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Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

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Section Aa: Title & PI

A1. Main Title

HIGH RESOLUTION MICROENDOSCOPY FOR THE DETECTION OF ESOPHAGEAL SQUAMOUS CELL NEOPLASIA: A RANDOMIZED, MULTICENTER TRIAL OF ACCURACY, YIELD, AND CLINICAL IMPACT

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A3a. Financial Conflict of Interest

Does any member of study personnel (Investigator (including investigator's spouse and/or dependent children)) that are involved in the design, conduct, or reporting of the research have a Significant Financial Interest (SFI) that would reasonably appear to be affected by the research for which funding is sought and/or associated with an entity/business that would reasonably appear to be affected by the research?

No

Section Ab: General Information

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A5. Funding Source:

Organization: NIH: NATIONAL INSTITUTES OF HEALTH

A6a. Institution(s) where work will be performed:

BCM: Baylor College of Medicine
Baylor St. Luke's Medical Center (BSLMC)
HCHD: Harris County Hospital District Ben Taub

A6b. Research conducted outside of the United States:

Country: CHINA
Facility/Institution: Cancer Institute, Chinese Academy of Medical Sciences
Contact/Investigator: Guiqi Wang, MD
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If documentation of assurances has not been sent to the Office of Research, please explain:

A7. Research Category:

Cancer Related, Cancer - Adult

A8. Therapeutic Intent

Does this trial have therapeutic intent?
No

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

Significance Esophageal squamous cell cancer is a common cause of digestive cancer all over the world. It is the 6th most common cause of cancer-related mortality worldwide. While the etiology is different from adenocarcinoma, the prognosis for this disease is similarly poor, and the 5 year survival rate is less than 15% due to late diagnosis when the cancer has already progressed to an advanced stage. To date, early detection is still regarded as the best method of improving survival from this disease and endoscopy is the most widley used technique for early detection and diagnosis. While the disease remains prevalent in the United States , incidence rates in Northern China exceed 1 per 1,000 individuals . In these regions, screening strategies have been implemented with limited success and the incidence to mortality ratio remains a dismal 1:1. Over the past several decades, advances in imaging technologies have led to the improvement of conventional endoscopy for the detection of esophageal pre-cancer (dysplasia) and cancer.While “dye-spray” techniques such as Lugol’s iodine can highlight large areas that need further evaluation, accuracy rates are not high. Moreover, such dye-staining is limited by poor specificity: multiple areas may appear abnormal with Lugol’s; however, not all of these are neoplastic (3). Indeed, inflammation and other abnormalities may often mimic neoplasia. Thus, complementary high resolution imaging technologies are needed which can improve the diagnostic accuracy of the standard upper endoscopy and biopsy. Such technologies may also improve the delineation of neoplastic mucosa, facilitating the use of minimally invasive, less costly therapies such as endoscopic mucosal resection, radiofrequency or cryoablation.

In vivo Optical Imaging Optical imaging is a new modality which is able to obtain real-time, high resolution imaging of epithelial tissue. Ideally, such imaging can be used to observe changes in cells that indicate neoplastic transformation. Such indicators may be in the form of changes in the size and internal structure of the nucleus, the disorganization of cells, pleomorphism, and other cellular changes that require resolution of a few microns or better. These changes can be detected through refractive index mismatch in reflectance microscopy (in the case of nuclear changes) or by fluorescence microscopy (requiring the binding of a fluorescently-labeled targeted contrast agent or observation of native tissue autofluorescence). Because these systems are inexpensive and portable, they have the potential to be used in vivo (through a conventional endoscope), to enhance endoscopic screening and surveillance and to define lesions for endoscopic therapy. Early identification of such lesions will not only improve patient survival but also avoid unnecessary esophagectomy, a procedure associated with significant morbidity and mortality.

The High Resolution Microendoscope Our collaborators at Rice University have created a first generation fiber bundle image guide-based microscope system (see Figure 1). The device is treated like a standard endoscope accessory and, thus, has received an IDE exemption from the FDA. Through miniaturization of the optics and use of optical fibers, they have created a 2 mm, flexible probe which can be inserted through the operating channel of a standard endoscope and provide high resolution, magnified images of the gastrointestinal epithelium. The optical fibers within the probe are bundled together in an array of parallel fibers. The fiber bundle is referred to as an image guide. These image guides are able to transfer a pixilated image from one face of the bundle to the other since each individual pixel element (fiber) is organized and parallel to each other (4). This type of fiber bundle can be used for biological microscopy applications since any tissue that is placed upon the surface of the bundle will yield an image on the proximal side that can be magnified through the

use of conventional optics. Fiber bundle image guides overcome the limitations of standard confocal imaging by delivering the light and the optics directly to the tissues that are to be imaged. This system uses inexpensive light emitting diodes (LEDs) as an illumination source. These have desirable spectral characteristics (small bandwidth, down to 20 nm FWHM) and illumination intensity (hundreds of milliwatts) and cost only dollars per unit. Thus, these fiber bundle microscope systems have the ability to be used as a low cost, high-volume screening tool to detect precancerous changes within the GI tract. During standard upper endoscopy, the probe can obtain real-time histologic images, which can assist the endoscopist to target biopsies. We are initiating this study to investigate the potential of this miniaturized microscope device to detect precancerous changes (dysplasia) within the esophagus in patients being screened for squamous cell cancer.

Preliminary Studies with the Image Guide Microscope In order to demonstrate the capabilities of the Image Guide Microscope, several in vivo imaging studies have been performed in Barrett's esophagus, colonic polyps and squamous cell neoplasia. In screening for squamous cell neoplasia, we have used topical proflavine 0.01% and have been able to obtain images of normal squamous mucosa, inflammation, squamous dysplasia, and squamous cell cancer. Differences in the different pathologic grades can be distinguished by changes in the organization and density of the nuclei. Since proflavine selectively enhances nuclear visualization (nuclei appear bright white), cancer can easily be distinguished by a marked increase in nuclear density, a marked increase in nuclear: cytoplasmic ratio and a loss of normal architecture with crowding and disorganization.

In a single arm, NIH-funded pilot trial in the United States and China, we were able to obtain a sensitivity and specificity of 100 and 79% when the HRME was used in conjunction with Lugol's chromoendoscopy in high-risk subjects undergoing endoscopic screening or surveillance. The negative predictive value of the HRME was 97% which suggests that use of the HRME may significantly decrease the number of mucosal biopsies needed during endoscopic evaluation. Given Lugol's known high sensitivity but low specificity (95% and < 60%) this is promising as the HRME may significantly reduce the false positive rate of Lugol's chromoendoscopic screening, the current standard of care. Research subjects recruited at the Jilin site will also be asked to complete a brief survey about beliefs and attitudes about esophageal cancer and screening. It is important to understand factors affecting patient decisions about cancer screening to increase utilization of new technologies and ultimately improve early detection of esophageal cancer in this high-risk population.

Section D: Purpose and Objectives

The overall objective of this multicenter trial is to determine whether use of a low-cost, high-resolution microendoscope during diagnostic upper endoscopy can improve the efficiency and accuracy of endoscopic screening for esophageal squamous cell neoplasia (ESCN). This is a trial of a novel technology, a miniaturized, low cost (<$3,500) microscope device which can be used during upper endoscopy to image the gastrointestinal epithelium. This portable, battery-operated high-resolution microendoscope (HRME) was developed by our collaborators at Rice University and provides greater than 1000X magnified images of the esophageal mucosa. In a single-arm, pilot study of the device in an enriched population of 60 high-risk subjects in China and the US, we used the microendoscope during routine Lugol's chromoendoscopic screening to categorize areas of abnormality (unstained areas). The sensitivity /specificity for the device seen in this study were 100% and 79%-a significant improvement over the sensitivity/specificity of Lugol's chromoendoscropy which were 97% and 52%. Thus, our presumption is that HRME can enhance the specificity (and lower the false positive rate) of Lugol's. As part of a National Cancer Institute R01 supplement (Figure 1), we have enhanced the current HRME technology by introducing an automated, ergonomic, augmented reality platform. The augmented reality platform displays, in real-time, the microscopic image colocalized with the endoscopic image, potentially allowing more targeted biopsies/treatment and increased accuracy. Our central hypothesis is that our approach can improve the efficiency and clinical impact of endoscopic screening and surveillance of ESCN by providing in-vivo optical biopsies comparable to standard histology. Specifically, HRME will facilitate accurate, rapid real-time endoscopic screening by non-expert clinicians. We also hypothesize the HRME will provide additional, more accurate information regarding the presence of neoplasia that will impact upon the physician's decision to obtain a mucosal biopsy or perform endoscopic therapy (endoscopic mucosal resection or ablation). This could potentially minimize the number of unnecessary biopsies and enable the physician to perform endoscopic therapy at the time of the initial examination, rather than delaying endoscopic treatment to another procedure following pathologic confirmation of the initial biopsies. We will compare (1) the current endoscopic "standard of care" (white light endoscopy with Lugol's iodine), (2) HRME with subjective, human interpretation, and (3) augmented reality HRME (software, 'machine' interpretation). The addition of (3) is the basis for our revision RO1 and this amended IRB. The accuracy, efficiency, clinical impact and cost-effectiveness of each approach in the diagnosis and management of ESCN will be determined in both the Chinese and US healthcare systems. Specific endpoints: 1. Efficiency: (a) Diagnostic Yield: The number of neoplastic biopsies/total number of biopsies obtained in patients who receive biopsies. (b) 'Patients saved': Number of patients who receive no biopsies (c) Procedure time: Total procedure time in each group 2. Clinical impact: Determine potential clinical impact of HRME by determining if use of the device (with both subjective and automated read) changes the decision to perform endoscopic therapy and perform, or not perform, a mucosal biopsy when compared to LC alone. 3. Prospectively compare the performance characteristics of HRME-LC to LC for the prediction of squamous esophageal neoplasia in flat mucosa and mucosal lesions using histopathology as the gold standard. (a) Determine the sensitivity, specificity, positive and negative predictive value for the identification of neoplasia on a per biopsy and per patient analysis. 4. Determine the cost-effectiveness of HRME-LC to LC alone for the endoscopic screening and surveillance of ESCN in the US and China.

Section E: Protocol Risks/Subjects

E1. Risk Category

Category 3: Research involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition.

E2. Subjects

Gender:
Both

Age:
Adult (18-64 yrs)

Ethnicity:
All Ethnicities

Primary Language:
Chinese, English, Spanish, Vietnamese

Groups to be recruited will include:
Patients

Which if any of the following vulnerable populations will be recruited as subjects?
Employees or lab personnel

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?
Among the HRME image analysis study, a small number of employees (current GI fellows) will be included in the novice endoscopist group. The PI and study staff will explain the study procedures verbally in addition to providing the letter describing the study with the PI contact info as part of the waiver for written documentation of informed consent. The staff will explain to the fellows that participation is voluntary, that their performance on the test will not affect their standing in their department, and that they are able to withdraw from the study at any time.

E3. Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E4. Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E5. Children

Will children be enrolled in the research?
No

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research:
t) Drug, Phase II, Multi Center

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.
The patient will be assigned to one of two groups: Group A: HRME-LC (HRME + Lugol's) or Group B (Lugol's alone). Randomization assignments (HRME-LC vs. LC) will be computer-generated with allocation concealment using sealed envelopes.

For the image analysis study, there is no randomization. All participants will complete the same study procedures.

Research subjects at the Jilin site will also be asked to complete a survey component addressing barriers to esophageal cancer screening.

Inclusion Criteria:

All-inclusive outpatients undergoing routine (standard of care) Lugol's chromoendoscopic evaluation for suspected or known squamous cell neoplasia will be enrolled as well as any outpatients referred to the clinic with any prior history of squamous cell dysplasia and/or neoplasia will also be considered eligible as they will serve as study population for the surveillance group. Patients seen in outpatient clinics who are high risk for esophageal dysplasia/neoplasia, including patients with known history of head/neck cancer or of Northern Chinese descent will also be eligible for enrollment.

Sixnovice and four expert endoscopists will be the research subjects for the post hoc image analysis project. The subjects will be practicing endoscopists or GIs fellows at current study sites or other institutions.

Exclusion Criteria:

- Allergy or prior reaction to the fluorescent contrast agent proflavine - Patients who are unable to give informed consent - known advanced squamous cell carcinoma of the distal esophagus, or dyplastic/suspected malignant esophageal lesion greater than or equal to 2cm in size not amenable to endoscopic therapy - Patient unable to undergo routine emdoscopy with biopsy: - women who are pregnant or breastfeeding - prothrombin time greater than 50% of control; PTT greater than 50 sec, or INR greater than 2.0 - inability to tolerate sedated upper endoscopy due to cardio-pulmonary instability or other significant medical issues

F2. Procedure

Written informed consent will be obtained prior to study participation using the IRB-approved consent form.

The patient will be assigned to one of two groups: Group A: HRME-LC (HRME + Lugol's) or Group B (Lugol's alone). Randomization assignments (HRME-LC vs. LC) will be computer-generated with allocation concealment using sealed envelopes. As part of the NCI R01 supplement, the HRME-LC arm will now include the augmented reality HRME component following the standard HRME image. The Augmented Reality (AR) glasses will allow the endoscopist to see the microendoscopic (HRME) and endoscopic image at the same time. We now can produce a colocalized image that can be seen on the glasses at the same time as the endoscopic image AND in the same field of view. This does NOT change patient care. Rather, it improves the visualization of the endoscopist as shown in Figure 1.

In both groups, per standard of care, endoscopic examination will be performed using white-light endoscopy with Lugol's dye-spray. In each subject, the location of each unstained area (level, quadrant) will be recorded and digital images obtained. The endoscopist's clinical impression will be recorded for each Lugol's abnormal area and visible lesion ('nonneoplastic'vs. 'neoplastic') as well as his/her proposed plan: a. no biopsy, b. biopsy, c. endoscopic treatment/removal. In the standard-of-care arm (Group B), biopsies will be obtained of all Lugol's abnormal areas. Likewise, Group A will receive the clinician subjective HRME read + augmented reality software HRME read, sequentially, of all Lugol's unstained (abnormal) areas prior to tissue biopsy. For imaging, 1-10 ml proflavine hemisulfate (0.01%) will be sprayed on the esophageal mucosa. The HRME probe placed gently on the mucosa and the augmented reality microscopic (HRME) image displayed on the glasses, with the endoscopic image (monitor) behind it. The endoscopist will first make a subjective interpretation (neoplasia vs. no neoplasia) and plan of action (biopsy, no biopsy, treat) WITHOUT the image-analysis software. Once this qualitative ("Human") read is recorded, the image analysis software will be turned on and the software diagnosis provided in real-time. This quantitative ("Machine") read and the revised plan of action will be recorded. The HRME procedure (including Human and Machine reads) as well as standard endoscopy and biopsy time will be recorded. The research coordinators will indicate the biopsy number/location on an esophageal map diagram. The biopsies from each site will be placed in formalin per standard of care and labeled according to biopsy location (quadrant: 12, 3, 6, 9 o'clock). In all subjects, all Lugol's abnormal areas will be biopsied (to uphold the standard of care, per IRB); however, HRME "non-neoplastic" sites will be considered not tissue-biopsied for purpose of the analysis. All biopsies will be submitted for consensus diagnosis by 2 expert GI pathologists.

A schematic of the existing trial with the proposed revision is shown in Figure 2. The IRB revision is shown in RED. We anticipate that this revision will add an additional 30-60 seconds per procedure but will otherwise not change patient care.

Endoscope Sterilization Procedures: The microendoscope is sterilized immediately after each procedure per standard endoscope accessory reprocessing guidelines. Any proflavine on the surface of the microendoscope is completely removed in the reprocessing procedure. This procedure has been approved by the FDA.

Patient Follow-Up for All Patients: All patients will recover from their procedures according to standard practice and be discharged home. To determine the safety of the HRME using topical proflavine, all pre, intra and immediate post-procedure adverse events will be recorded. Each patient will also receive a phone call from the research coordinator or co-investigator within 7 days from the study procedure to check for any post-procedure complications. In addition, prospective data will be collected on all patients at years 1,3,5 following index exam to determine whether they have progressed to a more advanced state of neoplasia.

Pathology Sample collection: Obtaining Tissue Samples from International Study Sites-Standard Operating Procedure

Biopsies from CICAMS and Jilin will be collected on H & E slides from clinical tissue blocks of all detected esophageal, high grade dysplasia and neoplasia.

The fixed biopsies will be oriented/embedded in paraffin and sectioned to facilitate comparison between histology and HRME images. Afterwards the serial sections will be routinely stained with hematoxylin and eosin for histopathologic examination.

The biopsies or resected specimens (from EMR) obtained from the examined areas will be routinely processed and interpreted by two expert GI pathologists (SD, DR) using standardized WHO classification criteria. Both pathologists will arrive at a consensus diagnosis which will be the official study read (gold standard).

The histopathologic diagnosis for each biopsy will be recorded on a standardized data collection form. The two central study pathologists will be reading ALL the specimens from China and the US and giving a consensus diagnosis. Image analysis will be performed comparing the actual histopathologic images to the "optical" images to develop image analysis algorithms and, potentially, image interpretations software. Rice University will be assisting in development of the image analysis algorithms for future software development.

Separately, 10 endoscopists (6 novice and 4 expert) will be asked to interpret a selection of the HRME images. The novices will include current GI fellows at BCM and novice endoscopists on the protocol, while the expert endoscopists will be experienced endoscopists listed on the protocol. The 10 subjects will receive information about the procedures verbally as a waiver of documentation of consent is requested. Each of the subjects will first receive training using a training set, and then will be evaluated using a testing set of images. They will be asked to give a read (neoplastic or non-neoplastic) and then to provide their confidence level (high or low) for each image determination. Following the subjective HRME image read, each image will be evaluated using the automated software algorithm, with the subjective and automated reads being blinded to each other, as well as to the gold standard consensus pathology read by 2 expert GI pathologists. The subjective reads will be compared to the automated reads and the consensus pathology reads.

Subjects at the Jilin site will be asked to complete a survey addressing barriers to esophageal cancer screenings. Subjects will be asked about beliefs and attitudes surrounding screening techniques.

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 300 Worldwide: 1300

Please indicate why you chose the sample size proposed:

This is an IRB revision and will NOT change our proposed sample size. Rather, in the remaining patients to be accrued, we will determine the accuracy of our revised (AR platform). Thus, the goals and sample size of the original trial will remain intact which is to compare LCE to LCE+HRME (subjective read).

Sample Size Calculation (This has NOT changed from original IRB): The sample sizes are calculated separately for the two risk groups (650 in surveillance group and 650 in screening group). Among the surveillance group, we want to test non-inferiority in sensitivity and superiority in specificity of LCE+HRME vs. LCE alone. The standard endoscopic evaluation using LCE has high sensitivity of about 95% but with low specificity at about 65%. Based on the preliminary data, we hypothesize that LCE+HRME has the sensitivity of at least 90% level, which is similar to that of LCE, but LCE+HRME would improve the specificity to 85%. With significance level of 0.05 and 80% power, we need 223 neoplastic patients and 65 benign patients in each arm (LCE and LCE+HRME) to conclude that LCE+HRME has similar sensitivity as LCE alone and had higher specificity than LCE alone. Hence, we need 446 neoplastic patients and 130 benign patients. The sample size calculation is based on the formula in Pepe (Chapter 8, The statistical Evaluation of Medical Tests for Classification and Prediction, 2003).

According to the preliminary results, greater than 80% patients in the surveillance group would have neoplasia. We anticipate the enrollment of total 650 patients in the surveillance group to ensure the accrual of 446 neoplastic patients and 130 benign patients.

In screening group, we will study the accuracy of LCE+HRME for the diagnosis of neoplasia, and test whether the negative predictive value (NPV) of LCE+HRME is higher than LCE alone. The NPV for using LCE alone is about 95%. We hypothesize that the NPV for LCE+HRME should be at least 99% to be useful. A sample of 300 per arm would provide 82.1% power for this hypothesis with a 5% type-I error. Assuming an 8% loss to follow-up or incomplete data, we need to recruit 325 subjects per arm in the screening population.

Power Calculation (Augmented Reality HRME Revision): We anticipate having at least 400-500 subjects remaining by the time the Augmented Reality HRME revision IRB is approved and funding from the NCI obtained. With 400 patient Augmented Reality HRME data, assuming an accuracy of 83% AND 650 LC patient, assuming an accuracy of 57%, the study should have >93% power to detect a statistically significant difference with an alpha error rate of 0.05.

For the HRME image interpretation study, the sample size of 10 endoscopists was selected based on a prior power analysis based on non-inferiority. The 10 endoscopists will review about 140 HRME images. It is hypothesized that software interpretation of the HRME iamges will be non-inferior to the endoscopist interpretation. Non-inferiority is defined as a 10% difference in specificity between the two groups with 90% power and alpha of 0.05.

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

Among the surveillance group, three analyses in testing the null hypotheses will be performed, including two interim analyses and one final analysis. The analysis will be performed when 220, 440 and 650 study subjects have been accrued, respectively.

The interim analysis will use a symmetric two sided group sequential design using a Hwang-Shih-DeCani spending function with beta spending of -4, which provides an O'Brien-Fleming-like conservative upper bound. This approach requires a two sided significance level of 0.0026 and 0.0114 for the interim analysis and 0.0464 for the final analysis of overall survival.

There will be no interim analysis for the screening population.

The primary analysis for the surveillance group is to test non-inferiority in sensitivity and superiority in specificity of LCE+HRME vs. LCE alone. The test statistic is based on the formula in Pepe (Chapter 8, The statistical Evaluation of Medical Tests for Classification and Prediction, 2003). Additionally, sensitivity and specificity of LCE+HRME vs. LCE alone will be estimated on a per patient basis with 95% confidence intervals. The primary goal for the screening group is to test whether the negative predictive value (NPV) of LCE+HRME is higher than LCE alone. This is done using Fisher’s exact test. Additionally, the negative predictive value will be summarized with 95% confidence intervals.

The secondary analysis includes diagnostic yield, clinical efficiency, clinical impact, progression rate, and the rate of adverse events.

Diagnostic yield: This is defined as the proportion of all biopsies that are truly neoplastic over the total number of biopsies obtained in patients who receive biopsies. A generalized linear model for logistic regression with multiple correlated binary outcomes within each patient will be used for data analysis. In this model the binary outcome for each biopsy specimen is whether the specimen is neoplastic or non-neoplastic, and the explanatory variable is the arm (LCE+HRME vs. LCE alone) stratified by group (screening and surveillance). PROC GLIMMIX in SAS will be used because of the correlations among samples from the same patient. The model will allow for testing whether the proportion of samples classified as neoplasia differs between the 2 arms.

‘Clinical efficiency’: For patients that have benign disease confirmed by histology, the true proportion of patients potentially saved any biopsy using HRME (Lugol’s + and HRME -) will be estimated by 95% confidence intervals (stratified by group). Proportions will be compared between groups by the chi-square test or Fisher’s exact test. Procedure time in the HRME+LC arm will be compared to the LC arm by analysis of variance, stratified by group (screening and surveillance). An interaction term will also be included to determine to what extent the difference in procedure time between the 2 arms varies between the 2 risk groups.

Clinical impact: For this, the proportion of patients who had a change in the decision to perform endoscopic therapy or mucosal biopsies as a result of LCE+HRME or LCE alone, will be estimated by a 95% confidence interval. This proportion will be compared between LCE+HRME and LCE alone by the chi-square test or Fisher’s exact test.

Progression rates: Five year follow-up of progression rates to more advanced pathology or esophageal cancer (EC) in the 2 arms will be conducted. Progression rates and theirs 95% confidence interval will be summarized and compared between LCE+HRME and LCE alone by the chi-square test or Fisher’s exact test.

Safety/Adverse Events: Immediate and 48 hour adverse event (AE) rates will be compared between the LCE+HRME arm and LCE alone arm by the chi-square test or Fisher’s exact test. The AE rates and their 95% confidence intervals will be summarized.

Among the HRME image interpretation study, the sensitivity, specificity, and accuracy for all participants, as well as novice vs. endoscopist participants, will be tabulated. Interrater reliability among all endoscopists and the level of agreement between the endoscopists and the automated software will be calculated using Kappa statistic.

Section H: Potential Risks/Discomforts

H1. Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

Possible risks associated with the study procedures are listed below. There may also be risks that are not known.

Many side effects go away soon after the procedure, but in some cases, side effects may be serious, long-lasting or permanent, and may even cause death. It is important that the participant tell the study staff about any side effects that he/she may have had even if he/she does not think it is related to the procedure.

Allergic reaction (anaphylaxis) There is the possibility of a severe allergic reaction to the Proflavine contrast dye in which participant may have difficulty breathing and the blood pressure may drop. There are procedures in place to treat participant in endoscopy room in the event that this happens.

Specimen Imaging Probe There are no known risks from the use of the imaging probe.

Anesthesia There may be additional risks from the added time of additional sedation, such as decreased blood pressure.

Aspiration (inhaling) of fluid into the lungs during endoscopy This might cause inflammation in the lungs. Safeguards to prevent this from happening while the participant is under anesthesia will be in place during and after the procedure, and participant's breathing and other vital signs will be carefully monitored.

If participant experience any symptoms other than those that the study doctor has informed the participant are associated with the procedure, please let the study doctor know.

Pregnancy Insufficient information is available on the use of Proflavine in pregnancy. Drugs can have harmful effects on the fetus at any stage of pregnancy.

Loss of Privacy

Subjects will be consented on the day of their procedure. Subjects will be taken to a private area where the study information will be discussed. No additional sensitive information will be requested from the subjects beyond what is required to perform a standard surveillance endoscopy. Subjects will be given an ID number for all forms, images, and communications. All data will be coded. Source documents will be redacted of all PHI before being sent from outside sites for data monitoring/data entry in the database. All PHI collected on BCM subjects will be stored in locked cabinets or password-protected files/computers where only the PI and study coordinator can see the names. All case report forms will use the assigned subject ID. Since the subject participation is only for one visit, there will be limited opportunity for privacy interests to arise between study recruitment and end of the study. The only extra intrusion of privacy will be an additional phone call within 7 days of the procedure to ensure that the subject has not suffered any adverse events. During the follow-up, only the study coordinator and/or the PI will have contact with the subject. Information pertaining to the study will only be discussed with the subject and messages containing identifiers of the subject's participation will not be left on voice-mail messages.

For the post hoc image analysis project, the risk to the research subjects are minimal. Loss of privacy is an inherent risk, but to mitigate this, each subject will be assigned an unique, random ID and any identifying information will not be stored.

H2. Data and safety monitoring plan

Do the study activities impart greater than minimal risk to subjects?
Yes

NOTE: The answer to the questions in H2 requires the completion of the form: 'Section H – Data and Safety Monitoring Plan' as an attachment in Section S.

H3. Coordination of information among sites for multi-site research

Is the BCM Principal Investigator acting as the SPONSOR-INVESTIGATOR for this multi-site research?
Yes

Is BCM the COORDINATING CENTER for this multi-site research?
Yes

If the answer to EITHER of the questions above is "Yes", please complete the following questions:

If this is a multicenter study and the BCM PI is an INVESTIGATOR with responsibilities of SPONSOR or if BCM is the COORDINATING CENTER, describe the management of information among the sites related to participant protections. Your description should include reporting of unanticipated problems, protocol modifications, IRB and/or institutional approvals, and interim results among the sites.

The approved BCM protocol and approved Informed consent document will be distributed to CICAMS, Beijing and First University Hospital , Jilin in China. These documents will be translated into Chinese and submitted to the collaborating site's IRB. Once approved is granted, the approved documents will be submitted to the Coordinating Center (BCM) and forwarded to the IRB for review. All investigators are aware of this requirement and will acquire and maintain documentation of all IRB actions at their sites.

IRB approval must be obtained, and an Initiation Site Visit conducted before enrollment can begin at collaborating sites. The PI a will travel to the collaborating sites to train the investigators on the proper use of the device and to ensure proper conduct of the study. Informed consent will obtained from each subject in compliance with HHS regulations as this is informed consent is obtained from each subject in compliance with HHS regulations as this is part of the standard operating procedures at these institutions.

All efforts will be made to ensure patient confidentiality and assurance of HIPAA compliance. Immediately after obtaining any specimens and microscopic images, subjects will be assigned a protocol specific unique code that will be used for all further data management. A list matching the patient medical record number to the protocol specific unique code will be kept in a locked cabinet in the office of the PI. The names of the patients will not be released to any outside organizations or to persons not involved in the investigation. They will not be revealed in written reports or publications detailing the research findings.

Patient's names, medical record numbers, and pathological information will be collected and stored in a locked drawer in the PI's office. The research data will be stored with the patient ID number and the sequential image number on a laptop that is associated with the imaging probe (the device has its own computer and hard drive) and will be password protected. The server is an internal password-protected, limited access system in which these image scans are uploaded onto so that the Rice team may also view the scans. This server comes from Rice's Information Technology department and is protected by a firewall on the network drive, much like the server at the Mount Sinai School of Medicine, so it does not require encrypting. Additionally, the device and laptop are stored in the PI's office in a locked drawer.

Study data will be collected at all clinical sites on paper CRFs identifiable by subject ID number. Copies of paper CRFs will be transferred to MSSM and then entered into a secure, password protected database. Data will be stored securely at the Coordinating Center. Data and safety monitoring will be performed by the study statistician.

Deidentified data (microscopic images) will be analyzed at Rice University, by the bioengineers who developed the devices and are collaborating on the project. The device being used in this study (the HRME) is manufactured in Dr. Kortum's lab at Rice University. The images collected from the clinical trial are used to build software that will work to automatically analyze data. Data will be transmitted as deidentified images only.

All histopathologic slides and optical images will be labeled with the subjects study ID number and will be presented to the pathologist who will read them in a blinded fashion. The subjects' clinical research forms with the associated optical biopsy read(s) are similarly labeled with the subjects study ID number.

All of the above information will be transferred to Baylor College of Medicine and entered into a secure database .Any linking information will only be available to the PIs, and will be stored in a locked cabinet in PIs¿ office. At Mount Sinai, only subject ID number will be available and stored in the d

When research is conducted in collaboration with outside entities or organizations, the PI must obtain the necessary approvals from those entities. The BCM IRB may request documentation that such approvals have been obtained. Please list and describe the planned sites for this multi-site research for which the BCM PI is either Sponsor-Investigator and/or Coordinating Center. Sites that do not meet the requirements for inclusion in section A6a of the protocol summary and BCM informed consent documents should be listed here.

Baylor College of Medicine, Texas, USA Cancer Institute, Chinese Academy of Medical Sciences (CICAMS), Beijing, China The First Hospital of Jilin University, Changchun, Jilin, China National Cancer Instutute Rice University, Texas, USA Harvard University School of Medicine, MA, USA

Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.

There may not be any benefit to participants from taking part in this research.

Describe potential benefit(s) to society of the planned work.

Participation in this study may help future patients with esophageal squamous cell cancer from what is learned in this study.

For the post hoc image analysis project, the benefit to society may be the introduction of an innovative, low cost screening technology for esophageal squamous cell carcinoma. Utilizing a reliable, automated HRME image interpretation could reduce the need for endoscopists trained in HRME, and allow for use of the HRME device in resource poor areas and countries. Have a real-time technology that aids in decision making may result in reduced biopsies, decreased costs, and help facilitate immediate treatment.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

The incremental risks of HRME with proflavine, added to the SOC white light with lLugol's iodine are minimal. White light endoscopy is standard of care and all subjects will be undergoing this SOC procedure.

Section J: Consent Procedures

J1. Waiver of Consent

Will any portion of this research require a waiver of consent and authorization?

Yes

Please describe the portion of the research for which a waiver is required. (Example: chart review to determine subject eligibility)

We will screen ENT clinic schedules at Ben Taub and BSLMC to identify current out patients who may be eligible for participation in our clinical trial. Eligible subjects approved by a GI physician will then be contacted via telephone to determine participation interest, followed up by written, in-person consent prior to the procedure.

Explain why the research and the use or disclosure of protected health information involves no more than minimal risk (including privacy risks) to the individuals.

We will only store minimally required information on individuals who meet our inclusion and exclusion criteria. This information will be stored electronically behind BCM's firewall, and only research staff on a need to know basis will have access to the list. We don't believe this chart review will present additional privacy risk beyond routine patient care including use of electronic medical records.

Explain why the waiver will not adversely affect the privacy rights and the welfare of the research subjects.

The subjects we are screening for this clinical trial include current outpatients at ENT clinics, including those with a past medical history of head and neck cancers. The ongoing surveillance for these patients would include upper endoscopy as history of head and neck cancer is a risk factor for subsequent development of esophageal squamous cell carcinoma. Therefore, we don't believe the chart review presents an unjustified review of medical information for a completely unrelated condition and may actually present benefit. Subjects who satisfy the initial inclusion criteria screen, but who do not wish to participate after discussing over the phone, are not contacted for participation in the trial in the future, nor would it affect their ongoing medical care with their current physician.

Explain why the research could not practicably be conducted without the waiver and could not practicably be conducted without access to and use of the protected health information.

Our trial requires screening patients for study enrollment. We believe the chart review of current out patients with known risk factors for esophageal squamous cell carcinoma offers an efficient process for identification of subjects for the clinical trial. The known alternatives would depend on physician recruitment and referral or for subjects to self-identify to research staff based on advertising, both of which might contribute to slower accrual.

Describe how an adequate plan exists in order to protect identifiers from improper use and disclosure.

Only members of the research team on a need to know basis will have access to the list of potential research subjects. This list will include only the minimum required information and will be stored electronically behind BCM's firewall.

Describe how an adequate plan exists in order to destroy identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

Information on individuals on the list who satisfy the inclusion and exclusion criteria, but who state they are not interested in participating in the trial, will be deleted. We will only retain the most basic identifying information on individuals so that they are not contacted again in the future regarding trial participation. Similarly, information on individuals who do participate in the trial will also be limited so that we will not screen their records again in the future. At the conclusion of the trial, the list will be permanently deleted.

Describe how adequate written assurances exist in order to ensure that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

Only research staff on a need to know basis will have access to the list. At present, this includes the Clinical Research Manager, research coordinator, and the GI physician. Research staff with access to this list have completed all human subjects and HIPPA training and are aware of human subjects protections in place and also understand the repercussions for improper use of such information. The information collected will only be used for the current trial, will not be shared with any outside party, will be stored with only the minimum required information behind the BCM firewall, and will be deleted at the earliest opportunity.

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.

Yes

Specific information concerning alcohol abuse:

Yes

Specific information concerning drug abuse:

Yes

Specific information concerning sickle cell anemia:

No

Specific information concerning HIV:

No

Specific information concerning psychiatry notes:

No

Demographic information (name, D.O.B., age, gender, race, etc.):
Yes

Full Social Security #:
No

Partial Social Security # (Last four digits):
No

Billing or financial records:
No

Photographs, videotapes, and/or audiotapes of you:
No

Other:
No

Will additional pertinent information be provided to subjects after participation?
No

If No, explain why providing subjects additional pertinent information after participation is not appropriate.
The information collected would include demographics and relevant clinical data. It would not include any additional information that could not be accessed by the patients through their own review of their medical record.

J1a. Waiver of requirement for written documentation of Consent

Will this research require a waiver of the requirement for written documentation of informed consent?
Yes

Explain how the research involves no more than minimal risk to the participants, and the specifics demonstrating that the research does not involve procedures for which written consent is normally required outside of the research context.
We are requesting a waiver of the requirement for written documentation of informed consent for the small 8 subject study evaluating the HRME image interpretation among novices and fellows only. We are not requesting a waiver for the larger 1300 subject trial. The 8 subject study involves no more than minimal risk to participants as the procedure is limited to completing a training and testing set for image interpretation, either in person or remotely. The procedure will be non invasive and short in duration (less than one hour per subject). The subjects are simply asked to interpret each image as appearing to be neoplastic or non-neoplastic, and then to provide their confidence level (high or low) for each response.

J2. Consent Procedures

Who will recruit subjects for this study?
PI
PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.
At this time we will focus our recruitment effort on the PI's patients and the patients of other co-investigators (Patel, Othman) at Ben Taub and Baylor St Luke's Medical Center. With an FDA IND, any endoscopist performing the research only procedure needs to be included on the FDA form 1572. We will screen the endoscopy schedule of the PI and co-investigators for subjects that are scheduled for upper endoscopy for known, suspected, or history of SCC per eligibility in the protocol. The medical records of subjects who seem to be eligible based on their endoscopy indication will be further reviewed to assess if they have SCC (e.g. eligible). Participation in the trial will be discussed with patients at a routine office visit prior to their endoscopy or on the day of their exam prior to the endoscopy by the study investigator or Research Coordinator.

For non-English speaking subjects, our bilingual study staff who are authorized to provide translation for consents will be doing the consents.

For the image interpretation study, the research subjects will be endoscopists at institutions currently participating in the research protocol, practicing endoscopists in other medical centers, or current trainees at institutions on the protocol. The research team will work to identify the subjects through professional connections and current relationships. The subjects will be contacted via email regarding participation and study details. The email script that will be used to notify potential subjects has been included in the attachments section of the protocol.

Are foreign language consent forms required for this protocol?

Yes

Which of the following ways will you document informed consent in languages other than English?
Short-Form consent documents

J3. Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?
No

J4. Children

Will children be enrolled in the research?
No

J5. Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?
No

J6. Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?
No

J7. Prisoners

Will Prisoners be enrolled in the research?
No

Section K: Research Related Health Information and Confidentiality

Will research data include identifiable subject information?
Yes

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
Yes

Specific information concerning alcohol abuse:
Yes

Specific information concerning drug abuse:
Yes

Specific information concerning sickle cell anemia:
No

Specific information concerning HIV:
No

Specific information concerning psychiatry notes:
No

Demographic information (name, D.O.B., age, gender, race, etc.):
Yes

Full Social Security #:
No

Partial Social Security # (Last four digits):
No

Billing or financial records:
No

Photographs, videotapes, and/or audiotapes of you:
No

Other:
No

At what institution will the physical research data be kept?
Baylor College of Medicine

How will such physical research data be secured?
Physical data will be stored in a lock filing cabinet in the PI's or Research Manager's locked office and monitored closely at all times.

At what institution will the electronic research data be kept?
Baylor College of Medicine

Such electronic research data will be secured via BCM IT Services- provided secured network storage of electronic research data (Non-Portable devices only):
Yes

Such electronic research data will be secured via Other:
No

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?
No

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.
If needed, transmission of PHI to sponsors and/or collaborators will be done by secure/encrypted e-mail

Will you obtain a Certificate of Confidentiality for this study?
No

Please further discuss any potential confidentiality issues related to this study.
N/A

Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.
Neither the subject nor subject's insurance will be responsible for research related costs. Research related costs are specifically the use of the Proflavine and the use of the imaging probe if subjects are randomized to the HRME after the standard of care Lugol's + upper endoscopy. The costs related to the clinically indicated upper endoscopy are not research and are covered by the subject or their insurance.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:
0

Distribution Plan:
Subjects will not be paid to participate in this research project.

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.
There is no genetic component to this study

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling

and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

Section N: Sample Collection

SAMPLE: Tissue

What is the purpose of the sample collection?

Tissue obtained by biopsy will be collected for clinical diagnosis. No tissue or samples are collected only for research. The slides/tissue blocks used for a clinical diagnosis will be available for re-review by the pathologists to confirm a final study diagnosis.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

n/a

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:

Pathology

Will the sample be stripped of identifiers?

No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?

Slides will be coded with the subject ID. Images will be sent to pathologists on protocol.

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

Only de-identified information will be shared with investigators on the protocol.

If sample will be banked for future use:

Where will the sample be banked and for how long?

no

Does the banking institution have an approved policy for the distribution of samples?

n/a

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?

n/a

Will samples be made available to the research subject (or his/her medical doctor) for other testing?

No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?

No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?

n/a

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?

n/a

Will study data or test results be recorded in the subject's medical records?

No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?

n/a

Please identify all third parties, including the subject's physician, to receive the test results.

n/a

Section O: Drug Studies

Does the research involve the use of ANY drug* or biologic? (*A drug is defined as any substance that is used to elicit a pharmacologic or physiologic response whether it is for treatment or diagnostic purposes)

Yes

Does the research involve the use of ANY gene transfer agent for human gene transfer research?

No

O1. Current Drugs

Drug : Proflavine Hemisulfate

Is this study placebo-controlled?

No

Will the research involve a radioactive drug that is not approved by the FDA?

No

Section P: Device Studies

Does this research study involve the use of ANY device?

Yes

Device 1: HRME

Section Q: Consent Form(s)

HRME BCM consent

Section R: Advertisements

None