Cover Page

Official Study Title	THE EFFECTIVENESS OF HIGH RESOLUTION MICROENDOSCOPY (HRME) IN HIGH GRADE INTRAEPITHELIAL LESIONS (HSIL) DIAGNOSIS FOR PEOPLE LIVING WITH HIV
NCT Number	04563754
Document/Version Date	24 March 2023

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

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Supported by:
The National Institutes of Health (NIH)
GRANT - 12622467

Study Intervention Provided by:
RICE UNIVERSITY

Sponsor of IND:

Proflavine Hemisulfate
Dr. Sharmila Anandasabapathy
IND # 102217

Tool Revision History

Version Number: 1.2
Version Date: 2023 Mar 24
Summary of Revisions Made:

Version Number:
Version Date:
Summary of Revisions Made:

Version Number:
Version Date:
Summary of Revisions Made:

Version Number:
Version Date:
Summary of Revisions Made:

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PRÉCIS

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, which is substantially higher than the incidence of cervical cancer prior to widespread screening with cervical cytology. The alarming increase in anal precancer and cancer in HIV- infected individuals has led to an increased emphasis on prevention. Current HIV primary care Guidelines (NY state HIV primary care guidelines, HIV Medical Association, and Infectious Diseases Society of America) both recommend annual anal cytology screening, with triage to high resolution anoscopy (HRA)-guided biopsy for histologic confirmation of anal high grade intraepithelial lesions (HSIL) among HIV-infected men who have sex with men (MSM), and certain HIV-infected women. However, HRA-guided histologic diagnosis of HSIL is resource intensive, and has several drawbacks, including: extensive clinician expertise/training; pathology cost, availability, interpretation expertise; separate patient visits for diagnosis and treatment; and patient discomfort associated with unnecessary, non-neoplastic biopsies, given the low specificity of HRA-based visual HSIL identification. Our group has developed a portable, battery-operated, high-resolution microendoscope (mHRME) that 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.

1. STUDY OBJECTIVES

1.1 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.

1.2 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.

2. BACKGROUND AND RATIONALE

2.1 Background

The alarming increase in anal precancerous and cancerous lesions among HIV-infected individuals, has led to an increasing emphasis on anal cancer prevention.6 The 2015 New York State HIV Primary Care Guidelines recommend annual anal cytology screening, with triage to high resolution anoscopy (HRA)-guided biopsy for histologic confirmation of anal high-grade intraepithelial lesions (HSIL) among HIV-infected men who have sex with men (MSM), and certain HIV-infected women.7 However, HRA-guided histologic diagnosis of 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.8,9 These drawbacks, in part, have led to limited adoption of anal cancer screening as evidenced by the fact that only 11% of HIV-infected MSM reported receiving screening in the preceding 6-12 months.10 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.

Mobile High-Resolution MicroEndoscopy (mHRME) provides subcellular resolutionof 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 diagnoses of anal HSIL, thereby decreasing patient discomfort and procedure cost. The mHRME has already been shown to have high sensitivity and specificity with histologic diagnoses in other pre-cancer screening studies, including cervical 11 and esophageal squamous neoplasia.12 Furthermore, in preliminary data, HRME was shown to have a sensitivity of 93% and a specificity of 87% for anal HSIL detection.13 We propose to: 1) optimize the diagnostic performance of mHRME with 3D image maps for anal HSIL detection, followed by determiningthe of anal mHRME compared to the gold standard of HRA-guided biopsy. Our hypothesis is that mHRME plus 3D mapping will improve the accuracy andefficiency of HSIL diagnoses.

2.2 Study Rationale

Squamous cell anal cancer (SCCA) rates in HIV-infected individuals have continued to increase over the past decade despite the widespread use of cART.[14-16] The availability of combined antiretroviral therapy (cART) has dramatically prolonged survival among HIV-infected individuals with life expectancy now approaching that of uninfected individuals.[17-19] Driven by the aging HIV-infected population, and the fact that the incidence of SCCA has continued to increase in the cART era, [20] SCCA has become one of the most common HIV-associated cancers.[21] The highest risks appear to be among HIV-infected men who have sex with men (MSM) who have an increased SCCA risk of approximately 40-80 times greater than the general population, and an incidence of approximately 89/100,000 HIV-infected men. Women are also at increased risk for anal cancer (8-14 times greater than the general population), with a current incidence rate of approximately 18-30 per 100,000 person-years.[4,20,22] The incidence of SCCA among HIV-infected MSM over the age of 60 is approximately 131/100,000 person-years, and the 10-year cumulative incidence of SCCA among men who have sex with men (MSM) over age 30 is approximately 1%.[1,4,23-25]

Furthermore, SCCA leads to significant morbid effects in HIV-infected persons, who develop the disease at much younger ages (approximately 10 years younger) than uninfected persons [26] and have higher rates of colostomy placement (in eventually >30% of cases),[26] higher rates of treatment failure,[27-30] increased disease recurrence,[31] and thus lower progression-free survival.[32] These poor outcomes highlight the need to implement screening strategies for earlier detection.

HIV-infected individuals have a high prevalence of anal high-risk (HR) HPV infection and anal HSIL, leading to recommendations for anal dysplasia screening. HPV has been detected in 99% of cervical cancers and 80 to 90% of anal cancers, with HPV types 16 or 18 detected in about 70% of cervical and 80% of anal cancers.[33] Persistent anal HPV infection, in conjunction with other factors (smoking, history of advanced AIDS, and longer time period of detectable HIV viremia)[34] leads to the development of anal intraepithelial neoplasia grade 2 and 3 (AIN 2 and 3) also called anal high-grade squamous intraepithelial lesions (HSIL), a likely precursor to anal cancer. [35,36] In meta-analyses and recent reviews, the prevalence of HR-HPV infection and HSIL in HIV-infected MSM been shown to be 73.5% (48.9%-94.4%) and 29.1% (20.8%- 42.9%), respectively.[37] Among HIV-infected women, the prevalence of HR-HPV infection are somewhat lower at 43% (16%-85%),[37] but anal HSIL rates have been reported as high as a26% in another recent study.[38,39] The rate of progression from anal dysplasia to invasive SCCA is also high;[40,41] with estimates of HSIL progression to anal cancer in HIV-infected individuals ranging from approximately 1 in 263 to 377 cases per year.[37,42,43] In a recent study of HIV-infected MSMs, 7% of 156 individuals with HSIL developed invasive anal cancer over a median period of 8.6 months.[44] Screening for anal cancer precursors is feasible and has been shown to be cost-effective.[45,46] Several research and practice groups have recommended anal cancer prevention strategies focusing on anal cytology followed by anal colposcopy for both HIV-infected men and women because of the high rates of progression from anal dysplasia to invasive SCCA, and because SCCA shares many biologic properties with cervical cancer.[47] Currently, consensus on specific screening and treatment strategies are lacking, thus the development of optimal screening strategies based are critical. This proposal will provide a novel alternative surveillance tool that would substantially improve HSIL screening and surveillance strategies.

Current Screening for HSIL and Its Limitations:
The New York State guidelines for primary care of HIV-infected individuals recommend screening HIV-infected MSM and women with a history of CIN and condyloma yearly with anal Pap tests.[7] If the cytology is normal, then the patient returns for routine screening again in one year. Because the specificity of anal pap smears is relatively low (ranging from 32%-59%), experts recommend performing anal colposcopy or high resolution anoscopy (HRA), a procedure similar to cervical colposcopy with acetic acid and Lugol's Iodine augmentation to identify high grade squamous intraepithelial lesions (HSIL), as the gold standard diagnostic test for any cytologic abnormality which includes: squamous cells of uncertain significance (ASCUS), low grade squamous intraepithelial lesions (LSIL), or high grade squamous intraepithelial lesions (HSIL).[49] At this time, current expert-guided anal dysplasia guidelines suggest either surveillance, ablative therapy (electrocautery, etc.) or topical treatment of anal HSIL because of the high rates of progression to invasive anal cancer among HIV-infected individuals.[50] Thus, with the current screening algorithm, patients need to return to the clinic at least three times from initiation of screening to HSIL treatment. Novel optimal imaging techniques, such as mobile high resolution microendoscopy (mHRME) to identify histologic HSIL could substantially simplify screening and surveillance algorithms.

In addition to the multiple visits needed for current anal dysplasia screening algorithms, the HRA procedure requires substantial training and expertise among practitioners. Anecdotally, the original group of researchers who brought HRA to the United States note a high degree of dexterity and technical prowess required to effectively visualize the entire anal canal and obtain reliable biopsy specimens.[51] One study demonstrated that new HRA practitioners needed approximately 200 cases before demonstrating no missed high grade lesions found on follow-up.[52] This substantial learning curve and the lack of practitioners trained formally in residency or fellowship has led to a scarcity of providers able to provide HRA. Due to both the low numbers of trained HRA practitioners, and the amount of health care resources needed to initiate an anal dysplasia screening program, anal cancer screening rates in HIV-infected individuals remain extremely low. For example, the CDC reported that only 11% (95% CI 9%-13%) of a nationally-representative cohort of HIV-positive MSM (highest risk individuals) had an anal cytology test in the preceding year.[10] Furthermore, a recent study found that among those who are screened, 35% of patients are lost to follow-up between HRA and biopsy and treatment.[53] Currently, there are several ongoing studies evaluating biomarkers for screening, and a large clinical trial called the ANal Cancer Outcomes Research (ANCHOR) evaluating the effectiveness of HSIL treatment on the incidence of invasive anal cancer. However, research focused on improving the visualization and diagnosis of HSIL through novel imaging technology are lacking.

Need for Low-Cost, High-Resolution Imaging: As HSIL treatment recommendations evolve, simplifying HSIL and/or early anal cancer screening, detection and surveillance will radically improve the access, cost and efficiency of anal cancer prevention. 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.*[54-56] 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 follow-up. Successful results can easily be translated to other epithelial cancers: colon, cervix, stomach, etc.

3. STUDY DESIGN

This is a Device, Phase II, Multicenter, Cross-sectional Research Study with the following objectives:

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

For all objectives:

- Consentable patients with documented HIV disease, and either previously documented HSIL or abnormal anal cytology within the past 2 years
- Ages 18 years and older
- Seen at the Baylor-affiliated Thomas Street Clinic (TSC), Mount Sinai Hospital and affiliated clinics

4.2 Exclusion Criteria

For all objectives:

- Patients with a platelet count less than 75,000 cells/mm3 and an absolute neutrophil count less than 1000 cells/mm3
- 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
- Allergy or prior reaction to the fluorescent contrast agent Proflavine or Iodine
- Patients who are unable to give informed consent.
- Patients who are pregnant

4.3 Study Enrollment Procedures

This study involves recruitment of 200 HIV infected men and women with evidence of anal dysplasia from the Anal Dysplasia Clinics. This study will be available for enrollment at Thomas Street Clinic (TSC), Baylor College of Medicine and at the Mount Sinai Anal Dysplasia Clinic. In order to recruit these subjects, we will distribute information to both clinics and also physicians and their clinical staff who are in charge of the care of the subjects. The subjects will talk with their own physician who will describe the study, and arrange for an appointment. After their questions have been addressed, women who remain interested will sign the informed consent form. Potential participants will be approached by a trained research assistant (RA) to determine eligibility. Patients who participate in the study and are identified with anal disease will have access to appropriate ongoing care after study completion and will be offered remuneration for travel and inconvenience.

Potential subjects will read the informed consent. The consenting clinician will answer all their questions. The subject will be given a copy of the signed consent. The signed consent

will be kept in a locked cabinet at the clinical site. We will explain all the procedures that will be performed, possible risks, benefits and alternatives.

Once the patient is enrolled, their information will be entered in the OnCore™ Database System, which is a collection of interrelated tables that contain information on various aspects of enrollment activities. Information about human subjects will only be available to the research clinicians of the originating site. There is a potential loss of confidentiality at these gatherings, so participants will be counseled regarding the loss of confidentiality and this risk will be documented in the informed consent form.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Study Drug – Proflavine Hemisulfate
Proflavine was used under FDA IND #102217; the HRME itself is an IDE-exempt device by the FDA. The contrast agent, proflavine, used in this study is the principal component of acriflavine and has been used for fluorescent imaging in the European, Asian and Australian gastrointestinal literature without any adverse events.

Study Intervention - ***mobile High Resolution Microendoscope (mHRME)***
Patients will have mHRME images taken of Lugol's negative (abnormal) areas and subsequent standard-of-care HRA biopsies at each image site. In addition, there will be at least one extra image and biopsy taken at a Lugol's positive (normal) site. Each patient will likely have ≥ 2 biopsies. We plan to enroll 200 patients, which will yield 225-300 images.

Our approach uses topical contrast (proflavine) that directly highlights cell nuclei change, the most important pathologic marker of squamous cell intraepithelial neoplasia. In addition, we will implement image-analysis software to highlight these changes in real time, enabling less experienced practitioners to accurately recognize the hallmarks of neoplasia. The high- resolution fiber-optic microendoscope (mHRME) proposed for use here delivers 0.5 mW of 455 nm light to the tissue through a 0.8 mm diameter fiber- optic bundle, corresponding to an irradiance level of 100mW/cm2.

5.2 Handling of Study Interventions

See Manual of Operations (Appendix 1) for detailed instructions of HRME intervention.

5.3 Concomitant Interventions

N/A

5.4 Adherence Assessment

N/A

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

See Appendix 2 for Study Calendar

6.2 Description of Evaluations

See Manual of Operations (Appendix 1) for a detailed description of the Evaluations

6.2.1 Screening Evaluation

All patients scheduled for HRA will be screened for eligibility for the study at each clinic date.

Consenting Procedure

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 affect 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.

Screening

The screening will be performed through secure electronic medical record system. 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 TSHC, 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 MSSM, 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.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

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.

Baseline Assessments

See Manual of Operations (Appendix 1) for a detailed description of the Baseline Assessments

Randomization

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

6.2.3 Blinding

NA

6.2.4 Follow-Up Visits

There will be no Follow-up Visits. See Manual of Operations (Appendix 1) for a detailed description of the Follow-up phone Calls.

6.2.5 Completion/Final Evaluation

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.

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

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).

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

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.

7.3 Adverse Events and Serious Adverse Events

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

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. 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. Because these patients will all have abnormal anal cytology, the HRA is a standard-of-care procedure.

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 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 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

7.4 Reporting Procedures

PI will inform local and IRB of record within 5 days of SAE reporting. AEs will be reported to the IRB annually at renewal. Any event that is reportable to IRB will also be reported to the DLDCCC Data Review Committee (DRC) via the Patient Safety Officer at dldcc-pso@bcm.edu.

Any event that is reportable to the BCM IRB must also be reported by the BCM PI to the FDA via safety reports and in the annual report. Unexpected fatal or life-threatening adverse drug experiences will be reported within 7 calendar days. Serious and unexpected adverse drug experiences will be reported within 15 calendar days.

7.5 Follow up for Adverse Events

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 laboratory or clinical findings will be followed until the condition resolves or stabilizes, or until the laboratory values are no longer considered clinically significant. 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 call or a clinic visit; if clinically indicated, a clinic visit should be performed along with relevant lab work.

Patients will be contacted via phone at 1- and 2-years post-appointment for follow up evaluation. See MOP for further details.

7.6 Safety Monitoring

100% of serious adverse events will be monitored by the PI and study team. Because this is a low risk study there is no Data Safety Monitoring Board. Adverse events will be reviewed annually by the IRB. Serious adverse events will be reported within 5 days by the PI to IRB. Any event that is reportable to the IRB will also be reported to the DRC and FDA in accordance with their polices.

8. INTERVENTION DISCONTINUATION

N/A

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The primary outcome of this cross- sectional study is to measure the operating characteristics including SN, SP, PPV and NPV comparing the physician- and algorithm-guided HRME-based image compared to the Lugol's- guided physician diagnosis of HSIL during HRA.

9.2 Sample Size and Randomization

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 Table 1 below. In order for 150 patients to complete study procedures, **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 30% of patients may not have evaluable optimized HRME images.

Precision calculation

The damage to precision due to within-subject correlation is mitigated by the fact that the average number of per-patient slides is at most 2. Correlation = 0.5 is a high estimate, but the table below shows precision values close to the original independence-assumption based ones.

SN/SP estimate	½ width CI for 225 slides		½ width CI for 300 slides	
	indep	corr = 0.5	indep	corr = 0.5
10%	4.66%	6.99%	3.94%	5.91%
15%	5.28%	7.93%	4.50%	6.75%
20%	5.74%	8.61%	4.91%	7.37%
25%	6.07%	9.10%	5.21%	7.82%
30%	6.30%	9.46%	5.43%	8.14%
35%	6.46%	9.69%	5.57%	8.35%
40%	6.54%	9.81%	5.65%	8.47%
45%	6.55%	9.82%	5.67%	8.50%
50%	6.50%	9.74%	5.63%	8.45%
55%	6.55%	9.82%	5.67%	8.50%
60%	6.54%	9.81%	5.65%	8.47%
65%	6.46%	9.69%	5.57%	8.35%
70%	6.30%	9.46%	5.43%	8.14%
75%	6.07%	9.10%	5.21%	7.82%
80%	5.74%	8.61%	4.91%	7.37%
85%	5.28%	7.93%	4.50%	6.75%

Treatment Assignment Procedures

All participants will undergo HRME-imaging prior to biopsy

9.3 Definition of Populations

HIV infected men and women with either previously documented HSIL or abnormal anal cytology within the past 2 years.

Please see section 4.1 and 4.2 for inclusion and exclusion criteria description

9.4 Interim Analyses and Stopping Rules

N/A

9.5 Outcomes

9.5.1 Primary Outcome

The primary outcome are the performance characteristics: SN, SP, PPV, NPV

9.5.2 Secondary Outcomes

The first secondary outcome is efficiency (number of potential biopsies averted, reduction in procedure time).

The second secondary outcome is 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.

9.6 Data Analyses

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.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Study data will be collected at all clinical sites on paper CRFs identifiable by subject ID number. The electronic CRFs in OnCore 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. CRF scans will be stored electronically in BCM-approved platform Box.

10.2 Data Management

Data will be stored securely at the Coordinating Center. Data and safety monitoring will be performed by the study statistician and external research coordinator (BCM Global Health). 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, Medical University of South Carolina, 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. Richards-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. While images are de-identified, some PHI will be transmitted (Date of Service only). A data use agreement will be issued stating this.

De-identified histopathologic slides will be shared with and read by a consensus pathologist at UCSF. 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. There is no PHI shared with the slides. Material transfer agreements between BCM-UCSF & Mt. Sinai-UCSF and will be issued.

10.3 Quality Assurance

10.3.1 Training

All study staff have undergone their institutions' human subjects research and good clinical practice training. They will undergo OnCore training, training on CRF completion and data quality assurance. In addition, during the study start-up visit, all study staff will undergo training in HRME care, disinfection, and technical support.

10.3.3 Metrics

Device qualification: Each mHRME and smart ring camera will undergo full quality control at the manufacturing facility prior to clinical use. Metrics to be evaluated include: illumination power & uniformity, spatial resolution, camera response, signal/noise ratio, accuracy of N/C area ratio and mean feature area as measured from standardized test targets. Illumination uniformity and camera response will be measured using a high-resolution imaging standard (e.g., 1951 USAF Hi-Resolution Target, Edmund Optics). Accuracy of N/C area ratio and mean feature area measurements will be evaluated using a test standard with a uniform standardized spatial pattern (e.g., 2285-26N image analysis standard slide, Ted Pella, Inc, or equivalent). Performance metrics will be required to be within 10% of target values prior to distribution to clinical sites.

Site performance: Initial visits to both sites will ensure proper training on the optimized mHRME, as well as allow for provider feedback on the modifications. Annual visits to the New York sites and weekly review of ALL video images from every patient accrued in the pilot trial provides assurance that the devices are performing consistently and uniformly. To insure further uniform performance, imaging test standards and training (described above) will be provided to technical personnel. Site technicians will be trained in device use, disinfection/sterilization, realignment and basic repairs; spare parts (LED modules, probes, cameras) will be available at all sites. Devices that cannot be repaired will be returned to Rice or Baylor for repair. An additional trip will be made at study initiation to ensure that the enhanced mHRME systems and image-assist software are standardized and functioning and at least annually thereafter.

The gold standard histologic diagnosis will be based on a consensus pathology review. After the result for the local pathologist is documented, the slides will be reviewed by another pathologist (who is blinded to the original review). If the two reads differ, then the histopathology slide will be adjudicated by a third pathologist. The final read will ensure consensus by 2 pathologists.

10.3.4 Protocol Deviations

All protocol deviations will be reported to IRB and DRC in accordance with their policies.

In the event of an emergency, the sponsor and the reviewing IRB and DRC will be notified of any deviation from the protocol to protect the life or physical well-being of a subject. Such notice shall be given no later than 5 working days after the emergency occurred.

Otherwise, the quality monitoring processes by which deviations were identified, and process changes to prevent unintended variances will be reported to the IRB and DRC at continuing review.

10.3.5 Monitoring

All the study data (including Mt. Sinai and Houston data) will be monitored regularly by the Data Review Committee (DRC) of the Dan L Duncan Comprehensive Cancer Center, at a frequency of at least once per year, in accordance with the DLDCCC Data and Safety Monitoring Plan. The DRC will monitor the study for progress and enrollment, toxicities, adverse events, and soundness of data. Additionally, an independent research coordinator from BCM will monitor and review 25% of the data for accuracy

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

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 proposed project will use the same protocol to conduct non-exempt human subjects research at four locations, and will not initiate human subjects research prior to obtaining sIRB approval.

sIRB – Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (BCM IRB), Houston, TX. 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. 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. The BCM IRB also will serve as a Privacy Board to fulfill the requirements of the HIPAA Privacy Rule for use or disclosure of protected health information for research purposes.

The BCM IRB operates under the BCM Federal Wide Assurance No. 00000286, as well as those of hospitals and institutions affiliated with the College.

Should the project add any new sites after award, those sites also will rely on the BCM IRB as the sIRB of record.

Participating Sites – All participating sites will adhere to the sIRB Policy and will rely on BCM IRB to carry out the functions that are required for institutional compliance with IRB review set forth in the HHS regulations at 45 CFR 46. Participating sites will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of the approved protocol, and reporting unanticipated problems and study progress to BCM IRB.

Participating sites will communicate relevant information necessary for the BCM IRB to consider local context issues and state/local regulatory requirements during its

deliberations. Participating sites are expected to rely on the BCM IRB to satisfy the regulatory requirements relevant to the ethical review. The investigators and local sites understand that although IRB ethical review at the local site level would be counter to the intent and goal of this policy, the policy does not prohibit any participating site from duplicating the sIRB. However, the PIs understand that if this approach is taken, NIH funds may not be used to pay for the cost of the duplicate review.

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.

Communications Between Participating Sites BCM IRB – BCM IRB will collaborate with the BCM PI to establish a mechanism for communication between BCM PI and the participating sites. The proposed plan is as follows:

1) The BCM uses the SMART IRB platform to initiate and establish authorization/reliance agreements and prior to any site initiating the research, each site will sign an authorization/reliance agreement that will clarify the roles and responsibilities of the BCM IRB and participating sites. These reliance agreements will be maintained at the BCM IRB office as well as with each participating site.
2) The BCM PI, with assistance from the BCM IRB office, will collect local context issues and federal/state/local regulatory requirements for each participating site.
3) The BCM 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.
4) After BCM IRB reviews and grants final approval, the BCM PI will provide the participating sites with the IRB-approved versions of all study documents.
5) 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.
6) The BCM PI will be responsible for communicating all IRB actions and determinations to all participating sites as well as maintaining the documentation of all required communications with participating sites under this plan.

11.2 Informed Consent Forms

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.

All participating sites will adhere to the sIRB Policy and will rely on BCM IRB to carry out the functions that are required for institutional compliance with IRB review set forth in the HHS regulations at 45 CFR 46. Participating sites will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of the approved protocol, and reporting unanticipated problems and study progress to BCM IRB.

11.3 Participant Confidentiality

Participation in research may involve loss of privacy. Research records will be handled as confidentially as possible within the law. All records linking patient identifiers with unique study identifiers will be coded and kept in password protected files, so that only the study investigators have access to them. All data and information will be stored in files that are stripped of identifiers. No individual identities will be used in any reports or publications resulting from this study. The subject records may be reviewed by the research staff, and the study site Institutional Review Board, the National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), and their designees.

We plan to obtain a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify the subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the DLDCCC DRC, the NIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected. The participant has the right to withdraw from the study at any time.

12. COMMITTEES

N/A

13. PUBLICATION OF RESEARCH FINDINGS

Publications will be reviewed by the co-PIs and the co-Is of the study

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15. SUPPLEMENTS/APPENDICES

Appendix 1: Manual of Operations

MOP - HRME at Thomas Street Clinic
H-44616: THE EFFECTIVENESS OF HIGH RESOLUTION MICROENDOSCOPY (HRME) IN HIGH GRADE INTRAEPITHELIAL LESIONS (HSIL) DIAGNOSIS FOR PEOPLE LIVING WITH HIV

Supplies to take:

- Proflavine (dispensed from Investigational Pharmacy)
- Pen
- Staple remover
- Stapler
- Research charts (Consent Forms, CRF, Questionnaires, Proflavine Order form)
- Watch/phone

4 Weeks Prior to Clinic:

1. Patient is identified either by looking at clinic schedule or in clinic by Physician. Physician notifies CRC (via email or phone) to provide consent form for patient's review.

2. Physician discusses procedure with patient and answers questions. Physician adds note in Epic that procedure was discussed (using templates below). If patient is interested and agrees to enroll, use Epic Note Template #1 and continue to Step 3. If patient wants to keep consent form and further review, use Epic Note Template #2 and instruct patient not to sign consent. If patient is not interested, use Epic Note Template #3 so they are not approached again.

Epic Note Templates

#1: If patient wants to enroll
"I discussed study H-44616 with the patient, including study procedures. Patient was enrolled on [date]. Study procedure is being scheduled."

#2: If patient wants to further review
"I discussed study H-44616 with the patient, including study procedures. A copy of the consent form was given to the patient for his/her review, with instructions not to sign the consent until they returned to clinic. The patient can contact clinical research coordinator to follow-up regarding questions and interest in participating."

#3: If patient is not interested
"I discussed study H-44616 with the patient, including study procedures. Patient was not interested in study and should not be approached again."

3. The CRC should sign and date the consent form after the patient has signed. If a translator and foreign language consent form were used, the translator will sign and date on translator line. The original consent form(s) will remain in the research chart. Make two copies of the signed consent form(s). Place one copy of all languages used in the medical chart for scanning

into Epic by the nurse and give a copy/copies to the subject. The subject's copy should have CRC's contact info written on it (or business card) so the subject can contact our office with any questions or concerns.

4. Take the patient ID stickers from the medical chart. Place a sticker on each page of the consent form. If a foreign language consent form is used, place stickers on each page of both consent forms.

5. CRC completes pages 1-2 of the CRF and questionnaire packet at time of consent in English or in Spanish (HRME Sexual Behaviors and Sexual History for men and women, EQ-5D-5L).

6. Procedure is scheduled (by research scheduler).

7. CRC verifies the appointments have been scheduled by reviewing Epic and confirms with patient over the phone.

8. CRC registers patient in OnCore and assigns patient study ID based on OnCore ID.

7 Days Prior to Clinic:

9. CRC completes the Proflavine order form for study by providing, name, DOB, MRN, and study ID (or placing patient sticker with above information). CRC verifies patient allergies in Epic (Iodine, Proflavine).

10. Send the completed Proflavine order form to Investigational Drug Service to prepare the Proflavine batch. Place confirmation (email/fax confirmation) and original Proflavine order form in the research chart.

11. CRC will inform HRME operator of the date and time of HRME clinic, and the anticipated number of HRME study patients.

2 Days Prior to Clinic:

12. CRC will send reminder email to physician and HRME operator to remind them of clinic schedule.

13. CRC prepares research charts for n+1 (extra) patients scheduled for that clinic. Research charts should include the following: consent form (English, Spanish), CRF, questionnaires, and Proflavine order form. Research charts will be stored in CRC's locked office file cabinet.

Day of Clinic: CRC will coordinate with the physician's clinic staff to block off appropriate number of slots.

14. CRC arrives at clinic 30 minutes before scheduled clinic appointment to set up. CRC picks up Proflavine from Investigational Drug Service.

15. Once a patient is checked in, CRC leads them back to research office or procedure room to complete any unfinished questionnaires and baseline symptoms screen.

16. Complete pages 2-10 of the CRF with the subject, using the translation services if necessary. The baseline symptoms form should be completed the day of the procedure.

17. Record the Proflavine lot number and expiration date from the syringe packaging in CRF.

18. Give Proflavine to nurse in procedure room to administer during procedure and log into Epic.

19. During the procedure, complete the CRF (pages 11-20).

    a. Record scope in time, HRA start time (page 12)
    b. Record first abnormal area as Biopsy 1 (page 13)
        i. Describe lesion, mark location, take anoscopy image
        ii. Record clinician HRA read, plan (standard of care)
    c. Go onto second abnormal area as Biopsy 2 (page 14)
        i. Describe lesion, mark location, take anoscopy image
        ii. Record clinician HRA read, plan (standard of care)
    d. Repeat above steps for each abnormal area using extra biopsy pages if necessary
    e. Record HRA end time. Apply Proflavine, insert HRME. Record HRME start time.
    f. Proceed to first abnormal area (Biopsy 1)
        i. Once feed is in focus, freeze HRME
        ii. Record clinician read and plan based on HRME image
        iii. Analyze image. Record image number and score.
        iv. Ask clinician if they are happy with this image or if they would like to take another. Take as many images as needed, using extra biopsy pages if necessary
        v. Select best image of site (most representative)
    g. Go onto Biopsy 2.
        i. Once feed is in focus, freeze HRME
        ii. Record clinician read and plan based on HRME image
        iii. Analyze image. Record image number and score.
        iv. Ask clinician if they are happy with this image or if they would like to take another. Take as many images as needed, using extra biopsy pages if necessary
        v. Select best image of site (most representative)
    h. Repeat above steps for each Biopsy using extra biopsy pages if necessary
    i. Record end HRME time. Remove HRME attachment and insert biopsy forceps. Record biopsy start time.
    j. Proceed to Biopsy 1, biopsy area. Place sample in labeled specimen container. Record specimen label.
    k. Repeat for each biopsy.

l. Record biopsy end time.
m. Record scope out time.

Within 2 Days of the Clinic:

20. Within 2 days of the procedure, CRC calls the study participant and complete the Follow Up Symptoms form. Be sure to provide the study participant with CRC and PI phone number (business card/consent form) in case of any adverse events. Any adverse events or serious adverse events reported during the phone call should be reported to PI within 24 hours of being reported. If applicable, the CRC and PI will complete the Serious Adverse Event form. The PI will inform the local and IRB of record if needed within 5 days.

Within 30 Days of the Clinic:

21. Within 30 days of the procedure, CRC calls the study participant and complete the Follow Up Symptoms form. Be sure to provide the study participant with CRC and PI phone number (business card/consent form) in case of any adverse events. Any adverse events or serious adverse events reported during the phone call should be reported to PI within 24 hours of being reported. If applicable, the CRC and PI will complete the Serious Adverse Event form. The PI will inform the local and IRB of record if needed within 5 days.

22. CRC obtains the HRA procedure report, local pathology diagnosis from Epic. Place them in study participant's research chart. Record the local pathology diagnosis for each biopsy in CRF.

23. Request images from HRME operator.

24. CRC reviews chart, source documents, consent form, and Epic record for each local subject.

25. After completion of all study requirements, CRC and site PI will sign and date the Study Completion Form.

26. CRC scans the de-identified CRF and HRA procedure report, collects HRME images, and uploads into Box.

27. Paper copy of the original CRF and print out of pathology report, along with consent form and print out of HRA procedure report, are filed in CRC's office. Research charts should be stored in locked file cabinet when not in use. Secure workstation (Epic, computer, charts) if away from desk.

28. CRC will complete data entry in OnCore.

29. Data entered into OnCore will be monitored by Project Manager at Baylor College of Medicine including 100% of adverse events and ICFs and 25% of all charts at both sites.

30. The BCM IRB will annually review all adverse events. SAEs will be reported and reviewed within 5 days. Any event that is reportable to the BCM IRB will also be reported to the DLDCCC DRC and FDA in accordance with their policies.

Follow Up Evaluation:
At 1 year and 2 years post-enrollment, patients will be contacted via phone to assess rates of disease progression and recurrence. Patients will be contacted 3 times within 3 months of follow up time point. If they are unable to be reached, they will be designated "lost to follow up".

Adverse Event/Serious Adverse Event Definition
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).

Data Safety Monitoring
We will follow the Cancer Therapy Evaluation Program (CTEP) guidelines for reporting of adverse events. All expedited adverse event reports are required to be submitted to the local Institutional Review Board (IRB) of the reporting institution. Baylor College of Medicine has a standardized system for data and safety monitoring used by all investigators conducting NIH-funded research on patients. This includes a preliminary evaluation by the Dan L. Duncan Cancer Center (DLDCC) PRMC during the scientific review process, and an Institutional Review Board (IRB) review of serious and unexpected adverse events. Additionally, an independent research coordinator from BCM will monitor and review 25% of the data for accuracy , and 25% of all charts at both sites. 100% of adverse events will be monitored by the PI and study team. On site audits will be conducted every 6 months. Madeleine Allman (Research Coordinator) and Dr. Anandasabapathy will handle all reporting to the FDA for IND for proflavine.

All the study data (including Mt. Sinai and Houston data) will be monitored regularly by the DLDCCC DRC Data Review Committee (DRC) of the Dan L Duncan Comprehensive Cancer Center, at a frequency of at least once per year, in accordance with the DLDCCC Data and Safety Monitoring Plan. The DRC will monitor the study for progress and enrollment, toxicities, adverse events, and soundness of data. Each site will plan to have weekly meetings. At each weekly meeting, the Project Coordinator will provide the following information: number of participants entering the study, status with respect to meeting recruitment targets, percentage of patients assessed who enter the study, number of drop-outs, reasons for drop-out, percentage of patients at each stage of the project, and percentage of assessments completed at each assessment point. Information about any adverse events (including IRB reporting of short- and long-term remedies) also will be presented. By examining this information, the data and safety monitoring team will keep abreast of critical issues regarding recruitment and data integrity. Study staff also will notify at least one supervisor immediately if at any point a patient shows the need for urgent treatment (e.g. diagnosis of cancer). A written report containing the current status the trial monitored while the IND is active, and when appropriate, any toxicity and outcome data, are sent to DRC members at a frequency specified by the DRC Charter, which is usually annually.

Helpful phone numbers:

Harris Health Translation Services
Thomas Street Translator: 713-873-9782

Investigational Drug Service (IDS): Celia Fenceroy, Pharmacist
Email: INVdrugs@harrishealth.org
Fax: 713 873-4455
Office: (713) 873-4457
Pager: (281) 963-0802

HRME Operator: Yubo Tang
Email: ytang@rice.edu
Cell: (281) 908-9364

Consent forms – who signs, who gets a copy?
Using translated short form:

	Short form	English long form
Subject	Signs, gets a copy	Gets a copy
Witness/translator	Signs	Signs
PI/designee	-	Signs

Using Spanish long form:

	Spanish long form	English long form
Subject	Signs, gets a copy	Gets a copy
Witness/translator	Signs	Signs
PI/designee	Signs	Signs

**If designee is fluent in Spanish, he/she can sign as translator but must have a witness fluent in both languages to sign as the witness

Appendix 2: Study Calendar

Form	Day 0 (Procedure Day)	Day 2	Day 30	Year 1	Year 2
Procedure Form					
Symptoms	**X**	**X**	**X**		
HRA Assessment	**X**				
Procedure Time	**X**				
HRME and Biopsy	**X**				
Pathology	**X**				
Medical History Form					
Medical History	**X**				
Physical Exam	**X**				
Cyto/Pathology Review	**X**				
Post Procedure Form					
Post Procedure Questionnaire	**X**				
Follow Up Evaluation				**X**	**X**