Compare

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: H-44616
Status: Approved
Initial Submit Date: 11/13/2018
Approval Period: 9/2/2020 - 9/1/2021

Section Aa: Title & PI

A1. Main Title

THE EFFECTIVENESS OF HIGH RESOLUTION MICROENDOSCOPY (HRME) IN HIGH GRADE INTRAEPITHELIAL LESIONS (HSIL) DIAGNOSIS FOR PEOPLE LIVING WITH HIV

A2. Principal Investigator

Name:	SHARMILA ANANDASABAPATHY	Phone:	713 7988105
Id:	184677	Fax:	
Department:	MEDICINE: GASTROENTEROLOGY	Email:	anandasa@bcm.edu
Center:		Mail Stn:	BCM271

A3. Administrative Contact

Name:	ZOE WILHELM	Phone:	713 7987542
Id:	206077	Fax:	713 7980951
		Email:	zwilhelm@bcm.edu
		Mail Stn:	BCM285

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

Name:	MENGFEN WU	Phone:	713 7982168
Id:	149255	Fax:	713 7981642
Department:		Email:	mengfenw@bcm.edu
Center:	DUNCAN CANCER CENTER	Mail Stn:	BCM600
Name:	TAO WANG	Phone:	713 7985388
Id:	160517	Fax:	713 7982716
Department:		Email:	taow@bcm.edu
Center:	DUNCAN CANCER CENTER	Mail Stn:	BCM305
Name:	SUCHISMITA RAYCHAUDHURY	Phone:	713-794-8666

Id: 196062
Department: MEDICINE: INFECTIOUS DISEASES
Center:
Fax: 713-798-8948
Email: raychaud@bcm.tmc.edu
Mail Stn: BCM285

Name: ELENA PETROVA
Id: 201265
Department: MEDICINE: GASTROENTEROLOGY
Center:
Phone: 713-798-4351
Fax:
Email: epetrov@bcm.tmc.edu
Mail Stn: BCM271

Name: DEBORAH CITRON
Id: 670988
Department: PATHOLOGY
Center:
Phone: 713-793-3212
Fax: 713-793-3214
Email: dcitron@bcm.tmc.edu
Mail Stn: BCM315

Name: REBECCA RICHARDS-KORTUM
Id: Non-Baylor
Institution: Rice University
Address: 6100 Main Street, MS 142
Phone: 713-348-3823
Fax:
Email: rkortum@rice.edu

Name: MAXIMILIAN GAISA
Id: Non-Baylor
Institution: Icahn School of Medicine at Mount Sinai
Address: One Gustave L. Levy Place
Phone: 212-241-3150
Fax:
Email: michael.gaisa@mssm.edu

Name: YUXIN LIU
Id: Non-Baylor
Institution: Icahn School of Medicine at Mount Sinai
Address: One Gustave L. Levy Place
Phone: 212-241-5283
Fax:
Email: yuxin.liu@mountsinai.org

Name: KEITH SIGEL
Id: Non-Baylor
Institution: Icahn School of Medicine at Mount Sinai
Address: One Gustave L. Levy Place
Phone: 212-824-7558
Fax:
Email: keith.sigel@mssm.edu

Name: TERESA DARRAGH
Id: Non-Baylor
Institution: University of California San Francisco
Address: 3333 California Street
Phone: 415-353-7861
Fax:
Email: Teresa.Darragh@ucsf.edu

Name: ASHISH DESHMUKH
Id: Non-Baylor
Institution: University of Texas School of Public Health
Address: E-329, 1200 Pressler Street, Houston, TX
Phone: 713-500-9180
Fax:
Email: ashish.a.deshmukh@uth.tmc.edu

Name: JOHN WINTERS
Id: Non-Baylor
Institution: Icahn School of Medicine at Mount Sinai
Address: One Gustave L. Levy Place
Phone:
Fax:
Email: john.winters@mssm.edu

Name: IVY COHEN
Id: Non-Baylor
Institution: Icahn School of Medicine at Mount Sinai
Address: One Gustave L. Levy Place
Phone:
Fax:
Email:

Name: COURTNEY CHAN
Id: Non-Baylor
Institution: Icahn School of Medicine at Mount Sinai
Address:
Phone:
Fax:
Email: courtney.chan@mountsinai.org

Name: RICHARD SILVERA
Id: Non-Baylor
Institution: Icahn School of Medicine at Mount Sinai
Address:
Phone:
Fax:
Email:

Name:	TINAYE MUTETWA	Phone:
Id:	Non-Baylor	Fax:
Institution:	Icahn School of Medicine at Mount Sinai	Email:
Address:		

Name:	ELIZABETH CHIAO	Phone:
Id:	Non-Baylor	Fax:
Institution:	MD Anderson Cancer Center	Email:
Address:		

A5. Funding Source:

Organization: NATIONAL INSTITUTES OF HEALTH (NIH)

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

HCHD: Thomas Street Clinic
Mount Sinai School of Medicine - New York

A6b. Research conducted outside of the United States:

Country:
Facility/Institution:
Contact/Investigator:
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. ClinicalTrails.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

Squamous cell cancer of the anus (SCCA) is one of the most common cancers among aging HIV-infected individuals in the United States. HIV-infected persons are at 40-80-times higher risk for SCCA than the general population, and recent cohort studies report that the incidence of SCCA among HIV-infected men is between 49-144/100,000 person-years. As the HIV-infected population ages, the number of HIV-infected individuals at risk of developing SCCA is expected to increase, reinforcing the need for accurate, accessible, and cost-effective screening technologies. The alarming increase in anal precancerous and cancerous lesions among HIV-infected individuals, has led to an increasing emphasis on anal cancer prevention. The 2015 New York State HIV Primary Care Guidelines recommend annual anal cytology screening. However, high resolution anoscopy (HRA) guided histologic diagnosis of anal high-grade intraepithelial lesions (HSIL) is resource intensive and has several drawbacks, including: extensive clinician expertise/training; pathology cost; separate patient visits for diagnosis and treatment; and patient discomfort associated with biopsies which are often negative or low grade. These drawbacks, in part, have led to limited adoption of anal cancer screening, only 11% of HIV-infected men who have sex with men (MSM) reported receiving screening in the preceding 6-12 months. Identifying novel, low cost, biopsy-free approaches which offer an accurate, real-time ¿optical biopsy¿ diagnosis could transform the current standard of practice by decreasing the numbers of procedures, reducing loss to follow up, and facilitating a ¿see and treat¿ approach. Optical imaging is a new modality which is able to obtain real-time, high resolution imaging of epithelial tissue. Ideally, such imaging can be used to observe changes in cells that indicate neoplastic transformation. Such indicators may be in the form of changes in the size and internal structure of the nucleus, the disorganization of cells, pleomorphism, and other cellular changes that require resolution of a few microns or better. These changes can be detected through refractive index mismatch in reflectance microscopy (in the case of nuclear changes) or by fluorescence microscopy (requiring the binding of a fluorescently-labeled targeted contrast agent or observation of native tissue autofluorescence). Because these systems are inexpensive and portable, they have the potential to be used in vivo (through a conventional endoscope), to enhance endoscopic screening and surveillance and to define lesions for therapy. Early identification of such lesions will not only improve patient survival but also avoid invasive procedures of treatment, and making treatment more site specific. A portable, battery-operated, high-resolution microendoscope (mHRME) has been developed by the engineering group at Rice. mHRME provides subcellular images of the anal epithelium, delineating the cellular and morphologic changes associated with neoplasia.

Our central hypothesis is that this 'optical' approach will increase the efficiency, clinical impact, and cost-effectiveness of the current standard of HRA-guided biopsy. In a recent pilot trial, the mHRME demonstrated a high sensitivity and specificity of anal HSIL diagnosis (94% and 92% respectively) compared to anal biopsy. Based on our significant preliminary data, we now propose to optimize and validate 3D imaging and HRME with a software interface that provides real- time image interpretation assistance, thus facilitating usage by less experienced clinicians in community-based or low-resource settings. To validate this, we will conduct a study to determine the efficiency and diagnostic characteristics of an mHRME 'optical biopsy' approach versus the current standard of HRA-based tissue biopsy. In addition, we will construct, refine and analyze a disease model of HRA-based screening with mHRME to determine the cost-effectiveness of incorporating HRME into HRA-based HSIL diagnosis. Successful results will allow for improved efficacy and resource utilization for cancer screening in HIV-infected individuals for anal cancer and other epithelial cancers including the cervix, oral cavity, bladder, and GI tract.

Section D: Purpose and Objectives

Mobile High-Resolution MicroEndoscopy (mHRME) provides subcellular resolution of epithelial images, (up to transverse resolution of 4 microns) which delineates cellular and morphologic features (nuclear size, and pleomorphism) of epithelial neoplasia. Using this technology assisted by visual 3D mapping of the anal canal during anoscopy, clinicians will be able to localize all potential HSIL lesions and obtain ¿optical biopsies¿ of each documented lesion. Thus, this novel technology will allow for comprehensive documentation and accurate biopsy-free diagnoses of anal HSIL, thereby decreasing patient discomfort and procedure cost as well as potentially allowing more targeted biopsies/treatment and increased accuracy. The mHRME has already been shown to have high sensitivity and specificity with histologic diagnoses in other pre-cancer screening studies, including cervical and esophageal squamous neoplasia. Furthermore, in preliminary data, HRME was shown to have a sensitivity of 93% and a specificity of 87% for anal HSIL detection. We propose to: 1) optimize the diagnostic performance of mHRME with 3D image maps for anal HSIL detection, followed

by determining: 2) the accuracy and 3) cost-effectiveness of anal mHRME compared to the gold standard of HRA-guided biopsy. 1) To compare the diagnostic performance and efficiency of the optimized mHRME during HRA to standard of care HRA-guided anal biopsies. Using the optimized mHRME during HRA, we will evaluate the diagnostic performance (sensitivity, specificity, positive predictive value, negative predictive value) of mHRME optical diagnosis compared to paired anal tissue histology.

2a) To compare the diagnostic performance and efficiency of the optimized mHRME during HRA to standard of care HRA-guided anal biopsies. Using the optimized mHRME during HRA, we will evaluate the the efficiency (number of potential biopsies averted, reduction in procedure time) 2b) To develop and optimize a) a mobile high-resolution microendoscope (mHRME) and 3D image mapping for anal HSIL diagnosis and b) image-analysis software during HRA. Our optimized mHRME will provide subcellular, anal epithelial images that can be rapidly obtained using a novel, rollerball probe. To facilitate rapid interpretation and biopsy correlation in community-based settings, we will develop and test two innovative features: mHRME enhanced 3D-mapping, as well as anal HSIL automated image-analysis software for correlation of anoscopic and mHRME images to allow clinicians to identify areas of HSIL in real time in feasibility study.

The goal of this multidisciplinary study is to radically improve HSIL diagnosis by improving efficiency, and reducing costs using a novel, low cost mHRME approach. We hypothesize that this ¿optical¿ approach will decrease screening barriers, and simplify HSIL diagnostic and treatment algorithms, thus improving access to anal cancer prevention for HIV-infected individuals.

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, Spanish

Groups to be recruited will include:
Patients

Which if any of the following vulnerable populations will be recruited as subjects?

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

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.

This is a single-arm study where all subjects will receive both standard of care HRA and experimental HRME imaging.

Primary Objective To compare the diagnostic performance and efficiency of the optimized mHRME during HRA to standard of care HRA-guided anal biopsies. Using the optimized mHRME during HRA, we will evaluate the diagnostic performance (sensitivity, specificity, positive predictive value, negative predictive value) of mHRME optical diagnosis compared to paired anal tissue histology. Secondary Objectives a) To compare the diagnostic performance and efficiency of the optimized mHRME during HRA to standard of care HRA-guided anal biopsies. Using the optimized mHRME during HRA, we will evaluate the efficiency (number of potential biopsies averted, reduction in procedure time) b) To develop and optimize i) a mobile high-resolution microendoscope (mHRME) and 3D image mapping for anal HSIL diagnosis and ii) image-analysis software during HRA. To facilitate rapid interpretation and biopsy correlation in community-based settings, we will develop and test two innovative features: mHRME enhanced 3D-mapping, as well as anal HSIL automated image-analysis software for correlation of anoscopic and mHRME images to allow clinicians to identify areas of HSIL in real time in feasibility study.

There is no randomization for any of the objectives in this protocol.

Inclusion Criteria:

For both all objectives: 1. Consentable patients with documented HIV disease 2. Either: 1) previously documented HSIL or 2) abnormal anal cytology within the past 2 years Ages 18 years and older 3. Seen at the Baylor-affiliated Thomas Street Health Center (TSHC), Mount Sinai Hospital and affiliated clinics

Exclusion Criteria:

For all objectives 1. Patients with a platelet count less than 75,000 cells/mm3 and an absolute neutrophil count less than 1000 cells/mm3 2. A known permanent or irreversible bleeding disorder that, in the opinion of the principal investigator (PI), would contraindicate any biopsy of the anal canal; current or prior history of anal cancer 3. Allergy or prior reaction to the fluorescent contrast agent Proflavine or Iodine 4. Patients who are unable to give informed consent. 5. Patients who are pregnant

F2. Procedure

All patients scheduled for HRA will be screened for eligibility for the study at each clinic date. The research population will be identified from patients at Thomas Street Health Center and the Anal Dysplasia clinic at the Mount Sinai Medical Center (Dr. Gaisa) in New York City. The patient will be given information regarding the study and will be given the appropriate amount of time to carefully weigh the risks and benefits of the study. If the patient agrees to consent to participating in the study, the patient/participant will be counseled regarding all alternatives to study enrollment and regarding the right to withdraw consent at any time. In addition, the participant will be reassured that participation in the clinical trial will not in any way effect the future medical care received. The only document linking the participant and the research will be the consent form which will be filed in the subject's medical record.

The screening will be performed through secure electronic medical record system (Epic). The study investigators and study staff will make sure that personal information is kept confidential. All participant information will be stored securely in locked file cabinets in areas with access limited to study staff. All reports, study data collection, and administrative forms will be identified only by a coded number to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointments books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Since Dr. Chiao is a medical provider at Thomas Street Health Center, this temporary access to patients' PHI to determine eligibility does not constitute more than minimal risk and will not adversely affect the privacy

rights and welfare of the individuals who are covered by the waiver. Since Dr. Gaisa is a medical provider at Mt. Sinai School of Medicine, this temporary access to patients' PHI to determine eligibility does not constitute more than minimal risk and will not adversely affect the privacy rights and welfare of the individuals who are covered by the waiver.

Patients who are then found to be eligible and enroll in the study would provide written consent to do so. The patients covered by the waiver (those who are screened for the study but who are found to be ineligible will have no information recorded about them. Patients who refuse enrollment will only have their name and demographic information recorded so that the research coordinators will not re-contact them.

For enrolled subjects, data will be collected via medical record review, including: Viral Load and CD4 Count:Nadir CD4 cell count; most recent CD4 cell count; most recent HIV viral load; most recent anal cytology.

Survey and demographic data will be collected for all patients via interview including: Demographics, use of tobacco, alcohol and illicit substances; history of genital condyloma; frequency of condom use; sexual behavior, date of HIV diagnosis; history of opportunistic infections; previous history and treatment of HPV-related anogenital disease; including history of anal cytology or HRA; use of hormonal agents; and HIV cART regimen, self-reported adherence, and the EQ-5D.

During the procedure, the clinician will perform an External Anogenital Exam: We will record the presence and size of condyloma, presence of other genital lesions on all subjects. A brief standardized exam to determine any external anogenital lesions or pathology will be performed by the clinician. A digital rectal exam will be done on all patients.Roche Anal HR HPV Testing will also be performed via Dacron swab premoistened with water to obtain cells and HPV DNA from the anal canal.

During the HRA each subject included in the pilot (n=50) will undergo 3D mapping (see Aim 1) to document all Lugol¿s unstained areas. Then all Lugol¿s unstained areas will be evaluated with mHRME imaging, with software-enhanced guidance overlaid on the screen and the location of each unstained area (level, quadrant) will be recorded and digital images obtained. Prior to mHRME imaging, Proflavine Hemisulfate (0.01%) will be placed on the epithelium. Proflavine Hemisulfate is a investigational antiseptic which is absorbed by epithelial cells and stains nuclei, allowing visualizing of nuclei at high magnification. Please see Section O for information regarding further IND information for Proflavine Hemisulfate. The clinician¿s clinical impression will be recorded for each Lugol¿s abnormal area and visible lesion a) HSIL, b) non- HSIL¿ as well as his/her clinical opinion: c) no potential biopsy, or d) potential biopsy. Subsequently, biopsies of ALL (but not more than 4) abnormal Lugol¿s areas mapped with mHRME will be obtained, as well as 1 Lugol¿s normal area. The mHRME procedure as well as standard HRA and biopsy time will be recorded. 4. Standard of Care HRA: All participants in the study will receive HRA at the initial visit to provide a visually-directed anal biopsy. Areas suspicious for AIN, as demonstrated by acetowhitening or vascular changes in the anal epithelium, will be sampled with cervical biopsy forceps. If greater than 2 Lugol¿s negative biopsies are obtained, then 1 normal biopsy will be obtained. Lugol's staining is an established method for identifiying areas of distrupted epithelium during magnified evaluation of both cervical and anal epithelium. (Lugol's unstained areas have been shown on pathology to have a high Sensitivity but low specificity for intraepithelial neoplasia in both cervical and anal samples.) If there are no suspicious lesions seen on HRA, a random biopsy, preferably in the left lateral quadrant, will be performed. As random biopsies are often collected during standard of care HRA procedures, these biopsies are not considered research-specific.

Anal Pathologic Classification: Pathology of anal biopsy specimens will be graded by consensus review of Drs. Darragh and Liu. Anal low-grade squamous intraepithelial lesion (LSIL) will be defined as the presence of anal intraepithelial neoplasia grade I (AIN I). High-grade squamous intraepithelial lesions will be defined as the presence of AIN II or AIN III. P-16 staining will be used to validate HSIL diagnoses. 6. Safety: All patients will be contacted at 48 hours, and at 1 month by a coordinator and adverse events recorded in both groups (bleeding, infection, and pain). The EQ-5D questionnaire will be administered to the patients at each follow-up contact.

The data will be utilized to measure the 1) performance characteristics: a. sensitivity (SN), b. specificity (SP),c. positive predictive value (PPV) and d. negative predictive value (NPV), as well as e. the receiver operating curve for the identification of neoplasia on a per biopsy and per patient basis. 2) Clinical Efficiency: a. ¿Diagnostic Yield¿: Percent of HRME diagnosed HSIL lesions that were classified as non-HSIL by clinician. b. ¿Biopsies averted¿: Percent of HRA visualized lesions that the clinician originally categorized as potentially needing a biopsy but on mHRME were appropriately down-graded, averting an unnecessary biopsy. c. Procedure time: Total procedure time (mHRME and HRA).

The study is a single visit study. Patients will be contacted by phone at 1 year and 2 years for follow up evaluation. See MOP for the phone contact details.There will be no Follow-up Visits

Section G: Sample Size/Data Analysis

G1. Sample Size

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

Local: 75 Worldwide: 200

Please indicate why you chose the sample size proposed:

The study will primarily be powered to determine the precision around the operating characteristics of mHRME imaging. We estimate that because the median number of lesions per patient is approximately 1.5-2, and HSIL prevalence of 30%, approximately 150 patients (225-300) lesions will be needed to estimate the confidence intervals around SN and SP estimates see Precision Calculation Table in attachments. In order to accrue 150 patients, we will target a total enrollment of 200, because we will also be improving the technology as a secondary objective and assume that up to 25% of patients may not have evaluable optimized HRME images.

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?

Objective 1. We will determine the performance characteristics of mHRME for the prediction of anal HSIL in flat mucosa and mucosal lesions using histopathology as the gold standard. Our hypothesis is that the sensitivity (SN) specificity (SP), positive predictive value (PPV) and negative predictive value (NPV), as well as the receiver operating curve for the identification of neoplasia on a per biopsy and per patient basis will be high. We will first compare the HRA-directed biopsy (as the gold standard) to the results of the mHRME HSIL diagnosis. The SN of mHRME diagnosis in detection of HSIL will be estimated with the binomial proportion of study participants who are positive for HSIL on HRA-guided biopsy at two thresholds of histology thresholds which are: 1) AIN 2+ threshold, and 2) AIN3+ threshold. SP will be estimated as the proportion of study participants who are negative for HSIL on HRA-guided biopsy at both thresholds. Positive and negative predictive values will be estimated using the binomial proportion and its 95% CI. In addition, the Cohens kappa statistic, and receiver operator characteristic curves will be generated if patient characteristics such as low CD4 count, cART utilization, or high HIV viral load impact the determination of SN and SP. The lab information will be collected and placed in the source document and entered in Oncore. SN and SP of mHRME-based HSIL diagnosis will be estimated on a per lesion and per patient basis with 95% confidence intervals and compared by McNemar's test. A generalized linear model for logistic regression with multiple correlated outcomes will compare SN and SP of each method on a per biopsy and per patient basis.For Device optimization. No Data Analyses are planned.

Objective 2a. Determine clinical efficiency of mHRME + HRA for the diagnosis of HSIL. Clinical efficiency is defined as: `Diagnostic Yield: Percent of HRME diagnosed HSIL lesions that were classified as non-HSIL by clinician. `Biopsies averted: Percent of HRA-visualized lesions that the clinician originally categorized as potentially needing a biopsy but on mHRME were appropriately down-graded, averting an unnecessary biopsy. Procedure time: Total procedure time (mHRME and HRA). For Diagnostic Yield and Biopsies Averted, we will estimate 95% confidence intervals. Total procedure time will be recorded. mHRME Procedure time will measured separately once mHRME is initiated. Median and standard deviation of procedure times and mHRME procedure times will be calculated.

Objective 2b. Images collected from the 50 patients will be compared to biopsies. Preliminary Sensitivity, Specificity, positive predictive value (PPV) and negative predictive values (NPV) will be estimated and precision of interval width calculations will be done.

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:

We will use Common Terminology Criteria for AE v5.0. Serious adverse events will count as Grade 3 (Severe or Medically Significant, but not Immediately Life Threatening: Hospitalization or Prolongation of

Hospitalization Indicated; Disabling; Limiting Self Care ADL), Grade 4 (Life-threatening consequences; urgent intervention indicated) or Grade 5 (Death related to AE).

Upon completion of the study imaging, subjects will be contacted to screen for adverse events after a period of 2 and 30 days from procedure. Patients with abnormal clinical findings will be followed until the condition resolves or stabilizes. Adverse events or serious adverse events that occur during the follow-up period will be recorded regardless of relatedness to the study procedure. The safety follow-up may be conducted by a phone visit or a clinic visit; if clinically indicated, a clinic visit should be performed along with relevant lab work. Patients will be contacted by phone at 1 and 2 years for follow up evaluation. See MOP for details.

We anticipate most AE/SAEs will be related to anoscopy (pain, bleeding). Proflavine has been administered to >1000 patients for use with HRME imaging under Dr. Anandasabapathy¿s studies and we have had 0 related adverse events or serious adverse events..

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

Most of the risks/Discomforts from this trial stem from the standard of care procedure, high resolution anoscopy (HRA). Many of the side effects of HRA 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: There is the possibility of an allergic reaction to the Proflavine contrast dye in which participant may have local irritation. The participant can receive anti-histamines and other anti-allergy medications if this happens.

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

Anal biopsies: The risk for anal biopsies are pain, bleeding, and infection. The biopsies are part of the standard of care procedure and would be obtained regardless of study enrollment.

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 study.. Subjects will be given an ID number for all forms, images, and communications. All data will be coded. Source documents will be redacted of all PHI before being sent from outside sites for data monitoring/data entry in the database. All PHI collected on HHS 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 at 2 and 30 days after 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.

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.

This project will comply with the National Institutes of Health (NIH) Policy on the Use of a Single Institutional Review Board (sIRB) of Record for Multi-Site Research. The BCM IRB will conduct the ethical review required by the Department of Health and Human Services regulations for the Protection of Human Subjects at 45 CFR Part 46 for all project sites IRB approval must be obtained, and an Initiation Site Visit conducted before enrollment can begin at collaborating sites.

All project sites (the Icahn School of Medicine at Mount Sinai, University of Florida, University of California, San Francisco and Rice University) have agreed to allow the BCM IRB to serve as the sIRB for this project.All participating sites will, prior to initiating the study, sign an authorization/reliance agreement that will clarify the roles and responsibilities of the BCM IRB and the participating sites. The BCM IRB will maintain records of the authorization/reliance agreements and of the communication plan.

The Baylor PI will develop master study specific templates for Informed Consent Form (ICF), as well as HIPAA authorization, which will include local context for all participating sites and submit a single protocol to the BCM IRB that will be reviewed, approved, and used at all participating sites. The BCM PI will be responsible for preparing and submitting IRB applications on behalf of all sites, including initial reviews, local amendments, personnel updates, local reportable events, and study wide information for continuing review.

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.Patient's names, medical record numbers, and pathological information will be collected and stored in a locked drawer in the PI's office. The research data will be stored with the patient ID number and the sequential image number on a laptop that is associated with the imaging probe (the device has its own computer and hard drive) and will be password protected.

Study data will be collected at all clinical sites on paper CRFs identifiable by subject ID number. The paper CRFs are the official study documents. Local CRCs will enter data for their site (Mt. Sinai CRC will enter Mt. Sinai data, BCM CRC will enter BCM data) into OnCore. The CRCs will enter data on both paper and OnCore. CRFs will be stored electronically in BCM-approved platform OneDrive.

Data will be stored securely at the Coordinating Center. Data and safety monitoring will be performed by the study statistician and research manager. Data will be entered into the web application by authorized research personnel via secure HTTPS connections. De-identified data will be shared with the Co-investigators at Baylor, Mount Sinai, UC San Francisco, UT School of Public Health and Rice University.

Only deidentified images (microscopic images) will be analyzed at Rice University, by the bioengineers who developed the devices and are collaborating on the project. The Rice team will not be responsible for other data analyses, interim/final or DRC report. The device being used in this study (the HRME) is manufactured in Dr. Kortum's lab at Rice University. The images collected from the clinical trial are used to build software that will work to automatically analyze data. Data will be transmitted as deidentified images only. All histopathologic slides and optical images will be labeled with the subjects study ID number and will be presented to the pathologist who will read them in a blinded fashion. The subjects' clinical research forms with the associated optical biopsy read(s) are similarly labeled with the subjects study ID number.

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.

All project sites (the Icahn School of Medicine at Mount Sinai, University of Texas, University of California, San Francisco and Rice University) have agreed to allow the BCM IRB to serve as the sIRB for this project.

1. THOMAS STREET HEALTH CENTER (Baylor- Affiliated)

2.. RICE UNIVERSITY- BioSciences Research Center Lab space. Dr. Richards-Kortum occupies research and office space in the newly constructed BioSciences Research Center (BRC) at Rice University.

3. ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI Clinical Resources: Mount Sinai Medical Center: Mount Sinai Medical Center consists of the Icahn School of Medicine (ISMMS) and the Mount Sinai Health System. Encompassing seven hospital campuses (Mount Sinai Hospital, Beth Israel Medical Center, Mount

Sinai Brooklyn, Mount Sinai Queens, New York Eye and Ear Infirmary, Mount Sinai West and St. Luke¿s Hospital), the Mount Sinai Health System is an integrated network providing distinguished care, conducting transformative research, and advancing biomedical education.

4. UNIVERSITY OF TEXAS SCHOOL OF PUBLIC HEALTH. The proposed research will be conducted in the department of Health Policy Division in the in the School of Public Health at the University of Texas, where the Principal Investigator, Dr. Ashish A. Deshmukh, PhD, MPH

5. UNIVERSITY OF CALIFORNIA, San Francisco UCSF's Department of Anatomic Pathology provides full service diagnostic pathology services. The Department of Pathology at the University of California, San Francisco, aims to achieve the highest standards in patient care, research, and education.

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 are no potential benefits for the subject in participation in this study.

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

Squamous cell anal cancer (SCCA) rates in HIV-infected individuals have continued to increase over the past decade despite the widespread use of cART. These poor outcomes highlight the need to implement screening strategies for earlier detection.This proposal will provide a novel alternative surveillance tool that would substantially improve HSIL screening and surveillance strategies.

This study may provide clinicians with information about the best, most cost-effective way to screen anal intraepithelial neoplasia. A robust, low-cost method of identifying HSIL or minimally invasive SCCA without need for biopsy would markedly improve existing HRA and histology-based diagnostic strategies. By offering an in vivo diagnosis, more selective biopsies can be performed. Additionally, the ability to delineate normal from neoplastic mucosa in real-time may reduce the number of patients lost to follow-up and facilitate ¿see and treat¿ approaches using minimally-invasive ablative therapies. We anticipate that the mHRME may enhance the efficiency and cost-effectiveness of current practice by preventing unnecessary biopsies, repeat procedures, and loss of patients to followup. Successful results can easily be translated to other epithelial cancers: colon, cervix, stomach, etc

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

Yes, the risks are minimal (there is no treatment in this study). The benefits are potentially very useful to the patients, the medical community and society due to the potential for decreasing the risks (pain, bleeding and infection) from anal biopsies, and decreased need for pathology resources.From preliminary data Safety of Device and Contrast Agent: In all subjects imaged to date, no adverse events have occurred from device or contrast agent. Our initial data suggests that this low-cost imaging approach can improve the efficiency, accuracy, and cost-effectiveness of the current standard of HSIL screening and surveillance by offering a real-time, in vivo diagnosis that reduces biopsy number and repeat procedures without compromising accuracy.

Section J: Consent Procedures

J1. Waiver of Consent

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

Yes

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

Chart review for screening and identification of potential study subjects.

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

Since Dr. Chiao is a medical provider at Thomas Street Health Center, this temporary access to patients' PHI to determine eligibility does not constitute more than minimal risk and will not adversely affect the privacy rights and welfare of the individuals who are covered by the waiver. Since Dr. Gaisa is a medical provider at Mt. Sinai School of Medicine, this temporary access to patients' PHI to determine eligibility does not constitute more than minimal risk and will not adversely affect the privacy rights and welfare of the individuals who are covered by the waiver.

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

Patients who are then found to be eligible and enroll in the study would provide written consent to do so. The patients covered by the waiver (those who are screened for the study but who are found to be ineligible will have no information recorded about them. Patients who refuse enrollment will only have their name and demographic information recorded so that the research coordinators will not re-contact them.

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

It would be impractical to approach and consent all patients for screening; indeed such a process would increase the risk of breach of confidentiality because additional identifiable records would be generated. However, screening with a waiver is practical and safe since it can be readily accomplished at Thomas Street Health Center /Mt. Sinai School of Medicine by reviewing electronic medical records for patients with scheduled appointments with no need to remove or record PHI. With this waiver, we will be able to efficiently screen and enroll participants without increasing the risk of loss of confidentiality. Thus the research could not practicably be conducted without access to and use of the PHI.

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

To maintain confidentiality, all laboratory specimens, mHRME images, evaluation forms, reports and other records will be identified by a coded number only and de-identified from the participant. Clinical information will not be released without written permission of the participant,

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

The screening will be performed through secure electronic medical record system (Epic). The study investigators and study staff will make sure that personal information is kept confidential. All participant information will be stored securely in locked file cabinets in areas with access limited to study staff. All reports, study data collection, and administrative forms will be identified only by a coded number to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointments books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

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

The study investigators and study staff will make sure that identifiers will be destroyed at the earliest opportunity consistent with conduct of the research absent a health or research justification for retaining them or a legal reason to do so.

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

Yes

Specific information concerning alcohol abuse:

Yes

Specific information concerning drug abuse:

Yes

Specific information concerning sickle cell anemia:

No

Specific information concerning HIV:

Yes

Specific information concerning psychiatry notes:

No

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

Yes

Full Social Security #:

Yes

Partial Social Security # (Last four digits):

Yes

Billing or financial records:
No

Photographs, videotapes, and/or audiotapes of you:
Yes

Other:
No

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

If No, explain why providing subjects additional pertinent information after participation is not appropriate.
The waiver is for screening and identification of potential study subjects only, therefore providing subjects additional information would not be appropriate.

J1a. Waiver of requirement for written documentation of Consent

Will this research require a waiver of the requirement for written documentation of informed consent?
No

J2. Consent Procedures

Who will recruit subjects for this study?
PI
PI's staff
Third Party: Mt. Sinai 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.
The research population will be identified from patients at Thomas Street Clinic and the Anal Dysplasia clinic at the Mount Sinai Medical Center (Dr. Gaisa) in New York City. The patient will be given information regarding the study and will be given the appropriate amount of time to carefully weigh the risks and benefits of the study. If the patient agrees to consent to participating in the study, the patient/participant will be counseled regarding all alternatives to study enrollment and regarding the right to withdraw consent at any time. In addition, the participant will be reassured that participation in the clinical trial will not in any way effect the future medical care received. The only document linking the participant and the research will be the consent form which will be filed in the subject's medical record.

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:
Yes

Specific information concerning sickle cell anemia:
No

Specific information concerning HIV:
Yes

Specific information concerning psychiatry notes:
No

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

Full Social Security #:
Yes

Partial Social Security # (Last four digits):
Yes

Billing or financial records:
No

Photographs, videotapes, and/or audiotapes of you:
Yes

Other:
No

At what institution will the physical research data be kept?
Physical data will be kept at Baylor College of Medicine in the Center for Global Health

6501 Fannin St. Methodist Neurosensory Building Office NA104 Houston, TX 77030, and Mount Sinai Section of Infectious Diseases

How will such physical research data be secured?
Physical research data will be secured in locked offices and/or locked cabinets; access is limited to relevant study personnel.

At what institution will the electronic research data be kept?
Electronic research data will be stored at BCM on BCM servers which are password-protected. Electronic research data will also be kept in the OnCore database on BCM's secure server with limited user-specific, password-protected access. Data are entered into the web application by authorized research personnel via secure HTTPS connections. BCM Research staff are authenticated securely with BCM's LDAP/Active Directory. BCM IT maintains a firewall, intrusion protection service, and F5 Big IP servers for further protecting data within OnCore. All hardware systems are housed in HIPAA-compliant facilities that have 24-hour guards and access restricted by proximity cards and keys.

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

Yes

Such electronic research data will be secured via Other:

No

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?

No

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.

Sensitive data that includes HIPAA identifiers are required by the study sponsor at registration, and will be sent outside the BCM system to the Sponsor via the NCI OPEN System (https://open.ctsu.org/open); this website is password-protected and accessible only by permitted research staff. Applicable HIPAA identifiers that may be sent at registration include: Subject's name (or initials), zip code, date of birth and hospital MRN. After the subject is registered, all subsequent data to the sponsor is coded with the subject's study number.

Other transmission of PHI to outside of BCM will be strictly limited to authorized entities, such as the study sponsor, and will be minimized as much as possible; whenever possible, PHI will be redacted from study records that must be sent outside of BCM, and will be coded with the subject's study ID. Electronic transmission of PHI outside of BCM will be via BCM Send Secure Messaging System (Secure Mail), which uses Proofpoint email encryption. De-identified imaging Data will be sent to Rice University, pathology data will be sent to Univerity of California, San Francisco, and behavioral, and clinical data will be sent to University of Texas School of Public Health for cost-effectiveness modeling. All data sent to non-Baylor institutions will be de-identified.

Will you obtain a Certificate of Confidentiality for this study?

No

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

Only authorized personnel will have access to records which could identify subjects by name. Subjects will not be identified by name on any study documents. Data will be recorded in the subject's study file using the unique subject identification number assigned at registration.

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.

All study procedures will be conducted by the study investigator, and research related costs are covered by research funds. 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 after the standard of care procedure. The costs related to the clinically indicated high resolution anoscopy (HRA) are not research and are covered by the subject or their insurance.

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

Dollar Amount:

50

Distribution Plan:

Subjects will be compensated $50 for one study visit.

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.

n/a

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?

The slides/tissue blocks used for a clinical and research 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, Other: Imaging

Will the sample be stripped of identifiers?

No

If sample will be released outside the hospital:

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

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

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

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

If sample will be banked for future use:

Where will the sample be banked and for how long?

Formalin Fixed Paraffin Embeded Tissue Specimens will be banked as part of standard banking protocols at the respective institutions (Department of Pathology).

The samples are stored for 10 years as per standard procedure.

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

Yes

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: mHRME (Mobile High Resolution Microendoscope)

Section Q: Consent Form(s)

HRME BCM Consent

Section R: Advertisements

None