Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: H-44015
Status: Approved
Initial Submit Date: 10/2/2018
Approval Period: 8/10/2021 - 8/3/2022

Section Aa: Title & PI

A1. Main Title

ACCEPTABILITY AND PERFORMANCE OF A MOBILE, AUTOMATED, AUGMENTED REALITY OPTICAL BIOPSY TECHNOLOGY FOR GASTROINTESTINAL CANCER SCREENING: A CLINICAL STUDY IN BRAZIL

A2. Principal Investigator

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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

A4. Co-Investigators

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A5. Funding Source:

Organization: NATIONAL INSTITUTES OF HEALTH (NIH)

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

BCM: Baylor College of Medicine
Rice University

A6b. Research conducted outside of the United States:

Country: BRAZIL
Facility/Institution: University of Sao Paulo
Contact/Investigator: Dr. Fauze Maluf-Fihlo
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:
University of Sao Paulo (USP)'s approval letter is attached in Section S.

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 GI cancers (esophageal, stomach) account for 14% of all global cancer mortality with five-year survival rates of 15-20% and a markedly greater burden of disease in the developing world due to delayed diagnosis. While endoscopy has been shown to dramatically improve survival in high-income countries that have implemented endoscopic screening nationally (Korea, Japan, etc.), Brazil and most of Latin America have severe capacity limitations (equipment, infrastructure, clinicians) precluding success. Indeed, survival rates drop dramatically once these tumors breach the mucosal layer, reinforcing the importance of early detection. Moreover, 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. Specifically, for esophageal squamous cell neoplasia (ESCN), this involves Lugol's chromoendoscopy with iodine staining and targeted biopsy of unstained (abnormal) areas. Screening is performed in high risk patients (head & neck cancer, high-prevalence regions). While Lugol's is the most sensitive method for ESCN detection, specificity is poor: areas of inflammation appear unstained and indistinguishable from cancer, leading to high false-positive rates. Other novel widefield modalities (autofluorescence , narrow-band imaging) have been proposed as red flag techniques but 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 increase in cost and risk. Confocal microendoscopy, a high-resolution imaging technique which evaluates the mucosa at a 1 μm resolution and 1100X magnification, has revolutionized the endoscopic surveillance of cancer, allowing endoscopists to see the mucosa at a subcellular level. When confocal is coupled with widefield Lugol's imaging, accuracy rates rise to 95% with a dramatic improvement in specificity. Nonetheless, confocal platforms are expensive (>$175,000), bulky, and available in only a handful of tertiary centers worldwide. Lastly, interpretation of the histopathology-like images, requires extensive training and experience a significant limitation in low-resource environments with less experienced clinicians. Given the limitation of existing approaches, the high cost and expertise of confocal imaging, and the dismal prognosis of esophageal cancer when it has breached the 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).

Section D: Purpose and Objectives

We have a current trial in China and the US which provides significant support for the safety, cost-effectiveness, accuracy and efficiency of a high resolution microendoscope (HRME)-guided approach in the hands of experienced clinicians. To improve functionality, portability and broader use of this device by non-experts, we recently developed a prototype marHRME platform with an automated, augmented reality (AR)-interpretation that provides an overlaid endoscopic + micro-endoscopic view, facilitating diagnosis and biopsy targeting. Our hypothesis is that this mobile device with automated, AR optical biopsy diagnoses can efficiently and accurately facilitate endoscopic cancer detection in LMICs with less experienced providers and is acceptable to providers and patients. Objective 1: Our first objective is to evaluate the marHRME technology in terms of performance, efficiency, and impact. In a single-arm, feasibility study (n=50) of high-risk subjects undergoing Lugol's chromoendoscopy (LCE) followed by marHRME for ESCN screening, we will evaluate the diagnostic performance and efficiency of this automated optical biopsy device. Our main hypothesis is that the marHRME will (1) increase the accuracy of Lugol's endoscopy (LCE), other exploratory hypotheses are (2) increase the accuracy of marHRME among novices and be non-inferior to experts, (3) increase user confidence among experts and novices and, subsequently, (4) increase the efficiency and impact of LCE by reducing biopsies and second procedures. For performance for marHRME vs. Standard of Care, we will compare the accuracy of the marHRME + LCE vs. LCE alone to the gold-standard histopathology (expert GI pathologist). For performance of the Machine vs. Man, we will compare accuracy of the marHRME software read to novice and expert clinicians' subjective read to gold-standard histopathology. 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 marHRME. Clinical impact will be determined by whether the marHRME diagnosis alters the clinician's decision at the point-of-care to biopsy vs. not biopsy vs. treat the visualized site. For efficiency (biopsy saving and diagnostic yield), we will determine the number of patients who are spared any biopsy due to marHRME. We will compare the diagnostic yield of marHRME+LCE vs. LCE alone (diagnostic yield= neoplastic biopsies/total number of biopsies obtained in biopsied patients). Objective 2: Our secondary objective is to evaluate the acceptability of the technology among patients and providers. All patients participating in the study will be invited to participate in a brief (20 min) interviewer-administered survey prior to undergoing endoscopy to assess attitudes and barriers to marHRME (T1), and a follow-up interview (7 days post-procedure) to determine experiences and acceptability (T2). Informed consent and the initial interview will be conducted in a private clinic room by trained study staff from the Brazilian team using a brief Portuguese-language survey. The follow-up interview will occur by phone, after a routine follow-up call by clinical staff. The endoscopists and trainees participating in the feasibility study will be invited to participate in a series of questionnaires and in- depth interviews administered at different time points of the study to assess provider acceptance. Informed consent will be obtained prior to the first interview. Clinicians will answer a brief questionnaire to assess acceptance of marHRME prior to undergoing raining (T1), after training (T2), and after conducting 25 procedures (T3). At T3, endoscopists and trainees will participate in a 30- minute semi-structured interview to assess marHRME experience. The interviews will be audio recorded, professionally transcribed, and

translated (Portuguese to English) for coding and analysis.

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:
English, Portugese

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?
The endoscopists and trainees participating in the feasibility study will be invited to participate in a series of questionnaires and in-depth interviews administered at different time points of the study. These interviews and questionnaires will not inquire about personal health or other personal information. Rather, they will be asked to provide their opinion on the 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.

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:
c) Pilot

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.
This is a single-arm feasibility study and the clinical procedure will not be performed at Baylor. Baylor is coordinating center and will receive the data and monitor/coordinate the study. The actual feasibility study (n=50) will be conducted at the University of Sao Paolo, Brazil under the local PI, Dr. Fauze Maluf. Dr. Anandasabapathy (Baylor) is the coordinating PI for the overall grant though this pilot project will occur solely in Brazil.

Baylor will travel to USP to initiate the study and provide training on data collection, use and storage of the drug and device, and study procedures. Baylor will oversee the initiation of the feasibility study and the first 25 cases to ensure valid data collection. Baylor will communicate monthly (or more often as needed) with USP research team to answer questions and monitor data collection procedures. Baylor will travel yearly to monitor progress and at the end of the study close-out procedures.

Patients undergoing endoscopy for ESCN screening (n=50) at USP will be recruited by Dr. Maluf and his team for the study. All study subjects will receive White Light Imaging and Lugol's Chromoendoscopy (LCE) which is the current standard of care procedure. We will record any LCE abnormal (suspicious) areas and record the clinician's plan of action (Biopsy vs. No Biopsy vs. Treat). Following LCE, all subjects will receive Mobile, Augmented Reality High Resolution Microendoscope (marHRME) imaging with the study contrast agent (Proflavine) of any LCE-identified abnormal areas as well as LCE normal areas (1:4 ratio abnormal to normal). We will record the subjective clinician read and confidence level in their diagnosis (high, low), and their plan of action (Biopsy vs. No Biopsy vs. Treat). Then we will image the same abnormal and normal areas with the marHRME and record the software read, clinician confidence level, and plan of action. Finally, the imaged areas will be biopsied or resected and evaluated by a pathologist. All subjects will receive both standard of care and marHRME imaging.

Once data is collected at USP, data will be removed of identifiers and coded and will be transferred to BCM. BCM will be responsible for data entry, management, and analysis.

Inclusion Criteria:

Outpatients undergoing routine (standard of care) Lugol's chromoendoscopic screening for squamous cell neoplasia will be eligible for enrollment including patients with known history of head/neck squamous cell cancer.

Patients must be >18 years old and able to give informed consent.

For the provider surveys and interviews, all providers (clinicians, trainees) who are working on the project will be eligible to participate. There is no obligation to participate in the study and this will be explained via the research letter included in Section S.

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 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

For the provider surveys and interviews, all providers (clinicians, trainees) who are working on the project will be eligible to participate. There is no obligation to participate in the study and this will be explained via the research letter included in Section S. Providers will be excluded if they decline participation or otherwise opt out of the proposed research project.

F2. Procedure

Dr. Maluf will accrue subjects (n=50) already scheduled for endoscopic screening due to a high risk for ESCC (head and neck cancer history; heavy smoking and alcohol, other dietary or geographic risk factors). Lugol's chromoendoscopy (LCE) is the current standard of care for esophageal cancer screening.

To uphold this standard of care and recruit patients already scheduled for endoscopy, LCE will be performed on all patients, followed by marHRME of Lugol's voiding (unstained areas). Subjects will be sedated per standard protocol (IV sedation) and undergo white-light endoscopy with application of Lugol's iodine. In each subject, the location of each Lugol's 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 lesions ('non-neoplastic' vs. 'neoplastic') as well as his/her proposed plan: a. no biopsy, b. biopsy, c. endoscopic treatment.

Subsequently, marHRME will be performed of all Lugol's unstained (abnormal) sites prior to tissue biopsy. The endoscopist will activate the marHRME glasses and marHRME performed: (1) 1-10 ml proflavine hemisulfate (0.01%) will be sprayed on the esophageal mucosa, (2) the marHRME probe placed gently on the Lugol's abnormal areas, (3) the 'optical biopsy' image will be displayed on the AR glasses (endoscopic image will remain displayed on the standard monitor behind it). (Proflavine is used under an IND #102217).

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 software.

Once this qualitative read is recorded, the image analysis software will be turned on (foot pedal) and the software diagnosis provided in real-time with display on the AR glasses. The quantitative ("Machine") read will be recorded, the confidence level of the endoscopist obtained again, and the (revised) plan of action recorded (a numerical score). The software output (score) will be determined neoplastic (cancer) or non-neoplastic (normal) based on a predetermined

algorithm threshold. This quantitative read may influence clinician read, plan, and confidence.

The HRME procedure (including "man" and "machine" reads), 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); 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 an expert GI pathologist. All patient adverse events (bleeding, infection, perforation) that occur within 7 days after the procedure will be recorded on follow up call.

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.

However, since Lugol¿s is used as an initial screen (and is the gold standard for initial screening), only Lugol¿s abnormal areas will be biopsied so no extra biopsies will be obtained and no additional costs incurred.

All patients participating in the feasibility study will be invited to participate in a brief (20 min) interviewer-administered survey prior to undergoing endoscopy to assess attitudes and barriers to marHRME (T1), and a follow-up interview (7 days post-procedure) to determine experiences and acceptability (T2). Informed consent and the initial interview will be conducted in a private clinic room by trained study staff from the Brazilian team using a brief Portuguese-language survey. The follow-up interview will occur by phone, after a routine follow-up call by clinical staff.

The endoscopists and trainees participating in the feasibility study will be invited to participate in a series of questionnaires and in-depth interviews administered at different time points of the study. Informed consent will be obtained prior to the first interview. Clinicians will answer a brief questionnaire to assess acceptance of marHRME prior to undergoing study training (T1), after training (T2), and after conducting 25 procedures (T3). Providers will be trained on use of the marHRME and review standard endoscopy procedures. Training of providers will be done using a cell phone app, a VR simulation of esophageal endoscopy, followed by directed guidance during the first 5 procedures. At T3, endoscopists and trainees will participate in a 30- minute semi-structured interview to assess marHRME experience. The interviews will be audio recorded, professionally transcribed, and translated (Portuguese to English) for coding and analysis.

Expert clinicians will be defined as any clinician with prior microendoscopy experience (>25 procedures) and novices are clinicians without any prior 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/EMR) at several timepoints: 1- Based solely on Lugol¿s (SOC), 2- Using HRME with no software (Qualitative Read), and 3- After software overlay (Quantitative Read). The marHRME 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.

Section G: Sample Size/Data Analysis

G1. Sample Size

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

Local: 0 Worldwide: 50

Please indicate why you chose the sample size proposed:

We will collect an average of 2-3 biopsies/subject in screening patients. All patients will have biopsies and their pathological diagnosis will be used to measure the accuracy of LCE and marHRME (man and machine). As mentioned, LCE has a sensitivity of > 95% but a specificity of <65% due to a high-false positive rate (82%) resulting in a low diagnostic yield (unnecessary benign biopsies) and, subsequently, increased cost. Our hypothesis is that the addition of marHRME to LCE will increase the accuracy, efficiency of marHRME, and clinical impact, particularly for novice endoscopists while increasing confidence levels in novice and experts. Based on the preliminary data, the accuracy of marHRME vs LCE was 83% (CI: 76-89%) vs 47% (CI: 39-55%). A sample size of 50 subjects will provide 87% power to detect a 35 % improvement in accuracy (80% for marHRME vs 45% for LCE) with a 5% two-sided significance level and 0.7 discordant pairs using McNemar's test for the paired data.

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?

Data of accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each method will be summarized using proportions and 95% confidence intervals, and compared using McNemar's tests. Our primary study endpoint is accuracy. Other exploratory endpoints include: Clinician confidence and clinical impact (decision

plan change: biopsy vs. not biopsy vs. treat) that will be summarized and presented in a cross table of pre/post software read. These parameters between expert and novice endoscopists will also be summarized descriptively. Biopsy saving and diagnostic yield will be calculated and presented with proportions and their 95% confidence intervals. Assuming a 80% response rate, we anticipate that 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 experiences of participants undergoing marHRME endoscopy. Associations with $p<0.05$ will be considered statistically significant.

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. 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 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 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. The potential risks/discomforts of participating in the provider survey are very minimal. There may be minimal psychological discomfort if participants feel uncomfortable disclosing their knowledge of endoscopy or esophageal cancer screening to project staff. However, we will reinforce that these data are only meant to guide and improve our provider training program, that their answers will be kept anonymous and confidential, and that their completion of the survey will not affect their employment at USP.

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 protocol has been approved by the USP IRB. The official translation of the approved informed consent document and IRB approval letter have been attached in Section S. All investigators are aware of IRB requirements 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 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 data will be monitored by an external monitor, Kirsten Tuck, a trained program manager at University of Michigan to ensure data accuracy and any adverse event monitoring. Kirsten Tuck will have access to digital CRFs in Box, OnCore database, and travel with the team for study initiation and close out at USP.

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.

University of Sao Paulo, Brazil: All patients will be enrolled from the University of Sao Paulo under Co-PI Dr. Maluf-Fihlo.

Rice University: Rice University will provide the HRME device and be responsible for bioengineering aspects of the study.

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. However, there is a chance that the mar-HRME may detect an area of neoplasia that was not detected by standard of care endoscopy. For physicians and trainees undergoing surveys, there may be no benefit of participation. Providers will become aware of their knowledge about endoscopy and esophageal cancer screening and the way in which they provide screening recommendations to patients and their families.

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

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

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

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

We are requesting a Waiver for the Written Documentation of Informed Consent for the Provider Survey component of this protocol. The potential risks associated with the Provider Survey are very minimal. There may be minimal psychological discomfort if the participant feels uncomfortable, for any reason, participating in the provider surveys. However, this risk is expected to be quite minimal. Prior to participating in the survey, providers will receive a research introduction letter, which will explain the purpose of the project, informed consent (consent will be given by completing and returning the survey), confidentiality (participation will be kept confidential), and that employment status will not be affected by choosing or refusing to participate. The risk for loss of confidentiality is minimal. All information that is gathered from the evaluations will be presented as a summary and will not be attributed to an individual participant. Data will be stored and secured on Baylor College of Medicine's password-protected server and/or in a locked office at Baylor College of Medicine. Data will not be stored on laptops or portable devices.

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.

Patients will be consented in a private exam room by the CRC and have the opportunity to discuss the examination procedure in detail with the physician. All of this will be done in Portuguese. In our experience, consent and retention are rarely an issue because the endoscopy itself is standard-of-care. In other words, patients are already undergoing sedation, already scheduled for endoscopic evaluation and the ¿research protocol¿ (marHRME) is only an additional 4-6 minutes per procedure. Moreover, follow up calls after endoscopy are routinely performed and, thus, there is minimal deviation from standard endoscopic protocols by the addition of 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?

No

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, University of Sao Paulo

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 medical record number to the protocol specific unique code will be kept in a locked cabinet in the office of the PI at USP. 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. 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 then entered into a secure, password protected database. 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 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 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 BCM, so it does not require encrypting. Additionally, the device and laptop are stored in the PI's office in a locked drawer. 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 feasibility study are used to build software that will work to automatically analyze data. Data will be transmitted as deidentified 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 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 which will be covered by the study. The actual screening endoscopy is standard of care (only patients previously scheduled for endoscopy are recruited). Thus, the costs related to the clinically indicated upper endoscopy are not research and are covered by the subject or their insurance.

In the event of an adverse event caused specifically by the use of the Proflavine or study device (marHRME), the subject will not be responsible for costs of care. If any standard of care injury is sustained (by 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:

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 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?
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?
No

Section P: Device Studies

Does this research study involve the use of ANY device?

Yes

Device 1: HRME

Section Q. Consent Form(s)

None

Section R: Advertisements

None