Official Title: Effectiveness and Performance of an Optical Biopsy Technology for Esophageal Cancer in Brazil and the United States

NCT number: Not yet assigned

Document Date: May 7, 2024

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: H-53483
Status: Approved
Initial Submit Date: 4/12/2023
Approval Period: 5/7/2024 - 4/23/2025

Section Aa: Title & PI

A1. Main Title

EFFECTIVENESS AND PERFORMANCE OF A MOBILE, AUTOMATED, OPTICAL BIOPSY TECHNOLOGY FOR ESOPHAGEAL CANCER SCREENING: A CLINICAL STUDY IN BRAZIL AND THE UNITED STATES

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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: NATIONAL CANCER INSTITUTE (NCI);NATIONAL INSTITUTES OF HEALTH (NIH)

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: BRAZIL
Facility/Institution: Instituto do Câncer do Estado de São Paulo; Barretos Cancer Center Hospital de Amor

Contact/Investigator: Fauze Maluf-Filho; Elisa Ryoka Baba
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:

A7. Research Category:

Cancer - Adult

A8. Therapeutic Intent

Does this trial have therapeutic intent?
No

A9. ClinicalTrials.gov Registration

Does this protocol/trial require registration on ClinicalTrials.gov due to it: meeting the definition of an Applicable Clinical Trial, being required under the terms and conditions of an award, or being proposed to be published in ICMJE journals?
Yes

Who will be responsible for registering and maintaining the registration of this Applicable Clinical Trial?
The BCM PI will register the trial because either:

- the trial is BCM PI-initiated,
- BCM is the lead site of this multicenter trial, or,
- the industry sponsor has instructed the BCM PI to register the trial, or,
- registration of this trail is required as a term and condition of the reward by the funding agency.

ClinicalTrials.gov Identifier:
NCT

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

Upper gastrointestinal (GI) cancers (esophageal, stomach) account for 14% of all global cancer mortality with 5-year survival rates of 15-20% and a markedly greater burden of disease in the developing world due to delayed diagnosis. While endoscopy has dramatically improved survival in high-income countries implementing endoscopic screening nationally (Korea, Japan, etc.), Brazil and most of Latin America have severe capacity limitations (equipment, infrastructure, clinicians), precluding success. Survival rates drop dramatically once these tumors breach the mucosal layer, reinforcing the importance of early detection. Early detection enables endoscopic therapy (ablation or endoscopic resection), a significantly less costly and safer alternative to surgical esophagectomy. The gold standard evaluation for all GI cancers is endoscopy. For esophageal squamous cell neoplasia (ESCN), this involves Lugol's chromoendoscopy (LCE) with iodine staining and targeted biopsy of unstained (abnormal) areas.

Screening is performed in high-risk patients (head and neck cancer, high-prevalence regions). While Lugol's is the most sensitive method for ESCN detection (95%), specificity is poor (less than 60%): areas of inflammation appear unstained and indistinguishable from cancer, leading to high false-positive rates. Other novel wide-field modalities (autofluorescence, narrow-band imaging [NBI]) have been proposed as red flag techniques. Still, they are less sensitive than Lugol's and similarly limited by high false-positive rates due to low spatial resolution. As a result, multiple unnecessary biopsies are taken with subsequent increases in cost and risk. Confocal microendoscopy, a high-resolution imaging technique that evaluates the mucosa at a 1 μm resolution and 1100X magnification, has revolutionized endoscopic cancer surveillance, allowing endoscopists to see the mucosa at a subcellular level. When confocal is coupled with wide-field Lugol's imaging, accuracy rates rise to 95% with a dramatic improvement in specificity.

Nonetheless, confocal platforms are expensive (more than $175,000), bulky, and available in only a handful of tertiary

centers worldwide. Lastly, interpreting histopathology-like images requires extensive training and experience, a significant limitation in low-resource environments with less experienced clinicians. Given the limitations of existing approaches, the high cost and expertise of confocal imaging, and the dismal prognosis of esophageal cancer when it has breached epithelium, there is a great need for more accurate and accessible technologies. A robust, low-cost, mobile, automated method of delineating ESCN could allow more accurate and selective biopsies, reduce the number of patients lost to follow-up, and facilitate immediate, minimally invasive endoscopic therapy (resection, ablation).

Please see attachment "H-53483 Section C Additional Background" for more details.

Section D: Purpose and Objectives

Objective 1: In a single-arm study (n=200) of high-risk subjects undergoing Lugol's chromoendoscopy (LCE) followed by AI-mHRME for ESCN screening in Brazil and the US, we will evaluate the diagnostic performance, efficiency, and impact of this automated optical biopsy device. Our main hypothesis is that AI-mHRME will increase the LCE accuracy. Other exploratory hypotheses are that AI-mHRME will (1) increase the mHRME accuracy in novices and be non-inferior to experts, (2) increase user confidence among experts and novices, and (3) increase the LCE efficiency and impact by reducing biopsies and second procedures.

We will compare the accuracy of the AI-mHRME software read to novice and expert clinicians' subjective reading to gold-standard histopathology (expert GI pathologist). For clinician confidence and clinical impact, we will determine the clinician's confidence level in the software diagnosis and the potential clinical impact of this diagnosis among novice and expert endoscopists using mHRME. The clinician reads will be part of the mHRME procedure and treatment "plan" (biopsy vs. not biopsy vs. treat). Clinicians are not considered study subjects in objective 1. The clinical impact will be determined by the change in the clinician's decision in the treatment "plan" before and after the AI-mHRME read. For efficiency (biopsy saving and diagnostic yield), we will determine the number of patients spared any biopsy due to AI-mHRME. We will compare the diagnostic yield of AI-mHRME + LCE vs. LCE alone (diagnostic yield = neoplastic biopsies/total number of biopsies obtained in biopsied patients).

Objective 2: This objective will have three study populations, with a total sample size of n=50 subjects. To determine barriers and facilitators to implementing AI-mHRME, we will form a Health Sector Stakeholder Advisory Board (HS-SAB) in the US as the first study population. The HS-SABs will include academic partners, primary care providers referring patients, doctors performing esophageal cancer screening, hospital administrators, and patient and caregiver representatives. HS-SAB sample size will be 6-10 members in the US, which is a standard number of participants for research advisory boards. We will collect feedback and input through focus group discussions (FGDs) at 6 time points across the project period per HS-SAB. FGD objectives will match the research stage: clinical trial planning (recruitment and retention plan refinement), data collection (stakeholders identification), result interpretation, and dissemination. An agenda for HS-SAB FGDs with example topics is attached to this IRB protocol.

For the second study population, we will conduct semi-structured individual interviews with implementers to assess barriers and facilitators to implementing AI-assisted cancer technologies (n=40). Interviews will be with patients and caregivers (n=10), GI clinicians (n=10), primary care physicians (n=10), and hospital and health leadership (n=10).

Lastly, we will conduct surveys with endoscopists (n=40) at the participating sites to understand their thoughts on HRME.

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), Geriatric (65+ yrs)

Ethnicity:
All Ethnicities

Primary Language:
English, Portugese, Spanish

Groups to be recruited will include:
Both patients and healthy, non-patient, normals

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?

The academic partners, primary care providers for referring institutions, clinicians performing esophageal cancer screening and treatment, hospital administrators, and patient and caregiver representatives in the Health Sector Stakeholder Advisory Board (HS-SAB) will be invited to participate in focus group discussions (FGDs) administered at different time points of the study. These FGDs will not inquire about personal health or other personal information. Rather, they will be asked to provide their opinion on the AI-mHRME technology. While we will not use a formal informed consent form, the providers will receive a research letter describing the purpose and procedures of the study. It will explain that their participation is completely voluntary. If they choose not to participate, there will be no impact on their careers, training, or evaluations based on their decision to participate or NOT to participate in the HS-SAB.

For semi-structured interviews, participants will be identified and recruited via members of the US and Brazil HS-SABs who will identify health system stakeholders at referral hospitals and referring institutions, including specialist physicians (i.e., gastroenterologists, n=10), primary care providers (n=10), hospital administrators (n=10), and patients/caregivers (n=10). Recruitment for the Provider Surveys and Stakeholder Advisory Board will be entirely voluntary.

We will interview 40 endoscopists at the study sites using a questionnaire for the endoscopist surveys. Based on prior participation in Brazil, we anticipate 90% participation in the surveys and the advisory board.

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:

j) Device, 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.

Endoscopy HRME procedure: This trial will be done at Baylor St. Luke’s Medical Center (BSLMC) and Harris Health Systems Ben Taub Hospital (BTGH), Houston, TX; Instituto do Câncer do Estado de São Paulo (ICESP), Sao Paulo, Brazil; and Barretos Cancer Center Hospital de Amor (BCC), Barretos, Brazil. Each site will have a single arm where patients will be screened for ESCN per standard of care (SOC) endoscopy and consented to Artificial Intelligence Mobile High-Resolution Microendoscope (AI-mHRME) imaging.

Patients (n=200) will be recruited by Drs. Anandasabapathy (BSLMC), Tan (BTGH), Maluf (ICESP), Hashimoto (BCC), and Ryoka Baba (BCC) and their teams. In Houston, staff will screen patients in EPIC. In Brazil, staff will screen and enroll patients prior to procedure in the waiting and pre-op areas with a screening questionnaire in the case report form. Eligible patients will be consented before the endoscopy procedures.

All subjects will receive White Light Imaging (with/without Narrow Band Imaging) and Lugol's Chromoendoscopy (LCE), the current SOC procedure. We will record any abnormal (suspicious) LCE areas and record the clinician's action plan (Biopsy vs. No Biopsy vs. Treat). Following LCE, all subjects will receive the AI-mHRME imaging with Proflavine Hemisulfate, contrast agent, of any LCE abnormal and LCE normal areas (1:4 ratio). We will record the subjective clinician read for white light and/or NBI and confidence level in their diagnoses (high, low), and action plan. We will image the same abnormal and normal areas with the AI-mHRME and record the software read, clinician confidence level, and action plan. Finally, the imaged abnormal areas will be biopsied, resected, and evaluated by a pathologist. All subjects will receive both SOC and AI-mHRME imaging.

Once data is collected at each site, data will be removed from identifiers, coded, and transferred to BCM. BCM will be responsible for coordinating data entry, management, and analysis.

Health Sector Stakeholder Advisory Board (HS-SAB), Semi-structured Interviews (SSIs), and Endoscopist Survey (ES): Site PIs will recruit SAB members in the US and Brazil. The members will include academic partners, primary care providers referring patients, doctors performing esophageal cancer screening, hospital administrators, and patient and caregiver representatives. Each HS-SAB will have 4-5 members (8-10 members total). We will collect feedback and input on AI-mHRME from the HS-SABs through focus group discussions (FGDs) that will reflect the stage of the research, including clinical trial planning (refinement of recruitment and retention plans), data collection (identification of stakeholders), interpretation of results, and dissemination of findings. The HS-SAB will meet semi-annually across the project period. SSIs (n=40) with patients and caregivers, GI clinicians, primary care physicians, and hospital health leadership will be recorded, transcribed, and translated by a trained research assistant in the US and Brazil. The ES is a previously developed survey (H-48152) that will be refined and implemented based on the SSI findings. This survey includes validated acceptability, feasibility, and appropriateness measures, which are our key constructs in implementing interventions. Endoscopists participating in the trial at each site (total n=40) will be invited to complete a 15-minute self-administered survey. We will survey both AI-mHRME users and non-users. For non-users, we will use the digital procedure simulation we developed.

ICESP and Barretos IRB approvals are pending in Brazil. We will not initiate research activities in Brazil until we have obtained and submitted approvals and documents as an IRB amendment. Studies will not start for Spanish speaking subjects at BTGH until the Spanish version of the informed consent is IRB approved and all approvals are secured at Harris Health system.

Inclusion Criteria:

Endoscopy + HRME inclusion criteria: - Outpatients undergoing routine (standard of care) Lugol's chromoendoscopic screening for squamous cell neoplasia will be eligible for enrollment, including patients with a known history of head/neck squamous cell cancer; heavy smoking and alcohol, other dietary or geographic risk factors or prior dysplasia - Patients >18 years old. - Patients of any sex or gender. - Patients who are willing and able to give informed consent.

HS-SAB Members inclusion criteria: - Academic partners, primary care providers for referring institutions, clinicians performing esophageal cancer screening and treatment, hospital administrators, and patient and caregiver representatives. - Participants >18 years old. - Participants of any sex or gender. - Participants who are willing and able to give informed consent. - Participants who are willing to participate in 6 focus group discussions. - Women (if they are in any of the professions or roles listed above) who are pregnant or breastfeeding.

There is no obligation to participate in the HS-SAB, which will be explained via the research letter in Section S.

Semi-structured Interviews inclusion criteria: - Participants >18 years old. - Participants of any sex or gender. - Participants who are willing and able to give informed consent. - Participants who are willing to participate in the semi-structured interview and identified by a member of one of the HS-SABs.

There is no obligation to participate in the SSI, which will be explained via the research letter in Section S.

Endoscopist Survey inclusion criteria: - Participants >18 years old. - Participants of any sex or gender. - Endoscopists participating in the trial at each site - Does not have to have experience using an HRME device

There is no obligation to participate in the Endoscopist Survey, which will be explained via the research letter in Section S.

Exclusion Criteria:

Endoscopy + HRME procedure exclusion criteria: - Allergy or prior reaction to the fluorescent contrast agent proflavine hemisulfate. - Patients who are unable to give informed consent. - Known advanced squamous cell carcinoma of the distal esophagus or dysplastic/suspected malignant esophageal lesion greater than or equal to 2 cm in size not amenable to endoscopic therapy. - Patient unable to undergo routine endoscopy 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.

HS-SAB exclusion criteria: - If they do not agree to participate in the focus group discussions. - Those who do not have any contact with endoscopy procedures - Doctors who have never performed endoscopies - Patients who never had an endoscopy or do not have ESCN - Administrators from other departments where endoscopies are unrelated - If they are unable to attend 6 focus group discussions

Semi-structured Interviews exclusion criteria: - Participants <18 years old. - Participants who are unwilling and unable to participate in the interview.

Endoscopist Survey exclusion criteria: - Participants <18 years old. - Endoscopist not at a participating study site

F2. Procedure

The PIs will accrue subjects (n=200) already scheduled for endoscopic screening or surveillance due to a high risk for ESCN (head and neck cancer history; heavy smoking and alcohol; other dietary or geographic risk factors; or prior dysplasia). Lugol's chromoendoscopy (LCE) is the current ESCN screening and surveillance standard of care. We anticipate enrolling approximately 140 screening and 60 surveillance patients in the US and Brazil.

To uphold this standard of care and recruit patients already scheduled for endoscopy, LCE will be performed on all patients, followed by HRME of Lugol's voiding (unstained areas). Subjects will be sedated per standard protocol (IV sedation) and undergo white-light endoscopy with the application of Lugol's iodine. In each subject, we will record the location of each Lugol's unstained area (level, quadrant) and obtain digital images. We will record the endoscopist's clinical impression for each Lugol's abnormal area and visible lesions ('non-neoplastic' vs. 'neoplastic') and his/her proposed plan: a. no biopsy, b. biopsy, or c. endoscopic treatment.

Subsequently, the endoscopist will perform HRME of all Lugol's unstained (abnormal) sites before tissue biopsy of those abnormal sites. For false-negative calculations, we will image by HRME the two endoscopically (Lugol's normal) areas, but we will not collect biopsies from those areas. For all imaged areas: (1) we will spray 1-10 ml proflavine hemisulfate (0.01%) on the esophageal mucosa, (2) gently place the HRME probe on the Lugol's abnormal areas, (3) display the 'optical biopsy' image on the laptop connected to the HRME device and probe (endoscopic image will remain displayed on the standard monitor behind it). Proflavine is used under IND #102217, where Dr. Anandasabapathy has done several studies using proflavine and the HRME to look at cells in the esophagus and other parts of the body. The FDA has approved the use of proflavine under this IND for this study.

The endoscopist will FIRST make a subjective interpretation ('non-neoplastic' vs. 'neoplastic'), record their confidence level in the diagnosis (high confidence vs. low confidence), and indicate their plan of action (a. biopsy, b. no biopsy, c. treat). All of this will be done WITHOUT the image-analysis AI software.

Once we record this qualitative read, we will turn on the AI image analysis software (foot pedal), and the software will provide a real-time diagnosis with the HRME laptop display. Then, we will record the quantitative ("Machine") read, the endoscopist's confidence level again, and the (revised) action plan (a numerical score, 1. biopsy, 2. no biopsy, 3. treatment). Based on a predetermined algorithm threshold, the software will determine the output (score) to be neoplastic (cancer) or non-neoplastic (normal). This quantitative read may influence clinician read, plan, and confidence.

We will record the HRME procedure (including "man" and "machine" reads), standard endoscopy, and biopsy time. 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, we will biopsy all Lugol's abnormal areas normally collected during standard-of-care procedures, no extra biopsies for research will be collected; however, we consider HRME "non-neoplastic" sites as not tissue-biopsied for analysis purposes. We will submit all standard-of-care biopsies for consensus diagnosis by an expert GI pathologist. We will record all patient adverse events (bleeding, infection, perforation) that occur within 7 days after the procedure on a follow-up call. All biopsies collected of Lugol's unstained areas are part of standard of care, not for research. During the study procedure, we are only taking pictures. We will use the pathology results from these biopsies to compare to our HRME results and clinician reads.

It is very possible that the HRME will increase the accuracy of standard Lugol's screening and may reduce unnecessary biopsies by improving specificity. With novices, the HRME + computer algorithms may be very likely to improve accuracy and performance, based on our preliminary data from China and Brazil (H-34973 and H-44015, respectively).

We will invite all patients participating to participate in a brief (20 min) interviewer-administered survey before undergoing endoscopy to assess attitudes and barriers to the device and a follow-up interview (7 days post-procedure) to determine experiences and acceptability. Trained study staff will conduct informed consent and the initial interview in a private clinic using a brief Portuguese-language survey. The follow-up interview will occur by phone, after a routine follow-up call by clinical staff.

Expert clinicians are any clinician with prior microendoscopy experience (>25 procedures), and novices are clinicians without experience. We will collect this information in the CRF and compare outcomes between the 2 groups of clinicians. The clinician will give a 'read' (Neoplastic/Non-neoplastic) and 'plan' (Biopsy, No Biopsy, Ablate, ESD, or EMR) at several time points: (1) Based solely on Lugol's (SOC), (2) Using HRME with no software (Qualitative Read), and (3) After software overlay (Quantitative Read). The HRME output is a numerical score (quantitative). Based on this score, clinicians may change their plan for the lesion. For ex: if they read the image without the overlay and aren't sure if they should biopsy, a high (neoplastic) score may increase confidence in their decision to biopsy, or a low (non-neoplastic) score may increase confidence to not biopsy the area.

HRME procedure participants will be contacted for follow-up 7 days after the procedure. This phone call will include questions on how they feel and if they have complications after the EGD procedure. This will be part of the participant's Case Report Form.

Stakeholder Survey: Our grant proposal aims to determine the acceptability, barriers, and feasibility of using AI-mHRME for ESCN management. It also aims to determine contextual factors influencing its adoption in diverse referral hospital settings in the USA and Brazil. This will be done through stakeholder interviews and an evaluation.

Methods:

Health Sector Stakeholder Advisory Board (HS-SAB): We will form HS-SABs in the US and Brazil of 8-10 members. The HS-SAB members will include academic partners (e.g., academic gastroenterologists, primary care providers for referring institutions, clinicians performing esophageal cancer screening and treatment, hospital administrators, and patient and

caregiver representatives. We will collect feedback from the HS-SAB through focus group discussions (FGDs) at 6 time points during the study. The objectives of specific FGDs will reflect the research stage: clinical trial planning (including recruitment refinement and retention plans), data collection, interpretation of results, and dissemination of findings.

The FGDs will use a meeting guide (attached). The HS-SAB will have 4 meetings in the first year, the first 3 are "live" (45 minutes each), and the 4th meeting is an email review of the data collection tool. A 5th meeting will be after conducting the Semi-Structured Interviews. In the following years, they will meet at least once per year. The moderators will be Dr. Jane Montealegre (English, US) and TBD (Portuguese, Brazil); the notetakers will be Madeleine Allman and/or US/Brazil CRCs in their respective languages. Participants do not need to be bilingual. We will use BCM Zoom to conduct the FGDs. Sessions will be video recorded, stored on a BCM secure drive, transcribed by trained research assistants, and deleted after study completion. In the US, HS-SAB members will be offered a $250 gift card at one time for participating in the FGD sessions. In Brazil, there will be no compensation for the HS-SAB members as it is unlawful to do so in their country.

To acquaint HS-SAB members with AI-mHRME, we will provide a graphical video of the AI-mHRME device and how it is used during the endoscopy procedure. This illustrative, 5-minute video will be developed for an 8th-grade level in English and Portuguese using cartoon graphics to demonstrate the procedure and use of AI-mHRME compared to standard endoscopy screening. This video will facilitate the understanding of AI-mHRME for stakeholders (including patients and caregivers) who speak different languages and have different levels of health literacy.

In FGD sessions 4 and 5, we will review a Semi-structured Interview (SSI) Guide. We will develop SSI using the Consolidated Framework for Implementation Research (CFIR) interview guide. It is a widely used framework in global implementation science due to its applicability, generic nature, and support platform availability. The interview guides will focus on understanding barriers and facilitators related to each construct. We will use cognitive interviewing techniques to assess key intervention characteristics informed by the Implementation Outcomes Framework (IOF), Diffusion of Innovation Theory (DIT), and Unified Theory of Acceptance and Use of Technology (UTAUT). As part of these FGD sessions, we will seek feedback from the HS-SAB to adapt and refine it for assessing barriers and facilitators for AI-mHRME.

Semi-structured interviews (SSIs): US and Brazil HS-SAB members will identify and recruit health system stakeholders (n=40, key informants, KI) at referral hospitals and institutions, including specialist physicians (i.e., gastroenterologists, n=10), primary care providers (n=10), hospital administrators (n=10), and patients/caregivers (n=10).

Endoscopist survey (ES): Findings from the SSIs will be used to refine a survey instrument we developed to evaluate the adoption and implementation of HRME for Barrett's esophagus screening (H-48152, PI: Tan). Items in the survey include validated acceptability, feasibility, and appropriateness measures, which are our key constructs in implementing interventions. The survey assesses constructs underlying the diffusion of innovation (i.e., perceived relative advantage, compatibility, complexity, observability, trialability), technology acceptance (e.g., performance and effort expectancy), and usability (e.g., intuitiveness, efficiency, satisfaction). Endoscopists participating in the trial at each site (total n=40) will be invited to complete a 15-minute self-administered survey. We will survey both AI-mHRME users and non-users. For non-users, we will use the digital procedure simulation we developed.

Research coordinators will conduct SSIs for approximately 1 hour in English or Portuguese. SSIs with patients/caregivers can take place in the pre-op area for endoscopy procedures while they wait for their procedure to start. For all other KI recruited, SSIs can be scheduled and done virtually. We will record, transcribe, and translate the audio from the SSIs. Transcribed SSI data will be saved in a survey in REDCap. All documents used will be translated from English to Portuguese using an official Brazilian translator that the ICESP has used in the past.

No study surveys will be conducted until they are developed and submitted to the IRB via an amendment.

Currently, IRB approvals are pending from ICESP and Barretos in Brazil. We will not initiate research activities in Brazil until we have obtained and submitted for BCM IRB review the adequate approvals and related documents as an amendment.

Section G: Sample Size/Data Analysis

G1. Sample Size

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

Local: 95 Worldwide: 195

Please indicate why you chose the sample size proposed:

The sample size above includes all participants across the two objectives. For local, 50 HRME procedure subjects, 5 HS-SAB members, 20 key informants, 20 endoscopists. All sample sizes worldwide are the same, except for 150 HRME procedure subjects.

Objective 1 - Endoscopy + HRME procedure: We will obtain biopsies and pathology results from all subjects to assess each modality's performance. We will compare their interpretations to the histopathologic gold standard read by 2 expert gastrointestinal pathologists (concordant read). We will estimate each modality's sensitivity, specificity, and positive and

negative predictive values on a per-patient and per-biopsy basis with 95% confidence intervals. We will generate repeated data in this study as each participant will receive an exam using each modality sequentially. We will compare paired novice endoscopists' clinical interpretation and AI-mHRME assessment using McNemar's tests. We will use descriptive methods to summarize clinicians' confidence levels, clinical impact, diagnostic yield, and biopsy efficiency. We will present changes in confidence level and decision plan at pre- and post-software in cross tables and compare using McNemar's tests.

Based on prior experiences and data from the China-US randomized control trial, each modality's sensitivity was consistently at 90%. However, the HRME specificity in novices' hands was considerably lower (17% in a surveillance population, 83% in a screening population, and 57% combined on a per-biopsy basis), resulting in a low diagnostic yield (unnecessary benign biopsies) and increased cost. In our Brazilian pilot trial, the deep learning (Y-NET) algorithm performed with an AUC of 0.864 and a specificity of 83%. We hypothesize that AI-mHRME will increase the specificity and clinical impact, particularly for novice endoscopists.

Power analysis is used to calculate sample size for the primary outcome of specificity. The expected neoplasia prevalence is 8% in the screening and 50% in the surveillance populations; among 200 subjects (140 in screening and 60 in surveillance), we expect 185 enrolled subjects with no evidence of biopsy-confirmed neoplasia. Assuming 80% of endoscopists are novices, 140 subjects without neoplasia will be examined by novice endoscopists. The 140 pairs of AI-mHRME and novice interpretations will provide 90% power to detect a 20% difference in specificity (80% for AI-mHRME vs 60% for novices) by McNemar's test of equality with 0.5 discordant pairs and a 5% two-sided significance level.

In the Brazil pilot, endoscopists chose to "biopsy or treat" 70% of subjects with benign biopsies. Assuming a plan change rate of 30% after using AI-mHRME software algorithm interpretation, we expect the proportion of subjects without neoplasia recommended for biopsy/treatment to drop to 55%. The study will have 95% power to detect the difference of 15% in pre- and post-plans (70% vs. 55%) at a 5% two-sided significance level.

Objective 2 HS-SABs: A sample size of 6-10 members for the HS-SAB (4-5 Brazil, 4-5 US) is customary for research advisory boards and balances the need for diverse perspectives with the logistical constraints of meeting as a group, with sufficient time to allow all members to have an active voice.

The sample size for SSIs and endoscopist surveys are based on the anticipated number of subjects needed to reach saturation in the qualitative data collected for each population. Saturation in qualitative research is when, through interviewing or observation, no new themes emerge in the data. Interviewing 40 key informants (20 Brazil, 20 US) will be sufficient to achieve thematic saturation. We anticipate 90% of endoscopists will participate in the survey based on our prior Brazil pilot. This will allow us to estimate the expected prevalence of moderate to high AI-mHRME acceptability (we anticipate 85%) with an 11.7% margin of error and 95% confidence.

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?

Endoscopy + HRME: Based on our experiences and prior data from the China-US randomized controlled trial, the sensitivity of each modality was consistently at 90%. However, the specificity of HRME in the hands of novices was considerably lower (17% in a surveillance population, 83% in a screening population, and 57% combined on a per-biopsy basis), resulting in a low diagnostic yield (unnecessary benign biopsies) and increased cost. In our Brazilian pilot trial, the deep learning (Y-NET) algorithm performed with an AUC of 0.864 and a specificity of 83%. We hypothesize that AI-mHRME will increase the specificity and clinical impact, particularly for novice endoscopists.

Biopsy saving and diagnostic yield will be calculated and presented with proportions and 95% confidence intervals.

Assuming an 80% response rate, we anticipate 40 patients will complete the survey. We will describe the prevalence of specific barriers to endoscopy with confidence intervals around the point estimate. Descriptive statistics will be used to identify the experiences of participants undergoing HRME endoscopy. Associations with $p<0.05$ will be considered statistically significant.

HS-SAB, Semi-structured Interviews, Endoscopist Surveys: Qualitative analyses will follow a semi-structured analytical approach. They will be led by Dr. Montealegre, who has qualitative methods and CFIR expertise to assess barriers and facilitators to adopting and implementing novel technologies. Interview transcripts will be coded in Atlas.ti software by two independent coders who will compare codes, assess inter-coding reliability, and reach a consensus on discrepancies. Coding will be based on CFIR, DIT, and UTAUT constructs. Thematic analyses will be conducted to collapse consensus codes into broader themes. In the quantitative analyses, scores and responses to individual survey items related to UTAUT and DIT constructs will be aggregated and reported as averages.

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:

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. The participant must 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 the participant may have difficulty breathing and may have blood pressure drop. If this happens, procedures are in place to treat participants in an endoscopy room. Specimen Imaging Probe There are no known risks from using the imaging probe.

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

Aspiration: Inhaling fluid into the lungs during endoscopy might cause lung inflammation. Safeguards to prevent this from happening while the participant is under anesthesia will be in place during and after the procedure, and the participant's breathing and other vital signs will be carefully monitored. If participants experience symptoms other than those 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 asked to give consent on the day of their procedure. Subjects will be taken to a private area to discuss the study information. All sensitive information will be requested from the subjects, and only what is required to perform a standard endoscopy. Subjects will be given an ID number for all forms, images, and communications. All data will be removed of identifiers and coded. Source documents of all PHI will be redacted 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 the end of the study. The only extra privacy intrusion will be an additional phone call within 7 days of the procedure to ensure that the subject has not suffered any adverse events. Only the study coordinator and/or the PI will contact the subject during the follow-up. Information about 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.

HS-SAB, Semi-structured Interviews, and endoscopist surveys: The potential risks/discomforts of participating in the HS-SAB interviews or surveys are minimal. There may be minimal psychological discomfort if participants feel uncomfortable disclosing their opinions and thoughts on implementing and using AI and HRME devices to project staff. However, we will reinforce that these data are only meant to guide us in how we may proceed with expanding HRME device implementation and acceptance, that their answers will be kept anonymous and confidential, and that their completion of the survey will not affect their employment at ICESP or BCC if they work there and were recruited from those sites.

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 â€“ 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 Informed consent document will be distributed to Rice University, The University of Texas MD Anderson Cancer Center in Houston, Texas, and ICESP and BCC in Brazil. These documents will be translated into Portuguese and submitted to the collaborating site's IRB. Once approval is granted, the approved documents will be submitted to the Coordinating Center (BCM) and forwarded to the IRB for review. All investigators know 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 must be conducted before enrollment can begin at collaborating sites. The PI will travel to the collaborating sites to train the investigators on the proper use of the device and to ensure the proper conduct of the study.

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's medical record number to the protocol-specific unique code will be kept in a locked cabinet in the office of the PI. The patients' names will not be released to outside organizations or 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 associated with the imaging probe (the device has its computer and hard drive) and password protected. The server is an internal password-protected, limited access system in which these image scans are uploaded 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 Mount Sinai School of Medicine server, so it does not require encrypting. The device and laptop are also stored in a locked drawer in the PI's office.

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 BCM and entered into a secure, password-protected database. Data will be stored securely at the Coordinating Center. The study statistician will perform data and safety monitoring. De-identified data (microscopic images) will be analyzed at Rice University by the bioengineers who developed the devices and are collaborating on the project. The device used in this study (the HRME) is manufactured in Dr. Kortum's research at Rice University. The images collected from the clinical trial are used to build software that analyzes data automatically. Data will be transmitted as de-identified images only.

All histopathologic slides and optical images will be labeled with the subject's study ID number and presented to the pathologist, who will read them blindly. The subjects' clinical research forms with the associated optical biopsy read(s) are similarly labeled with the subject's study ID number. 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 stored in a locked cabinet in the PI's office.

For the HS-SAB, each board member will be assigned a unique ID and will use that ID throughout the focus group discussions. Only the study staff will keep the members' names and their assigned unique IDs. For the Semi-structured Interviews and endoscopist surveys, all participants will be given a unique ID. All other data will be kept de-identified, stored, and entered into a secure, password-protected database.

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.

Instituto do Câncer do Estado de São Paulo, Sao Paulo, Brazil Barretos Cancer Center Hospital de Amor, Sao Paulo, Brazil

Section I: Potential Benefits

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

Objective 1: Subjects may not directly benefit from participating in this research. However, the HRME may detect an area of neoplasia not detected by standard-of-care endoscopy and Lugol's chromoendoscopy.

Objective 2: HS-SABs: HS-SAB members may benefit from contributing to the study's conduct and interpretation of results. The US members will receive compensation for their time. In Brazil, the members will not receive compensation as it is not allowed by the country to do so.

Semi-structured interviewees: Interviewees will not directly benefit from participating in the interviews. Interviewees' insights will directly impact the assessment of barriers and facilitators of implementing the HRME in an endoscopy unit in Brazil and the US, as well as how to mitigate any potential barriers. Research subjects may gain some sense of satisfaction from contributing the research

Endoscopist surveys: Physicians and trainees who will participate in the endoscopist surveys do not directly benefit from participating. Research subjects may gain some sense of satisfaction from contributing the research

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

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

Objective 1: The potential societal benefit will be to help increase the specificity of Lugol's chromoendoscopy when combined with HRME, allowing for earlier detection of esophageal cancer or pre-cancerous lesions and quicker time to treatment. This may potentially increase survival rates for esophageal cancer as well. Societal benefits will be lower endoscopy and screening costs, time saved, and quicker turnaround for treatment.

Objective 2: HS-SABs: The members' insights from their roles in the medical system involving endoscopies and

esophageal cancer screening will ultimately benefit those diagnosed and treated earlier when cancer is detected, as they will influence the questions that will be asked to assess the barriers and facilitators of implementing HRME in endoscopies.

Semi-structured interviewees: The results of the interviews will be used to assess barriers and facilitators of implementing the HRME in an endoscopy unit in Brazil and the US and how to mitigate any potential barriers. This may serve as examples of how to proceed with implementing HRME in other countries besides the US and Brazil.

Endoscopist surveys: The surveys will provide insight on how to approach physicians in the US and Brazil to help them understand HRME and how it can help with esophageal cancer screening. This will help physicians become aware of their knowledge about endoscopy and esophageal cancer screening and how they provide screening recommendations to patients and their families.

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

Objective 1: The incremental risks of HRME added to the SOC white light with Lugol's iodine are minimal. We have had NO serious adverse events in >1000 subjects imaged with the HRME. No risks related to either the drug (proflavine) or the device have been noted. White light endoscopy is the standard of care, and all subjects will be undergoing this SOC procedure so that ALL patients will be receiving (at minimum) the standard of care.

Objective 2: HS-SABs: Participating in the HS-SABs does not provide direct benefits, and there are no risks involved. Participants will know each other's names, and research staff will provide participants' names and contact information. Their thoughts, opinions, and experiences will be used only to guide the questions in the semi-structured interviews and what they believe are important topics to ask for implementing the HRME device. The lead investigator is very experienced in leading focus group discussions and using standardized methods for collecting data from FGDs. The benefits outweigh the risks of participating in being an HS-SAB member.

Semi-structured interviews: Participating in semi-structured interviews does not provide direct benefits, and the risks are minimal. Data collected from the interviews is completely de-identified and there will be no identifying questions in the interview, and they will be conducted in a private room. Loss of confidentiality is minimal if non-existent. The benefits outweigh the risks of participating in the interviews.

Endoscopist surveys: For the provider surveys, considering the opportunity to improve understanding of endoscopy and esophageal screening and the minimal risks associated with participation, we believe the benefits outweigh the risks.

Section J: Consent Procedures

J1. Waiver of Consent

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

No

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.

HS-SAB: Participants will be recruited via email with a research letter, waiving the written consent documentation requirement. Please see the Research Letter in the attachments. No significant risks are associated with HS-SAB participation, so we request a waiver of this requirement.

Semi-structured interviews: Participants will be recruited via email with a research letter, which waives the requirement of written documentation of consent. Please see the Research Letter in the attachments. No significant risks are associated with semi-structured interviews, so we request a waiver of this requirement.

Endoscopist survey: Participants will be recruited via email with a research letter waiving the written consent documentation requirement. Please see the Research Letter in the attachments. No significant risks are associated with surveys, so we request a waiver of this requirement.

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.

Endoscopy + HRME procedure: At all 4 study sites (BSLMC, BTGH, ICESP, BCC), patients will be consented in a private exam or pre-operative room by the research staff or site PI and have the opportunity to discuss the examination procedure in detail with the research staff and/or site PI. Consent procedures will be done in English (BSLMC, BTGH). Spanish (BTGH), or in Portuguese (ICESP, BCC). At BSLMC and BTGH, if the eligible patient does not speak English, or the research staff consenting does not speak Spanish, they will use the on site interpretation services to go through the consent process with the patient. If a research staff speaks Spanish, they will go through the necessary HHS approvals to use Spanish at an HHS facility to conduct research activities in the hospital.

In our experience, consent and retention are rarely issues because the endoscopy is the standard of care. In other words, patients are already undergoing sedation and scheduled for endoscopic evaluation, and the 'research protocol' (HRME) is only an additional 4-6 minutes per procedure. Moreover, follow-up calls after an endoscopy are routinely performed; thus, there is a minimal deviation from standard endoscopic protocols by adding our feasibility study. Thus, we do not anticipate any issues with retention and, again, have not had significant retention issues in prior studies of similar devices.

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?

A full-length informed consent document

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:

No

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:
Yes

Identifiable biospecimens
No

Other:
No

At what institution will the physical research data be kept?
Baylor College of Medicine Instituto do Câncer do Estado de São Paulo, Sao Paulo, Brazil Barretos Cancer Center Hospital de Amor, Sao Paulo, Brazil

How will such physical research data be secured?
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's medical record number to the protocol-specific unique code will be kept in a locked cabinet in the office of the PI at ICESP and BCC. The patients' names will not be released to outside organizations or 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. 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 BCM and entered into a secure, password-protected database. All histopathologic slides and optical images will be labeled with the subject's study ID number and 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 subject's study ID number. 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 stored in a locked cabinet in the PI's office.

At what institution will the electronic research data be kept?
BCM, Rice University

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:
Yes, (describe below):
The research data will be stored with the patient ID number and the sequential image number on a laptop associated with the imaging probe (the device has its own computer and hard drive) and password protected. The server is an internal password-protected, limited access system in which these image scans are uploaded 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 BCM, so it does not require encrypting. The device and laptop are also stored in a locked drawer in the PI's office. Data will be stored securely at the Coordinating Center. The study statistician will perform data and safety monitoring. De-identified data (microscopic images) will be analyzed at Rice University, by the bioengineers who developed the devices and are collaborating on the project. The device used in this study (the HRME) is manufactured in Dr. Kortum's research at Rice University. The images collected from the feasibility study are used to build software to automatically analyze data. Data will be transmitted as de-identified images only.

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 the subject's insurance will be responsible for research-related costs. Research-related costs are specifically related to using the Proflavine and the imaging probe, which the study will cover.

Since endoscopic biopsies are billed per bottle, we will NOT submit extra bottles per procedure. If the CRC needs to indicate an imaged specimen, this specimen will be inked and placed in a standard-of-care bottle for routine processing as we have done in the past; hence, NO additional bottles will be obtained beyond what is submitted for the standard-of-care.

The screening endoscopy is the standard of care (only patients previously scheduled for endoscopy are recruited). Thus, the costs of the clinically indicated upper endoscopy are not research and are covered by the subject or their insurance.

In the event of an adverse event explicitly caused by the use of the Proflavine or study device (HRME), the subject will not be responsible for care costs. If any standard-of-care injury is sustained (by the standard-of-care endoscopy procedures), the costs of care will not be covered by the study.

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:

450

Distribution Plan:

Subjects in the US will be paid to participate in the HS-SAB: in the first year after the first 4 meetings, they will receive $250, and then $50 for each subsequent study year (years 2, 3, 4, and 5).

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?

N/A

Section N: Sample Collection

SAMPLE: Tissue

What is the purpose of the sample collection?

Biopsies will be collected for clinical diagnosis and sent to pathology as part of the standard of care upper endoscopy. No tissue or samples are collected for research. The slides/tissue blocks used for a clinical diagnosis will be available for re-review by the pathologists to confirm a final diagnosis used in the study analysis.

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 removed of identifiers and coded and sent to the pathologists on protocol.

Will sample material be sold or transferred to any third parties? Will the information be de-identified?
Only coded 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?
Samples will not be banked for the study.

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?

No

Section P: Device Studies

Does this research study involve the use of ANY device?

Yes

Device 1: Artificial intelligence-based mobile high resolution microendoscope (AI-mHRME)

Section Q: Consent Form(s)

AI-mHRME

Section R: Advertisements

None