaging technology that became commercially available in the United States in 2013 (NvisionVLE® imaging System, NinePoint Medical Inc., Bedford, MA). The VLE procedure uses an FDA-cleared second-generation optical coherence tomography (OCT) technology. It uses infrared light to produce real time high-resolution cross sectional imaging of the esophagus. The NvisionVLE system can scan a 6 cm length of the esophagus in approximately 90 seconds, providing surface and subsurface wide-field cross-sectional imaging with an axial resolution of 7 μm, and to a depth of 3 mm.[8,9] The VLE imaging system consists of a console, monitor, and optical probe contained within a Mylar balloon on an 8Fr, 260 cm catheter. The distal end of the catheter connects to the console. The probe is available in 14 mm, 17 mm, and 20 mm diameter balloons that are 6 cm in length. The balloon is positioned such that the distal margin of the balloon is located 1 cm distal to the gastroesophageal junction. This allows a single scan to image the gastric cardia, the gastro-esophageal (GE) junction, and the distal esophagus. The balloon is inflated to 15 psi, though depending on anatomy the balloon inflation pressure may be modified accordingly. The inflated balloon allows for centering and anchoring of the probe while helical scanning occurs. Imaging is performed during automatic retraction of the probe from the distal to proximal end of the balloon over a 90 second period, creating real time 360-degree images. Twelve hundred cross sectional scans are generated over the 6 cm segment. VLE scans are viewed by using a software interface that allows real time viewing of cross-sectional, transverse, and longitudinal views. There is a registration line on the balloon and

the VLE images that allows for orientation of VLE images with endoscopic imaging.

A recent upgrade to the imaging platform includes the ability to perform superficial laser marking of the esophageal epithelium when suspicious areas are identified on VLE to provide more precise targeting for biopsies or endoscopic resection .[10] A safety and efficacy study was performed evaluating VLE with a prototype laser marking device in 16 BE patients with 222 laser marks placed.[11] The study showed that laser marking was safe and efficacious with an 85% positional accuracy rate of the laser marks.

Scoring systems for OCT and VLE images have been developed to help detect neoplasia (HGD and intramucosal cancer) in BE.[12,13] These scoring systems were developed by VLE scanning *ex vivo* endoscopic resection specimens and correlating VLE features to histology.[14–16] A potential advantage of VLE is its ability to detect subepithelial disease in BE,[16–18] though the clinical relevance of these findings remains uncertain.[19]

Multiple case reports and case series have demonstrated the potential of VLE to identify dysplasia in BE not detected by high-definition white light endoscopy or electronic chromoendoscopy.[14–16,20] A large single center retrospective series found an incremental yield of dysplasia detection using VLE with laser marking compared to VLE without laser marking or random biopsies.[21] A study looked at the interobserver agreement between users at high-volume academic centers based on still images and found strong agreement for non-neoplastic and neoplastic BE (kappa 0.66 and 0.79).[22] Although the learning curve for interpretation of VLE images appears to be favorable,[23] a large amount of complex data is interpreted by the endoscopist in real-time. Thus, computer-aided analysis of VLE data could aid in image interpretation mid-procedure. [12, 13, 24] One academic group has developed computer algorithms to aid with the detection of BE neoplasia, evaluating a prototype computer-aided detection program using 60 VLE images of

ex vivo endoscopic resection specimens.[25] The study found that the computer-aided detection was able to detect neoplasia with a 90% sensitivity and 93% specificity. An artificial intelligence algorithm to segment and display commonly observed esophageal features [12, 13, 24] has been commercially developed, and is cleared by the FDA. This product is termed intelligent real-time image segmentation (IRIS). The computer software highlights three VLE features that could be associated with dysplasia according to previous literature [12, 13, 24]. The aim of this study is to evaluate the impact of IRIS for management of patients with Barrett's Esophagus and Barrett's related dysplasia with experts in VLE.

Intelligent Real-time Image Segmentation (IRIS)

The IRIS upgrade has the ability to identify and display three specific images features that may correlate with dysplasia. The three features are represented in different color schemes to help identify the features (FIGURE 1). The three features of interest include a hyper-reflective surface, hypo-reflective structures, and a lack of layering. A hyper-reflective surface indicates a high surface signal relative to the subsurface and is calculated by signal drop off over depth. The image feature is represented by a pink color bar at the tissue surface. The pink intensity increases with greater signal drop-off between the surface and subsurface. Layering indicates a separation of a homogeneous, low-signal layer from a hyper-reflective interface below. This image feature is represented by an orange color bar at the exterior edge of the VLE image space. The orange, when present, indicates lack of layering while black indicates strong layering. The last feature highlighted in IRIS is a hyo-reflective structure. These are closed low signal regions that stand out from surrounding tissue texture. The image feature is represented by a blue image overlay on top of the identified hypo-reflective structure.

IRIS features are controlled from the physician screen on the VLE console or by the hand controller.

4. OBJECTIVE(S)/SPECIFIC AIMS AND HYPOTHESES

- *A concise statement of the goal(s) of the current study.*
- *The rationale for and specific objectives of the study.*
- *The goals and the hypothesis to be tested should be stated.*

1. To determine if IRIS facilitates interpretation of VLE images compared to VLE alone
2. To determine if IRIS increases the diagnostic yield for dysplasia compared to VLE alone and random biopsies
3. To determine if IRIS decreases the number of biopsies needed to identify dysplasia compared to VLE alone and random biopsies

5. RESOURCES AVAILABLE TO CONDUCT THE HUMAN RESEARCH

- *Explain the feasibility of meeting recruitment goals of this project and demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period*
  - *How many potential subjects do you have access to?*
- *Describe your process to ensure that all persons assisting with the trial are adequately informed about the protocol and their trial related duties and functions*

Patients approached for participating in this study will be scheduled per standard of care procedures for their condition. The volume of patients who meet this criteria is more than sufficient to achieve the enrollment goal of 200 patients.

6. RECRUITMENT METHODS

- *Describe the source of potential subjects*
- *Describe the methods that will be used to identify potential subjects*
- *Describe any materials that will be used to recruit subjects. A copy of any advertisements (flyers, radio scripts, etc.) should be submitted along with the protocol.*
- *If monetary compensation is to be offered, this should be indicated in the protocol*

Patients 18 years of age and older with Barrett's esophagus greater than 2cm in length and who are scheduled to undergo an upper endoscopy with VLE exam for surveillance as standard of care will be approached before their scheduled exam to obtain informed consent to participate in this study. No recruitment materials or

advertisements will be used in this study. Subjects will not receive monetary compensation for their participation.

We are fortunate that the two participants of the trial (Dr Trindade and Dr McKinley) have high volume Barrett's esophagus practices. Both physicians routinely perform VLE. Thus patients who are undergoing VLE as standard of care will be asked if they wish to participate in the trial.

.

7. ELIGIBILITY CRITERIA

- *Describe the characteristics of the subject population, including their anticipated number, age, ranges, sex, ethnic background, and health status. Identify the criteria for inclusion or exclusion of any subpopulation.*
- *Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners or other institutionalized individuals, or others who are likely to be vulnerable. You cannot include these populations in your research, unless you indicate such in the protocol*
- *Similarly, detail exclusionary criteria: age limits, special populations (minors, pregnant women, decisionally impaired), use of concomitant medications, subjects with other diseases, severity of illness, etc.*

Inclusion criteria:

1. 18 years of age or older at the time of informed consent
2. Barrett's esophagus greater than 2 cm in length
3. Undergoing a scheduled upper endoscopy with VLE exam for surveillance as standard of care

Exclusion criteria:

1. Less than 18 years old at the time of informed consent
2. Unable to provide written informed consent
3. Esophageal stenosis/stricture preventing VLE
4. Esophagitis
5. Severe medical comorbidities preventing endoscopy
6. Pregnancy
7. Uncontrolled coagulopathy

8. NUMBER OF SUBJECTS

- *Indicate the total number of subjects to be accrued locally. If applicable, distinguish between the number of subjects who are expected to be pre-screened, enrolled (consent obtained), randomized and complete the research procedures.*
- *If your study includes different cohorts, include the total number of subjects in each cohort.*
- *If this is multisite study, include total number of subjects across all sites.*

This is a multi-site randomized trial with an anticipated enrollment of 200 patients. We anticipate adding up to 3 other sites. Half of all patients should have a prior diagnosis of dysplasia to ensure a sample that has an adequate number of dysplastic patients.

The primary outcome will be time to interpretation of a VLE scan with and without IRIS. Dysplasia detected in each arm and number of biopsies are secondary outcomes and not expected to be that much different as expert VLE users will be involved in the study. The expected mean time for a VLE without IRIS is 5 min +/- 3 min. The mean time for a VLE without IRIS (standard) is 3 min. With a CI of 95% and power of 90%, the sample size for 1:1 randomization is 94 (47 in each group). Our sample size is 200 to allow for screen failures.

9. STUDY TIMELINES

- *Describe the duration of an individuals participation in the study*
- *Describe the duration anticipated to enroll all study subjects*
- *The estimated date of study completion*

Subjects enrolled in this study will participate on the day of their scheduled upper endoscopic procedure, which will last for about 1 hour. Subsequently, these patients will be followed for a period of about 1 year via their electronic medical

records. After the day of the initial procedure, they will not be contacted for study related purposes.

10. ENDPOINTS

- *Describe the primary and secondary study endpoints*
- *Describe any primary or secondary safety endpoints*

The following outcomes will be measured:

- Primary Outcome: The time for image interpretation in each arm will be compared. Time will be a surrogate for ease of interpretation. Time will be recorded from start of image interpretation to the end of image interpretation. Length of Barrett's will be taken into account (time per cm of Barrett's) when comparing this outcome between patients and procedures.

- Secondary Outcome: Biopsy yield of dysplasia/diagnosis of dysplasia (dysplasia present versus not) of IRIS biopsies (double laser mark) will be compared to VLE without IRIS biopsies (single laser mark) and random biopsies.

- Secondary Outcome: The number of biopsies will be compared among all groups.

11. RESEARCH PROCEDURES

- *Include a detailed description of all procedures to be performed on the research subject and the schedule for each procedure.*
- *Include any screening procedures for eligibility and/or baseline diagnostic tests*
- *Include procedures being performed to monitor subjects for safety or minimize risks*
- *Include information about drug washout periods*
- *If drugs or biologics are being administered provide information on dosing and route of administration*
- *Clearly indicate which procedures are only being conducted for research purposes.*
- *If any specimens will be used for this research, explain whether they are being collected specifically for research purposes.*
- *Describe any source records that will be used to collect data about subjects*
- *Indicate the data to be collected, including long term follow-up*

This is a prospective randomized clinical trial examining how IRIS (Intelligent Real-time Image Segmentation) affects biopsy patterns in VLE (Volumetric laser endomicroscopy). Patients will undergo a VLE exam with and without IRIS per the standard of care. All patients regardless of the study participation in this study would receive VLE with and without IRIS clinically. Thus randomization into a particular order will not require more procedure time. They will be randomized into VLE without IRIS first vs VLE with IRIS first. Subjects will be randomized with the BUDDY Randomization System provided for use by the Northwell Health Biostatistics Unit. Randomization will occur before the procedure starts. Randomization will be stratified based on prior diagnosis of dysplasia. The order the patient is randomized to will be recorded on the case report form. There will be concealed allocation as the study coordinator performing the randomization will not know the order of the next allocation.

Both VLE and IRIS imaging are being performed as standard of care. However, randomization of the order allows for comparison of the two. Regions of interest (ROI) will be recorded using a full scan and recorded on the case report form. The time to identification of ROIs will also be recorded (from start of image interpretation to the end). Each group will then cross over such that the VLE without IRIS group will then have IRIS turned on ROI will then be recorded for each group based on full scans. A consensus ROI will be recorded based on the two exams. Only one ROI per centimeter will be allowed to avoid overlapping of laser marks. In addition VLE without IRIS and IRIS marks within 75 frames of each other or 2 hours (on a clock face orientation) will be considered the same target.

Laser marking will then be performed. A double laser mark will be applied to all IRIS ROIs. A single laser mark will be applied to VLE ROIs. Targeted biopsies will be taken of all laser marks and placed in separate biopsy jars. Biopsies will be taken in between the laser marks for double laser marked areas. For single laser marks, biopsies will be taken on either side of the laser mark. Resection of visible

lesions will then occur per standard of care (if present) followed by random biopsies of the segment. Random biopsies are pinch biopsies every 1 cm the length of the Barrett's in a 4 quadrant fashion per gastrointestinal society guidelines.This is all per standard of care. There are no additional research biopsies being performed outside this study. The targeted biopsies are based on the VLE features that are suspicious for dysplasia and thus standard of care. The other biopsies being performed here are random biopsies which are also being performed for standard of care. Biopsied samples will be stored per standard of care procedures per the pathology department. They will not be stored for future research purposes.

Following each procedure, the physician will be asked a series of Likert Scale questions to assess the utility of IRIS in that procedure, including how it impacts their confidence in image interpretation, their ability to assimilate data more easily and quickly, and their overall perception of the technology.

Although the VLE with IRIS and VLE without IRIS are being performed as standard of care, all adverse events will be recorded and reported to the IRB.

All data will be entered into a central encrypted REDCap database housed within the Northwell server.

Expert pathologists who specialize in gastrointestinal pathology will read the histology. A second gastrointestinal pathologist will confirm any histologic diagnosis of dysplasia. This is the standard of care at Northwell Health and academic medical centers per gastrointestinal society guidelines.

All procedures (upper endoscopy, volumetric laser endomicroscopy, and IRIS enhanced VLE) will be performed as standard of care. The prospective data collection and initial randomization of order of use of IRIS will be the research component. All data collected will be de-identified before being transferred into a

database. This will be kept in a safe place that is only accessible to the research team.

12. STATISTICAL ANALYSIS

- *Describe how your data will be used to test the hypotheses.*
- *State clearly what variables will be tested and what statistical tests will be used.*
- *Include sample size calculations.*
- *If this is a pilot study, state which variables will be examined for hypothesis generation in later studies.*

The categorical variables will be compared using Fisher exact tests (eg: presence of dysplasia). Continuous variables between the two groups will be analyzed using the student t-test. All statistical tests will be 2-sided, and $P < .05$ will considered significant. All statistics will be run using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Time to interpretation is likely normally distributed. For outcomes like number of biopsies, if post study analysis shows this is not normally distributed, we can use median values instead of means or perform a log correction.

13. SPECIMEN BANKING

- *If specimens will be banked for future research, describe where the specimens will be stored, how long they will be stored, how they will be accessed and who will have access to the specimens*
- *List the information that will be stored with each specimen, including how specimens are labeled/coded*
- *Describe the procedures to release the specimens, including: the process to request release, approvals required for release, who can obtain the specimens, and the information to be provided with the specimens.*

N/A

14. DATA MANAGEMENT AND CONFIDENTIALITY

- *Describe the data and specimens to be sent out or received. As applicable, describe:*

- *What information will be included in that data or associated with the specimens?*
- *Where and how data and specimens will be stored?*
- *How long the data will be stored?*
- *Who will have access to the data?*
- *Who is responsible for receipt or transmission of data and specimens?*

- *Describe the steps that will be taken to secure the data during storage, use and transmission.*

Data being collected for this study will adhere to the institutional policies related to research. Data related to the procedure and device will be recorded, including date of procedure, indication for procedure, concurrent medications. Medical history will also be recorded, including previous histopathological diagnoses, previous medications, and previous therapy for Barrett's esophagus. The data will be stored on Northwell's REDCap server.

15. DATA AND SAFETY MONITORING PLAN

A specific data and safety monitoring plan is only required for greater than minimal risk research. For guidance on creating this plan, please see the Guidance Document *on the HRPP website.*

Part I – this part should be completed for all studies that require a DSMP.
Part II – This part should be completed when your study needs a Data and Safety Monitoring Board or Committee (DSMB/C) as part of your Data and Safety Monitoring Plan.

Part I: Elements of the Data and Safety Monitoring Plan

- *Indicate who will perform the data and safety monitoring for this study.*
- *Justify your choice of monitor, in terms of assessed risk to the research subject's health and well being. In studies where the monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and rationale for selection*
- *List the specific items that will be monitored for safety (e.g. adverse events, protocol compliance, etc)*
- *Indicate the frequency at which accumulated safety and data information (items listed in # above) will be reviewed by the monitor (s) or the DSMB/C.*
- *Where applicable, describe rules which will guide interruption or alteration of the study design.*
- *Where applicable, indicate dose selection procedures that will be used to minimize toxicity.*
- *Should a temporary or permanent suspension of your study occur, in addition to the IRB, indicate to whom will you report the occurrence.*

Data will be closely monitored by the PI. This monitoring will be done on an ongoing basis and will focus on any adverse events or unanticipated problems which will be reported immediately to the PI. These will be analyzed for relatedness, although no relatedness to research is anticipated since this is data collection only. Protocol compliance will be monitored via data entry in REDCap and by verification of source documentation when required.

Part II: Data and Safety Monitoring Board or Committee

- *When appropriate, attach a description of the DSMB.*
- *Provide the number of members and area of professional expertise.*
- *Provide confirmation that the members of the board are all independent of the study.*

N/A

16. WITHDRAWAL OF SUBJECTS

- *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent*
- *Describe procedures for orderly termination*
- *Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.*

If the subject consents to the study and meets all criteria at the time of the initial procedure, they will be considered enrolled unless the patient provides written documentation of their decision to withdraw from the study.

17. RISKS TO SUBJECTS

- *Describe any potential risks and discomforts to the subject (physical, psychological, social, legal, or other) and assess their likelihood and seriousness and whether side effects are reversible. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.*
- *Include risks to others , like sexual partners (if appropriate)*
- *Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to results*

- *Describe the procedures for protecting against or minimizing any potential risks, including risks to confidentiality, and assess their likely effectiveness.*

There are no additional risks or discomforts anticipated for the patient if he or she decides to participate in this research. Subjects' alternatives are to not participate in the research study.

18. RESEARCH RELATED HARM/INJURY

- *Describe the availability of medical or psychological resources that subjects might need as a result of anticipated problems that may be known to be associated with the research.*
- *If the research is greater than minimal risk, explain any medical treatments that are available if research-related injury occurs, who will provide it, what will be provided, and who will pay for it.*

Subjects will be undergoing VLE with and without computer enhancement as part of their standard of care. They are aware of and consent to this procedure and associate risks separately from this research study. The research component will involve recording information during the exam. It is not anticipated that this causes any additional risk. De-identified data will be recorded in an encrypted database. While there is always a potential for breach of information, every effort is in place to ensure this security.

19. POTENTIAL BENEFIT TO SUBJECTS

- *Explain what benefits might be derived from participation in the study, noting in particular the benefit over standard treatment (e.g. a once-a-day administration instead of four times a day, an oral formulation over an IV administration).*
- *Also state if there are no known benefits to subjects, but detail the value of knowledge to be gained*

While this research will likely not provide subjects' any direct benefit, it will potentially benefit patients with the same disease in the future.

20. PROVISIONS TO PROTECT PRIVACY INTERESTS OF SUBJECTS

- *Describe the methods used to identify potential research subjects, obtain consent and gather information about subjects to ensure that their privacy is not invaded.*
- *In addition consider privacy protections that may be needed due to communications with subjects (such as phone messages or mail).*

Research related documents used to record information for this study, such as data stored on paper (informed consent forms, case report forms, procedure reports, pathology reports) will be stored in locked cabinets which are only accessible to those approved to participate in this study. Electronic information will be kept within the HIPAA compliant database, REDCap. Any email correspondence with potentially-identifying information will be encrypted.

21. COSTS TO SUBJECTS

- *Describe any foreseeable costs that subjects may incur through participation in the research*
- *Indicate whether research procedures will be billed to insurance or paid for by the research study.*

There are no additional costs to subjects if they choose to participate in this study.

22. PAYMENT TO SUBJECTS

- *Describe the amount of payment to subjects, in what form payment will be received and the timing of the payments.*

Subjects will not be paid for participating in this study.

23. CONSENT PROCESS

If obtaining consent for this study, describe:

- *Who will be obtaining consent*
- *Where consent will be obtained*
- *Any waiting period available between informing the prospective participant and obtaining consent*

- *Steps that will be taken to assure the participants' understanding*
- *Any tools that will be utilized during the consent process*
- *Information about how the consent will be documented in writing. If using a standard consent form, indicate such.*
- *Procedures for maintaining informed consent.*

Consent for this study will only be obtained by those approved to do so. At the time of consent, the investigator will explain in detail the data that will be collected as part of this study. It will be explained to subjects why they are eligible to participate. Before signing the consent form, patients will be asked if they understand what their participation involves. Original copies of the consent forms will be stored in a study binder accessible to the research staff. Subjects will be given a copy of the signed consent form for their records. The subject, investigator, and a witness will print and sign their names and the date the informed consent process takes place. Enrollment notes will be written to outline the process and these will be signed by the investigator.

In the state of NY, any participants under the age of 18 are considered children. If your study involves children, additional information should be provided to describe:

- *How parental permission will be obtained*
- *From how many parents will parental permission be obtained*
- *Whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. The process used to determine these individual's authority to consent for the child should be provided*
- *Whether or not assent will be obtained from the child*
- *How will assent be documented*
- *Whether child subjects may be expected to attain legal age to consent to the procedures for research prior to the completion of their participation in the research. If so, describe the process that will be used to obtain their legal consent to continue participation in the study. Indicate what will occur if consent is not obtained from the now-adult subjects.*

N/A

If the study involves cognitively impaired adults, additional information should be provided to describe:

- *The process to determine whether an individual is capable of consent*
- *Indicate who will make this assessment*

- *The plan should indicate that documentation of the determination and assessment will be placed in the medical record, when applicable, in addition to the research record.*
- *If permission of a legally authorized representative will be obtained,*
  - *list the individuals from who permission will be obtained in order of priority*
  - *Describe the process for assent of subjects; indicate whether assent will be required of all, some or none of the subjects. If some, which subjects will be required to assent and which will not.*
  - *If assent will not be obtained from some or all subjects, provide an explanation as to why not*
  - *Describe whether assent will be documented and the process to document assent*
  - *Indicate if the subject could regain capacity and at what point you would obtain their consent for continued participation in the study*

N/A

If the study will enroll non-English speaking subjects:

- *Indicate what language(s) other than English are understood by prospective subjects or representatives*
- *Indicate whether or not consent forms will be translated into a language other than English*
- *Describe the process to ensure that the oral and written information provided to those subjects will be in that language*
- *If non-English speaking subjects will be excluded, provide a justification for doing so*

N/A

24. WAIVER OR ALTERATION OF THE CONSENT PROCESS ☒ N/A

Complete this section if you are seeking an alteration or complete waiver of the consent process.

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk to the subject:*
- *Explain why the waiver/ alteration will not adversely affect the rights and welfare of subjects*
- *Explain why it is impracticable to conduct this research if informed consent is required*
- *Explain why it is not possible to conduct this research without using the information or biospecimens in an identifiable form*
- *If appropriate, explain how the subjects will be provided with additional pertinent information after participation. If not appropriate to do so, explain why.*

N/A

Complete this section if you are obtaining informed consent but you are requesting a waiver of the documentation of consent (i.e., verbal consent will be obtained). *To proceed with a waiver based on these criteria, each subject must be asked whether they wish to have documentation linking them to this study.* ***Only complete subsection 1 OR subsection 2.***

SUBSECTION 1

- *Explain how the only record linking the subject to the research would be the consent document.*
- *Explain how the principal risk of this study would be the potential harm resulting from a breach in the confidentiality*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

N/A

SUBSECTION 2

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk.*
- *Confirm that the research only involves procedure for which consent is not normally required outside the research context.*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

N/A

.

25. WAIVER OF HIPAA AUTHORIZATION ☐ N/A

Complete this section if you seek to obtain a full waiver of HIPAA authorization to use and/or disclose protected health information.

- *Describe the risks to privacy involved in this study and explain why the study involves no more than minimal risk to privacy:*
- *Describe your plan to protect identifiers from improper use or disclosure and to destroy them at the earliest time.*
- *Indicate why it is not possible to seek subjects' authorization for use or disclosure of PHI.*
- *Indicate why it is not possible to conduct this research without use or disclosure of the PHI.*
- *Indicate if PHI will be disclosed outside NSLIJ Health System, and if so, to whom. Note: PHI disclosed outside NSLIJ Health System, without HIPAA authorization needs to be tracked. Please see guidance at www.nslij.com/irb for information about tracking disclosures.*

N/A

Complete this section if you seek to obtain a partial waiver of the patient's authorization for screening/recruitment purposes *(i.e., the researcher does not have access to patient records as s/he is not part of the covered entity)*

Note: Information collected through a partial waiver for recruitment cannot be shared or disclosed to any other person or entity.

- *Describe how data will be collected and used:*
- *Indicate why you need the PHI (e.g.PHI is required to determine eligibility, identifiers are necessary to contact the individual to discuss participation, other)*
- *Indicate why the research cannot practicably be conducted without the partial waiver (e.g. no access to medical records or contact information of the targeted population, no treating clinician to assist in recruitment of the study population, other)*

A partial waiver of HIPAA authorization would be required for this study to ensure a patient's medical history (i.e. pathological diagnosis of Barrett's esophagus and endoscopic length of disease, medical comorbidities, other exclusionary criteria) meets inclusion criteria prior to approaching the patient for written informed consent. These elements would be recorded as part of the research if the patient does consent to participate. If the patient does not meet the criteria during pre-screening, the data elements would not be collected or stored.

26. VULNERABLE POPULATIONS:

Indicate whether you will include any of these vulnerable populations. If indicated, submit the appropriate appendix to the IRB for review:

- ☐ *Children or viable neonate*
- ☐ *Cognitively impaired*
- ☐ *Pregnant Women, Fetuses or neonates of uncertain viability or nonviable*
- ☐ *Prisoners*
- ☐ *NSLIJ Employees, residents, fellows, etc*
- ☐ *poor/uninsured*
- ☐ *Students*
- ☐ *Minorities*
- ☐ *Elderly*
- ☐ *Healthy Controls*

If any of these populations are included in the study, describe additional safeguards that will be used to protect their rights and welfare.

N/A

27. MULTI-SITE HUMAN RESEARCH (COORDINATING CENTER)

If this is a multi-site study where you are the lead investigator, describe the management of information (e.g. results, new information, unanticipated problems involving risks to subjects or others, or protocol modifications) among sites to protect subjects.

Information related to the study will be promptly disseminated to participating sites. This information will include any interim analysis, adverse events, or protocol modifications. Confirmation of receipt of important documents will be requested. Copies of each site's IRB approvals will be kept at the main site to ensure that all sites are adequately approved. Representatives from the research teams will be given access to the REDCap project, where they will be able to enter data only into their respective Data Access Groups. Access to the BUDDY Randomization System will be allocated to each site, where the lead PI will be copied on all correspondence related to randomization allocations and enrollment updates.

28. REFERENCES/BIBIOGRAPHY

Provide a reasonable list of references directly related to the study. Any diagrams for new medical devices or brief reprints from journals might also prove useful.

1 Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol 2016; 111: 30–50; quiz 51 Im Internet: http://dx.doi.org/10.1038/ajg.2013.196

2 Spechler SJ, Souza RF. Barrett's Esophagus. N Engl J Med 2014; 371: 836–845 Im Internet: http://www.nejm.org/doi/abs/10.1056/NEJMra1314704

3 Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked

increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005; 97: 142–146

4 Bhat SK, McManus DT, Coleman HG, Johnston BT, Cardwell CR, McMenamin Ú, Bannon F, Hicks B, Kennedy G, Gavin AT, Murray LJ. Oesophageal adenocarcinoma and prior diagnosis of Barrett's oesophagus: a population-based study. Gut 2015; 64: 20–25 Im Internet: http://gut.bmj.com/lookup/doi/10.1136/gutjnl-2013-305506

5 Corley DA, Mehtani K, Quesenberry C, Zhao W, de Boer J, Weiss NS. Impact of endoscopic surveillance on mortality from Barrett's esophagus-associated esophageal adenocarcinomas. Gastroenterology 2013; 145: 312–9.e1 Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/23673354

6 Levine DS, Haggitt RC, Blount PL, Rabinovitch PS, Rusch VW, Reid BJ. An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. Gastroenterology 1993; 105: 40–50 Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/8514061

7 Jankowski M, Wani S. Diagnostic and Management Implications of Basic Science Advances in Barrett's Esophagus. Curr Treat Options Gastroenterol 2015; 13: 16–29 Im Internet: http://link.springer.com/10.1007/s11938-014-0040-9

8 Trindade AJ, Smith MS, Pleskow DK. The new kid on the block for advanced imaging in Barrett's esophagus: a review of volumetric laser endomicroscopy. Therap Adv Gastroenterol 2016; 9: 408–416 Im Internet: http://tag.sagepub.com/cgi/doi/10.1177/1756283X16639003

9 Wolfsen HC, Sharma P, Wallace MB, Leggett C, Tearney G, Wang KK. Safety and feasibility of volumetric laser endomicroscopy in patients with Barrett's esophagus (with videos). Gastrointest Endosc 2015; 82: 631–640 Im Internet: http://linkinghub.elsevier.com/retrieve/pii/S0016510715022786

10 Trindade AJ, Leggett CL, Chang KJ. Volumetric laser endomicroscopy in the management of Barrett's esophagus. Curr Opin Gastroenterol 2017; Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/28402993

11 Swager A, de Groof AJ, Meijer SL, Weusten BL, Curvers WL, Bergman JJ.

Feasibility of laser marking in Barrett's esophagus with Volumetric laser endomicroscopy First-in-man pilot study. Gastrointest Endosc 2017; Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/28161451

12 Swager A-F, Tearney GJ, Leggett CL, van Oijen MGH, Meijer SL, Weusten BL, Curvers WL, Bergman JJGHM. Identification of volumetric laser endomicroscopy features predictive for early neoplasia in Barrett's esophagus using high-quality histological correlation. Gastrointest Endosc 2016; Im Internet: http://dx.doi.org/10.1016/j.gie.2016.09.012

13 Leggett CL, Gorospe EC, Chan DK, Muppa P, Owens V, Smyrk TC, Anderson M, Lutzke LS, Tearney G, Wang KK. Comparative diagnostic performance of volumetric laser endomicroscopy and confocal laser endomicroscopy in the detection of dysplasia associated with Barrett's esophagus. Gastrointest Endosc 2015; Im Internet: http://linkinghub.elsevier.com/retrieve/pii/S0016510715028229

14 Trindade AJ, Vamadevan AS, Sejpal D V. Finding a needle in a haystack: use of volumetric laser endomicroscopy in targeting focal dysplasia in long-segment Barrett's esophagus. Gastrointest Endosc 2015; 82: 756–757 Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/26005011

15 Trindade AJ, George BJ, Berkowitz J, Sejpal D V, McKinley MJ. Volumetric laser endomicroscopy can target neoplasia not detected by conventional endoscopic measures in long segment Barrett's esophagus. Endosc Int open 2016; 4: E318-22 Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/27004250

16 Leggett CL, Gorospe E, Owens VL, Anderson M, Lutzke L, Wang KK. Volumetric laser endomicroscopy detects subsquamous Barrett's adenocarcinoma. Am J Gastroenterol 2014; 109: 298–299 Im Internet: http://www.nature.com/ajg/journal/v109/n2/pdf/ajg2013422a.pdf

17 Swager A-F, Boerwinkel DF, de Bruin DM, Faber DJ, van Leeuwen TG, Weusten BL, Meijer SL, Bergman JJ, Curvers WL. Detection of buried Barrett's glands after radiofrequency ablation with volumetric laser endomicroscopy. Gastrointest Endosc 2015; 1–9 Im Internet: http://linkinghub.elsevier.com/retrieve/pii/S0016510715024827

[18] Trindade AJ, Sideridis K, Thomas RM. Buried Barrett's Esophagus Presenting as a Subepithelial Nodule. Am J Gastroenterol 2016; 111: 1378 Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/27694877

[19] Mashimo H. Subsquamous intestinal metaplasia after ablation of Barrett's esophagus: frequency and importance. Curr Opin Gastroenterol 2013; 29: 454–459 Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/23674187

[20] Atkinson C, Singh S, Fisichella PM. Volumetric laser endomicroscopy in the detection of neoplastic lesions of the esophagus. Dig Liver Dis 2016; 48: 692 Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/26976783

[21] Alshelleh M, Inamdar S, McKinley M, Stewart M, Novak JS, Greenberg RE, Sultan K, Devito B, Cheung M, Cerulli MA, Miller LS, Sejpal D V., Vegesna AK, Trindade AJ. Incremental yield of dysplasia detection in Barrett's esophagus using volumetric laser endomicroscopy with and without laser marking compared with a standardized random biopsy protocol. Gastrointest Endosc 2018; Im Internet: http://linkinghub.elsevier.com/retrieve/pii/S0016510718300956

[22] Trindade AJ, Inamdar S, Smith MS, Chang KJ, Leggett CL, Lightdale CJ, Pleskow DK, Sejpal D V, Tearney GJ, Thomas RM, Wallace MB. Volumetric laser endomicroscopy in Barrett's esophagus: interobserver agreement for interpretation of Barrett's esophagus and associated neoplasia among high-frequency users. Gastrointest Endosc 2017; 86: 133–139 Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/27899321

[23] Trindade AJ, Inamdar S, Smith MS, Rosen L, Han D, Chang KJ, Leggett CL, Lightdale CJ, Pleskow DK, Sejpal D V, Tearney GJ, Thomas RM, Wallace MB. Learning curve and competence for volumetric laser endomicroscopy in Barrett's esophagus using cumulative sum analysis. Endoscopy 2017; Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/29179229

[24] Evans J a., Poneros JM, Bouma BE, Bressner J, Halpern EF, Shishkov M, Lauwers GY, Mino-Kenudson M, Nishioka NS, Tearney GJ. Optical coherence tomography to identify intramucosal carcinoma and high-grade dysplasia in Barrett's esophagus. Clin Gastroenterol Hepatol 2006; 4: 38–43

[25] Swager A-F, van der Sommen F, Klomp SR, Zinger S, Meijer SL, Schoon EJ, Bergman JJGHM, de With PH, Curvers WL. Computer-aided detection of early Barrett's neoplasia using volumetric laser endomicroscopy. Gastrointest Endosc 2017; Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/28322771

[26] Alvarez Herrero L, Curvers WL, van Vilsteren FGI, Wolfsen H, Ragunath K, Wong Kee Song L-M, Mallant-Hent RC, van Oijen A, Scholten P, Schoon EJ, Schenk EBE, Weusten BLAM, Bergman JGHM. Validation of the Prague C&M classification of Barrett's esophagus in clinical practice. Endoscopy 2013; 45: 876–882 Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/24165812

[27] The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003; 58: S3-43 Im Internet: http://www.ncbi.nlm.nih.gov/pubmed/14652541

List of Figures

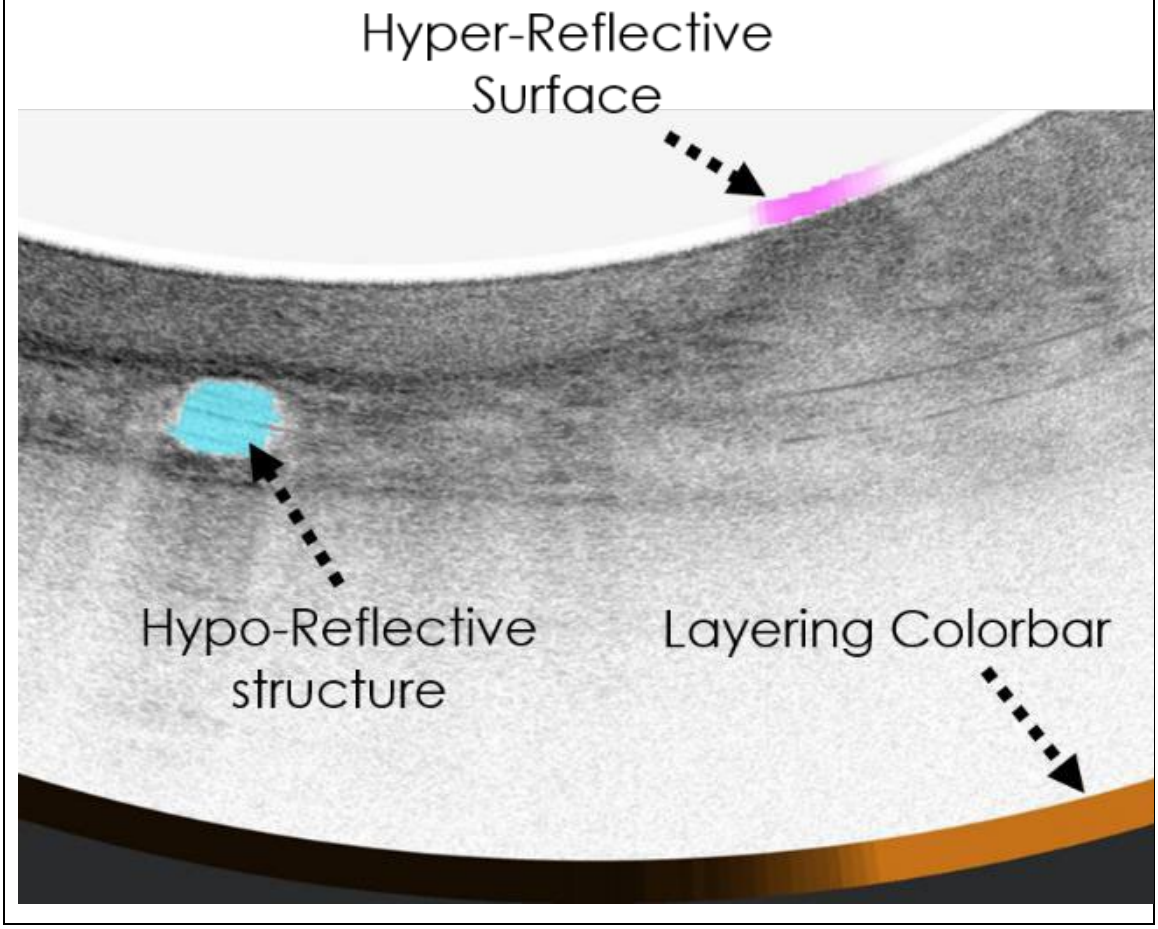

FIGURE 1: A VLE image showing the three color schemes representing different features that could represent dysplasia.

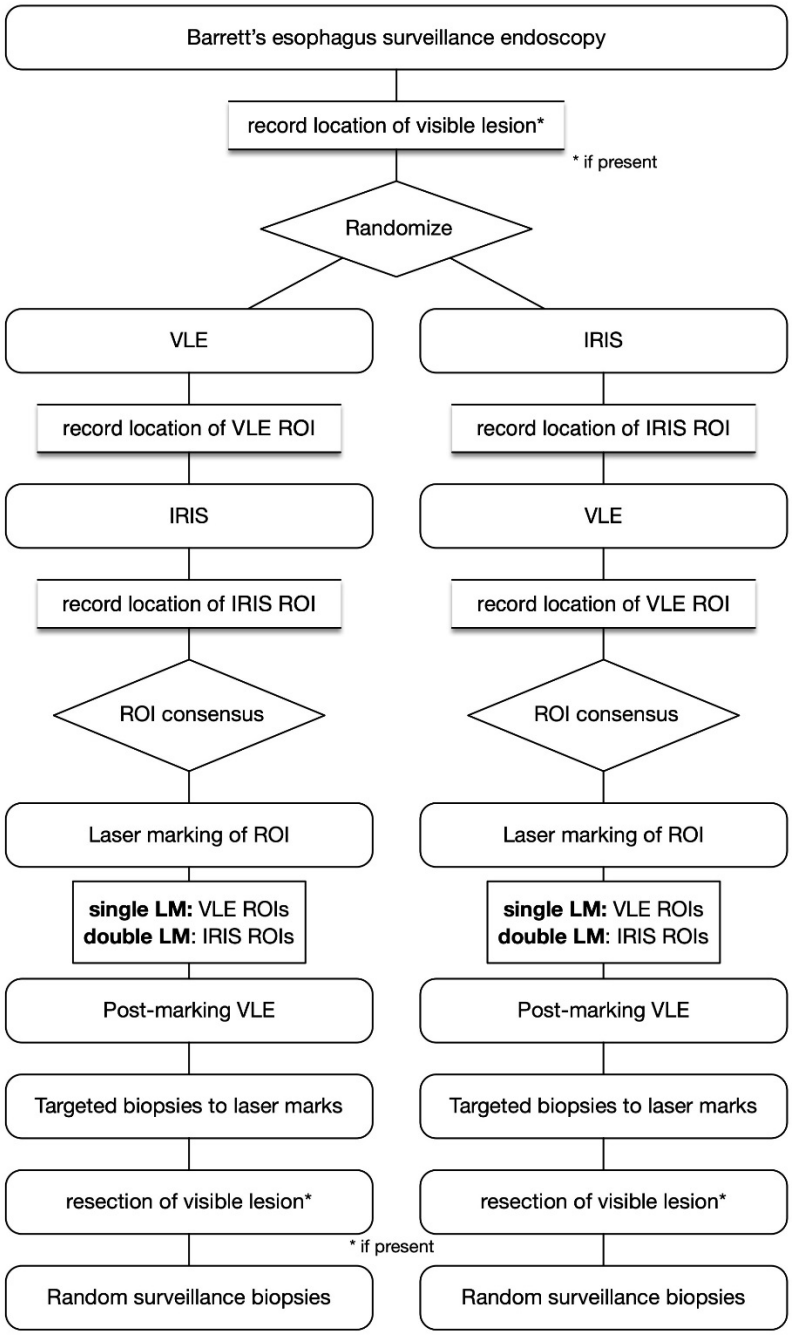

FIGURE 2: The flow diagram of study procedures.