DUHS IRB Application (Version 1.20)

General Information

*Please enter the full title of your protocol:		
Compare the performance of the Pocket colposcope to VIA/VILI for triage of HPV+ women in Kenya		
***Please enter the Short Title you would like to use to reference the study:**		
1:1 Pocket Colposcope in Kenya * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		

Document Date: 05/03/2024
NCT04998318

◆

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

Primary
1.Compare the performance of the Pocket colposcope to Visual Inspection with Acetic Acid (VIA) and Visual Inspection with Lugol's Iodine (VILI) for detection of precancerous lesions among HPV+ women in Kenya.
2.Determine sensitivity, specificity and positive/negative predictive values of different triage strategies for HPV+ women.

Secondary
1.Analyze patient and provider pre-exam surveys to address possible obstacles in routine cervical cancer screening and build awareness.
2.Analyze patient and provider post-exam surveys to gather their perspective on use of Pocket system.

Tertiary
1. Use the de-identified colposcopy images to test our automated algorithm named CARE. This is a retrospective analysis for modeling and development of the algorithm, not guiding clinical care. The addition of the cellphone camera images will help facilitate this algorithm.

Background & Significance

- Should support the scientific aims of the research

Invasive cervical cancer (ICC) affects the lives of 500,000 women worldwide each year, resulting in more than 270,000 deaths [1]. Unlike most cancers, ICC is highly preventable through the screening, diagnosis and treatment of cervical precursor lesions [2]. The *Papanicolaou (Pap) smear*, a highly effective screening method available in most developed countries, is not generally available in low- and middle- income countries (LMICs) due to cost and infrastructure requirements. To address this disparity, the World Health Organization (WHO) recommends adoption of alternative protocols that employ low-cost or simple-to-use screening technologies and treat all women who are positive based on these tests [3]. One such screening strategy, human papillomavirus (HPV) testing, has been shown to reduce the incidence and mortality from cervical cancer when coupled directly with outpatient treatment (generally cryotherapy) for women with HPV-positive results [4]. However, recent guidelines have moved back from this "screen & treat" approach, given concerns about overtreatment [5]. The American Society of Clinical Oncology (ASCO) recently released guidelines recommending that HPV be used as a screening test, followed by triage with Visual Inspection with Acetic Acid (VIA) to confirm the presence of lesions prior to treatment.

VIA involves applying acetic acid to the cervix, examining the cervix with the naked eye, and making a diagnosis. While this may decrease the rate of overtreatment, VIA remains a poor triage test for the following reasons. VIA has high variability depending on provider experience, patient age, and size of lesion and has diminished sensitivity due to lack of magnification [2], [6]. Because there is no capability to capture images with VIA, there is no documentation to assess front-line health workers' performance, limiting quality monitoring and opportunities for skills improvement [7], [8]. Moreover, acetic acid enhancement lacks both sensitivity and specificity compared to the case in which it is combined with visualization of glycogen depletion and/or neovascularization [9]- [11] . In short, because VIA is not an effective triage solution for HPV+ women, there remains a crucial need for an appropriate second test that

is low-cost, easy-to-use and will identify, microscopic disease and at the same time, prevent overtreatment.

Colposcopy with biopsy is the gold standard for diagnosis of pre-cancerous lesions in high-income settings. It involves the use of a low magnification microscope by an expert physician to visualize the cervix for a variety of features including acetowhitening (similar to VIA but visualized with a colposcope), glycogen depletion (using Lugol's iodine staining) and neovascularization (using a green filter on the white light colposcope). Colposcopy-directed cervical biopsy is the standard confirmatory test for women with positive screening results. Colposcopes are expensive and require referral to a facility that can house this machine, a trained colposcopist who can interpret the images, and a pathologist and laboratory that can process and read the biopsy. These factors make colposcopy and biopsy inaccessible to the many women in LMICs who are at greatest risk for developing cervical cancer.

Given the exam limitations inherent in treatment of HPV positive women based on VIA results, and the cost and access limitations in a colposcopy and biopsy-based treatment scheme, many low-resource settings offer treatment based on HPV result alone, or are deferring implementation of an HPV-based testing protocol. In Kenya, where this team has been working for the past 15 years, HPV-testing has been introduced in Ministry of Health supported clinics using a screen & treat protocol, in which women with HPV are all referred for treatment. Prior to determining treatment modality (in-clinic ablation or referral for an excisional procedure) women undergo a VIA Assessment for Treatment (VAT) to assure that they do not have a lesion too extensive or concerning for cancer, and are good candidates for ablative therapy.

Design & Procedures

- Describe the study, providing details regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

The Pocket colposcope has 510k FDA clearance and has been successfully used in almost 1500 unique patients globally (Figure 1) in Duke and non-Duke protocols to date. 1056 women who are HPV-positive and planned to undergo treatment at 6 Ministry of Health-supported outpatient clinics in Kisumu County will be recruited to the study. After providing informed consent, participants will be randomized 1:1 to either standard-of-care visual inspection or colposcopy with the Pocket Colposcope (Figure 2). The women randomized to the pocket colposcope will also have a de-identified image obtained using a cellphone. This cellphone does not have access to a cellular network. We are testing out the camera quality found in an ordinary cellphone.
Figure 1: Global Pocket Colposcope enrollment
Figure 2: Pocket Colposcope

Women randomized to the standard-of-care arm will undergo VIA followed by Visual Inspection with Lugol' s Iodine (VILI). Women randomized to the Pocket Colposcope arm will undergo Pocket-Assisted VIA (PA-VIA), green light imaging, and VILI using the Pocket Colposcope. Women in both arms will have biopsies taken of any suspicious lesions, or two biopsies taken in random locations if no lesions are visible. The locations of the biopsies will be based on provider impression. After their study-exams and biopsies are taken, women who are eligible for ablative treatment will be immediately treated in the clinic. Those with larger lesions or lesions concerning for invasive cancer will be referred to the local hospital for an excisional procedure. Figure 3 demonstrates the study schema in greater detail below.

Figure 3: Study Scheme

Standard-of-care arm

·*Visual Inspection with Acetic Acid (VIA):* First, the cervix should be wiped with a cotton swab to remove any preexisting mucous and/or blood. A 3-5% acetic acid solution will be applied to the cervix using a spray bottle or fox swab. After approximately 1-minute, any changes to the cervix using the naked eye will be noted. Acetic acid may be reapplied if acetowhitening diminishes during visual inspection.

·*Visual Inspection with Lugol's Iodine (VILI):* After imaging with Acetic acid, Lugol's iodine will be applied using a fox swab noting any yellow or non-staining areas. Lesion location(s) will be noted on a clock-face diagram and used to direct biopsy if a lesion is present or random biopsies will be obtained from two quadrants in the absence of a visible lesion.

Pocket Colposcope arm

·*Pocket-Assisted Visual Inspection with Acetic Acid (PA-VIA)*: First, the cervix should be wiped with a cotton swab to remove any preexisting mucous and/or blood. A 3-5% acetic acid solution will be applied to the cervix using a spray bottle or fox swab. After approximately 1-minute, using the Pocket Colposcope any changes to the cervix will be noted. Using the Calla Health image acquisition software, both white and green images of the cervix will be captured at low-resolution. High-resolution green light images will be obtained at the provider's discretion. Acetic acid may be reapplied between white and green imaging at the provider's discretion if acetowhitening diminishes. A cellphone camera image will be obtained as well.

·*Pocket-Assisted Visual Inspection with Lugol's Iodine (PA-VILI):* After imaing with Acetic acid, Lugol's iodine will be applied using a fox swab noting any yellow or non-staining areas. Using the Pocket Colposcope, images will be acquired and used to direct biopsy if a lesion is present. Random biopsies will be obtained from two quadrants in the absence of a visible lesion. A cellphone camera image will obtained as well.

Biopsy procedure: Biopsies will be collected and processed per the following procedures. Fade-resistant, and waterproof thermal printed QR (barcode) stickers will mark all specimen containers from patients consenting to the study. These QR codes will not have any protected health information (PHI) on them, but will be electronically registered to provide 2 unique identifiers with a secure digital database allowing study personnel with a secure digital scanning device to track and register the diagnostic findings with the patient sample to enhance quality assurance and prevent misidentification. Biopsies will be processed and diagnosed according to the standard surgical pathology procedures. Two hematoxylin and eosin (H&E)-stained slides will be processed from each biopsy. Dr. Edwin Walong, pathologist at the University of Narobi, will review each slide and give a diagnosis of negative, low-grade dysplasia (CIN-1), high-grade dysplasia (CIN-2/CIN-3), or invasive carcinoma.

Treatment: The Kenyan sites follow the Ministries of Health guidelines for cervical cancer screening which is referred to as "screen and treat". All HPV-positive women should receive treatment to reduce current and future risk of disease. Treatment will take place immediately after the biopsy, as described above. The physician will contact the patient approximately 30 days later for a follow-up phone call to assess any adverse events.

Clarification: Standard of Care "SoC" in Kenya is a naked eye exam. While Colposcope is an option for triage, in practice, there is almost no availability of colposcopy in the region where we will be working, so it's all naked eye (VIA).

High-level Disinfection: After each use, the Pocket Colposcope will be disinfected using the FDA-cleared reprocessing procedure which as also been validated by a third-party laboratory. There are 8 steps to be followed in order to disinfect the Pocket Colposcope. You will need the following items to complete disinfection: 1) Sterile water, 2) Enzol, 3) Cidex OPA, 4) 70% Isopropyl alcohol, 5) Lint free cloths (~8), 6) Thermometer, 7) Two soaking containers, and 8) Personal Protective Equipment (PPE). **Note:** The Cidex OPA solution has demonstrated disinfection efficacy in the presence of 5% organic soil contamination and microbiological burden during reuse. Cidex OPA may be reused for up to a maximum of 14 days provided the required conditions of *ortho*-phthalaldehyde concentration and temperature exist based upon monitoring described in the Directions for Use. DO NOT rely solely on days in use. Concentration of this product during its reuse life must be verified by the Cidex OPA solution test strip prior to each use to determine that the concentration of *ortho*-phthalaldehyde is above the minimum effective concentration (MEC) of 0.3%. The product must be discarded after 14 days, even if the Cidex OPA Solution Test Strip indicates a concentration above the MEC.

Figure 4: Pocket Colposcope Labeling

Given the large volume of subjects seen in these rural clinics, we do not have adequate time to reprocess the colposcope after each use to the lengths described below. As a result, we plan to use a medical grade /FDA approved sheath to cover the colposcope. This is called SealSkin which has FDA approval. The Sealskin will be changed after each usage and the probe will be wiped with alcohol. This is a SOP used for most medical equipment such as transvaginal ultrasounds, lymphoseek, etc.

Disinfection Steps:

Step 1: Verify that the **Cidex OPA** (0.55% ortho-phthaldehyde) solution meets minimum effective concentration (MEC) recommendations following the manufacturer guidelines.

Step 2: Fill a **soaking container** with **Cidex OPA** up to the appropriate level (Do NOT fill above the submersion line).

Step 3: Verify that the **Cidex OPA** solution is at 20°C with a theramometer. The temperature of the solution should remain at 20°C throughout the high-level disinfection procedure.

Step 4: Insert the probe into the Cidex OPA solution up to the submersion line and agitate to remove any air bubbles on the outside of the probe.

Step 5: Allow the probe to soak for 12 minutes.

Step 6: With **sterile water**, thoroughly rinse the part of the probe that was immersed. Repeat this step 3 times, using new **sterile water** each time.

Step 7: Dry the pocket colposcope using a clean, lint-free cloth.

Step 8: Store the colposcope in a clean, lint-free cloth, with cloth separating the cord from the probe. The device can also be stored in a sterile container.

The cord and handle also require cleaning and you must follow these 3 steps. Evenly dampen a clean, lint-free cloth with isopropyl alcohol or 70% Cidex OPA. Wipe all surfaces of the cord and handle. Pay attention to the crevices around the control strip and focus slider. Finally, evenly dampen a clean, lint-free cloth with sterile water. Wipe the cord and handle taking care to avoid letting liquid pool on the device. Note, if there is visible soil present you must first prepare an enzymatic detergent and follow the steps described above to remove it prior to sanitization.

Colposcopic Automated Risk Evaluation (CARE) aka Imaging Algorithm - The colposcopy images obtained will be used in the future in hopes to test and vet our image processing algorithm which has not been FDA approved. The algorithm is not part of study participation for each subject. The de-identified images will be compiled to assist in machine learning to differentiate concerning lesions versus normal colposcopy images. Again, the cellphone camera images will be used for developing this algorithm as well.

Addition of checkbox to permit contact on future research studies.

We plan to proceed with prospective enrollment of 550 subjects in the research arm only. Therefore we will no longer have possible randomization into standard of care treatment. The past and newly obtained cervical images will be used to generate the treatment algorithm as described in the objective field (tertiary).

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

The subjects will be recruited from 6 different sites in Kenya. No subjects will be recruited/enrolled at DUMC.

Selection of Subjects:

Inclusion Criteria
1.Age $\geq$ 25 years old and $\leq$ 65 years old
2.Sex: Female
3.Positive HPV test within past 6 months
4.HIV+ women

Exclusion Criteria
1.Pregnant women (cannot perform a cervical biopsy on a patient who is pregnant unless absolutely indicated)
2.Women with a negative HPV test
3.Patients incapable of giving informed consent
4.Women with a history of cervical cancer
5.Pelvic exam concerning for cervical cancer or cervical infection

The rationale for the pregnant women exclusion is merely based on standard of care NOT for research. As a general rule, providers do not perform cervical biopsies on pregnant patients unless absolutely needed.

Subject Recruitment and Compensation

- Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

The collaborating clinicians will identify subjects who are HPV+ and require visual inspection. The population will include those who are undergoing screening for the diagnosis of cervical cancer. The collaborating healthcare provider will introduce the study to potential subjects. The research team will explain the purpose and background of the study, the selection criteria, the subject's involvement, benefits, risks, compensation (for injury), costs, alternatives, confidentiality and disclosure issues with the patient. Informed written consent will be obtained from patients who are willing to participate at the time of the colposcopy visit. In addition to obtaining informed written consent, the patient's ethnicity and race will be collected. Finally, pathologic information, age, and BMI will also be obtained. A total of 400 patients will be recruited for the study.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

Subjects who are not competent to give consent will not be included. Specficially, subjects who are not able to understand the consent form or the reasons why the study is being conducted will not be included. If the subject cannot read, the RA (Jeniffer Ambaka) has the option of reading the consent form to the subject aloud.

Study Interventions

- If not already presented in #4 above, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i.e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

The subject agrees to participate and signs the informed consent document. The subject will be randomized to either the standard of care visual inspection (VIA) arm OR the pocket-assisted visual inspection (PA-VIA) arm. The study scheme is described above in Figure 3. Once the procedure is complete, all subjects will have a follow-up phone call within 1 month to assess any post-procedural problems and/or adverse events. Once this occurs, the research procedures are considered complete.

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant individuals, imprisoned persons or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

The Pocket Colposcope is not intended to come into contact with the patient as it is intended to be used inside a vaginal speculum. However, there is a small chance that the user could unintentionally touch the patient with the device for short durations of time, see Table 1 (uploaded as Pocket risk document). Therefore, to demonstrate safety of the materials, the following table describes the components and materials of the Pocket Colposcope that have the greatest probability of patient contact. The associated materials were assessed for cleaning, high level disinfection, and biocompatibility according to the requirements and testing prescribed in ISO 10993#1:2009**[1]** and FDA's corresponding guidance document**[2]**for devices with transient/ limited exposure (< 60 minutes – Category A) and Surface-contacting with possible mucosal membrane contact. Failure Modes and Effects Analysis (FMEA) was used to assess the risk impact of the Pocket Colposcope System. Risk severity ratings from this analysis provide the severity levels that were used to determine the design verification and validation activities that were required. The risk
management activities, conducted in accordance with ISO 14971:2012**[1]**, have concluded that the mitigation of risk balanced against the benefits of the Pocket Colposcope System results in an acceptable product risk level that is safe for human use.

There is no direct benefit to the subject for participating in this study. We hope the information learned from this study will benefit other patients in the future by providing accurate methods for early detection of cervical pre-cancer and cancer.

[1]ISO 10993-1:2009 *Biological evaluation of medical devices – Part 1: Evaluation and testing*
[2]FDA Guidance - *Use of international standard ISO-10993, "Biological evaluation of medical devices – Part 1: Evaluation and Testing within a risk management process. June 16, 2016*
[3]*ISO 14971:2012 Medical Devices – Application of risk management to medical devices.*

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

There will be no costs to the patient for participating in the research study.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

Pocket Colposcope images will be evaluated 1) at the time of the initial exam, 2) by expert colposcopists and, 3) by our image processing algorithm [12]. Provider impression of the Pocket Colposcope images, provider impression of the standard-of-care VIA/VILI and the algorithm output will be compared against pathology. The diagnostic information gained will be used to determine the sensitivity and specificity of the algorithm. Specifically, the two-sided McNemar's test will be used to determine statistically significant differences in specificity and sensitivity for each comparison 1) VIA/VILI impression vs. Pocket-provider impression during the exam, 2) expert provider interpretation vs. Pocket--algorithm-based results post-study and 3) VIA/VILI and Pocket Colposcopy based impressions (during exam) vs. algorithm-based results (post- study) to test our hypothesis that provider based interpretation of the Pocket images and the algorithm perform significantly better than VIA/VILI, and that the automated algorithm performs comparably to an expert. To obtain a better understanding of the performance of the three tests, we will carry out a standard and weighted Kappa to look at the agreement between tests and the impact of disease severity on agreement. The literature suggests that approximately 20% of the patients from each arm will have a CIN2/3 diagnosis.

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

All data will be obtained at the sites in Kenya. The Duke team will be in communication with local PIs/CRCs to ensure the images and data are uploaded correctly. Data monitoring will be conducted on a routine basis by the PI and study team as spefied below in Section 13. As necessary, the PI will make source documentation and protocol data available to appropriate regulatory agencies, which may include but is not limited to the DCI Monitoring Team, the DCI Cancer Protocol Committee, the DUHS IRB, the Duke University SOM's Office of Regulatory Affairs and Quality (ORAQ) and the National Cancer Institute.