mHealth-supported Telecolposcopy for Cervical Cancer Programs in Low-resource Settings: Evaluation (mIVAA)

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1. Protocol Title:

mHealth-supported telecolposcopy for cervical cancer programs in low-resource settings: Evaluation

2. Research Abstract

Our long-term goal is to facilitate early cervical cancer prevention and treatment behaviors that are critical for positive clinical outcomes such as reduced cancer progression and increased survival.

The cervical cancer prevention cascade involves several touchpoints. For instance, women screened with visual inspection with acetic acid (VIA) and suspected to have precancerous or cancerous lesions require additional visits with trained ob-gyn specialists/colposcopists who can conduct further clinical evaluation (e.g., using colposcopy or biopsy). In Lima, Peru, our study partners, Liga Contra el Cáncer-Perú (La Liga) use mobile units to provide community-based cervical cancer screening with VIA and/or Pap. In addition, they provide follow-up clinical evaluation at their brick and mortar clinics (detection centers) in Lima for women who are VIA+ and/or Pap+. However, approximately 77% of VIA+ women screened by La Liga in community settings do not present for follow-up clinical evaluation at one of La Liga's detection centers.

To address this issue, we seek to develop and evaluate mIVAA (mobile Inspección Visual con Ácido Acético – Spanish for Visual Inspection with Acetic Acid (VIA). mIVAA is described in the intervention section.

The central hypothesis is that use of mIVAA will increase the proportion of VIA positive women who complete follow-up clinical evaluation compared to VIA positive women in situations in which mIVAA was not used, thus potentially improving cervical cancer treatment and survival rates. The study will collect qualitative and quantitative data to examine the feasibility and preliminary impact of mIVAA on reducing attrition for follow-up clinical evaluations. The primary outcome is the percentage of referred women who are lost to follow-up in intervention versus control arm. Secondary outcomes include provider and patient satisfaction with the mIVAA system, and decisional conflict about follow-up. Multivariable modeling will examine correlates of follow-up.

Research Summary

3. Purpose of the Study:

Our long-term goal is to facilitate early cervical cancer prevention and treatment behaviors that are critical for positive clinical outcomes such as reduced cancer progression and increased survival.

In the short-term, we seek to develop and evaluate mIVAA (mobile Inspección Visual con Ácido Acético – Spanish for Visual Inspection with Acetic Acid (VIA)). mIVAA is described in the intervention section.

The central hypothesis is that use of mIVAA will increase the proportion of VIA positive women who complete follow-up clinical evaluation compared to VIA positive women in situations in which mIVAA was not used, thus potentially improving cervical cancer treatment and survival rates. The study will collect qualitative and quantitative data to examine the feasibility and preliminary impact of mIVAA on reducing attrition for follow-up clinical evaluations. The primary outcome is the percentage of referred women who are lost to follow-up in intervention versus control arm. Secondary outcomes include provider and patient satisfaction with the mIVAA system, and decisional conflict about follow-up. Multivariable modeling will examine correlates of follow-up.

This study has two specific aims:

Aim 1: To pilot test mIVAA in a community-based setting in Peru.

Aim 2: To evaluate effectiveness of mIVAA by comparing the attendance for follow-up clinical evaluation among women screened with mIVAA compared to historical data on women referred for follow-up without mIVAA.

4. Background & Significance:

Cervical cancer is the leading cause of death among women of reproductive age in Peru. Every 5 hours, a woman in Peru dies from cervical cancer. [13] Development of cervical cancer is preventable when precancerous lesions are detected and treated. However, precancerous lesions are typically asymptomatic and, in absence of preventative screening, cancers are detected at advanced incurable stages. In Peru, 80% of cervical cancer cases are detected at advanced stages. [1]

In low-resource settings, Visual Inspection with Acetic acid (VIA) and Pap smears (Pap) are widely used as a primary screening approaches due to their scalability. Both VIA and Pap have poor sensitivity, and where resources allow, are coupled with a more specific evaluation step such as colposcopy, the visualization of the cervix using a low-powered microscope to determine whether the woman should be treated or not, and/or biopsy.

A key barrier to implementing colposcopy, especially in rural and remote communities, is low access to expert colposcopists trained to evaluate cervical images. As a result, women who screen positive in community settings are often referred to distant health facilities with expert colposcopists for further clinical evaluation. The burden of follow-up contributes to high rates of post-referral attrition and failure of women to receive appropriate treatment. [2-8]

Liga Contra el Cáncer-Perú (La Liga), a collaborating institution on the study, has five mobile units (MUs) traveling to communities across Lima and Callao to offer cervical cancer screening services. Each mobile unit consists of a midwife who performs the Pap screening tests and VIA, and a nursing technician who supports administrative tasks, data entry, and triage. Currently, many districts served by MUs have low-income

populations. MUs screen between 200-800 women each per month with 10% of women referred for follow-up colposcopy. La Liga's administrative data indicate that 77% of the women referred do not show up for a follow-up appointment.

Hence, strategies for reducing post-referral attrition are vital for improving rates of diagnosis, treatment, and survival. One strategy is to expedite the decision on whether follow-up is needed, by improving women's access to expert colposcopists at the location of the primary screening (i.e., in communities) using telemedicine.

Given the rapidly growing mobile network infrastructure in Peru, the use of mIVAA represents a key opportunity to bypass the need for stationary systems (e.g., computers), and costly fixed broadband connections associated with traditional telemedicine infrastructure to achieve scalability of enhanced visual inspection to rural and remote settings. [9] This proposal brings together a multidisciplinary team at Duke University, USA with expertise in mHealth, cervical cancer, and implementation science, in close partnership with two Peruvian organizations, Liga Contra el Cáncer-Perú (The League against Cancer-Peru) and Medical Innovation & Technology.

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5. Design & Procedures:

Study design: Observational design. There is no treatment intervention in this study.

This study will evaluate the use of mIVAA to facilitate communication between providers, and will collect data through observations, surveys and interviews. No specimens will be collected.

Study location: We will conduct the study in Lima and Callao, Peru.

Cervical cancer screening standard of care:
La Liga mobile units are set up close to busy locations (e.g., a market) in pre-selected communities. Screening is offered 9 am-3:00 pm every weekday for 1-2 weeks per community. Women receive Pap, VIA, breast, thyroid and rectal exams and each clinical encounter typically lasts 15 min (see Table 1). La Liga also has two central administrative offices and clinics (detection centers) where cancer-related screening and treatment is offered by health providers including expert colposcopists, and where administrative staff are based. Training has been conducted on use and reprocessing of the Pocket device, however it is not currently in use in clinics.

Currently, if VIA+ (any evidence of whitening after application of acetic acid; determined at the same time as the exam), women are advised during screening that follow-up clinical evaluation with a medical expert (colposcopist) is required, however no referrals for care are made until Pap smear results are received in about 30 days, unless there is a suspicion of cancer. Patient information and the diagnosis is entered into an electronic database at La Liga (WebLiga). La Liga staff contact women who screen positive and are diagnosed with cervical cancer or pre-cancer to schedule follow-up appointments for care, management and treatment. If the woman misses the colposcopy appointment, La Liga staff call to reschedule. After three attempts at rescheduling, the woman is considered lost-to-follow-up.

Table 1: Standard of care and proposed intervention (mIVAA)

Standard of care	**mIVAA**
Screen with VIA (IVAA) and Pap in MUs	Screen with VIA, Pap and mIVAA (digital imaging device component) in MUs
No expert review	Expert reviews digital images of the cervix remotely using mIVAA's telemedicine component and refers for follow-up appointments for care, management and treatment, if positive
Refer women for colposcopy based on Pap results 3-4 weeks later	For any women not referred already, refer if needed based on Pap results, per standard of care

Perform diagnostic colposcopy and biopsy and treat, if possible, at central La Liga clinic in Lima	Perform confirmatory colposcopy and biopsy and treat, if possible, at central La Liga clinic in Lima
Additional visits to complete treatment, per standard of care.	Additional visits to complete treatment, per standard of care.

Description of intervention and framework for development:
This study's intervention will be referred to as mIVAA. mIVAA is comprised of two components: 1) a digital image capture device for magnification and documentation of the cervix during VIA screening done by midwives staffing La Liga's mobile units. Digital imaging devices used in this study will be the Pocket (device developed at Duke University) and/or digital camera of a mobile phone; and 2) a telemedicine platform that enables two-way communication between midwives and colposcopists (Gynecologist-Oncologist). mIVAA can facilitate visual inspection of the cervix through magnification and documentation for midwives, and allows for remote evaluation of cervical images by a colposcopist to determine the need for follow-up clinical evaluation for women with a positive VIA screen.

mIVAA will be implemented in the mobile units (MUs), with support from 1 to 4 expert colposcopists who work at La Liga detection centers in Lima. In the mobile units, midwives will acquire cervical images using a digital imaging device. The images will be transmitted to an expert colposcopists using a mobile device over cellular/WiFi networks.

We will use an adaptation of an existing telemedicine platform developed by MI&T to facilitate the evaluation of cervical images by colposcopists and communication with providers at mobile units. Women being screened in the mobile units will receive an expert evaluation of their cervical images, a management plan and a follow-up appointment for colposcopy and biopsy, as necessary, will be scheduled. As part of the study, we will assess how soon the evaluation, management plan and follow-up appointment are possible after the cervical cancer screening, i.e., within a few hours, same day, within a week etc. For women without suspected lesions, a referral will be possible as per standard of care once Pap results are available and if positive.

Aim 1: To pilot test mIVAA in a community-based setting in Peru.
Methodology:

For this aim, we will enroll approximately 102 women attending any one of five La Liga mobile units for cancer screening, and approximately 18 La Liga health providers and administrative staff.

As part of the pilot, we will:

- Test the feasibility of integrating mIVAA into the existing workflow at the mobile units.
- Assess mIVAA for image quality, network stability, challenges with image transmission, and ability and time to reach experts and receive feedback from experts (two-way communication between health providers).
- Assess mIVAA system for burden on midwives and nurse technicians.

- Collect survey data from women who get cancer screening at La Liga mobile units to evaluate correlates of follow-up clinical evaluation.

Study activities with enrolled women

Approximately 102 women in total from up to 5 mobile units will be enrolled.

- First, we will consent, screen for eligibility, and enroll up to 102 women who come for cancer screening at any one of five La Liga mobile units.

Women who consent may complete the following study activities:

Activity 1: Allow mIVAA system to be used during VIA procedure for cervical cancer screening.

Activity 2: Complete a survey. The survey will include:

- Socio-demographic characteristics, reproductive and clinical history, knowledge of cervical cancer, social support, household decision making, experience with screening, barriers and facilitators to attending follow-up clinical evaluations, mobile phone use and feedback on the intervention.
- Contact information (including primary and back-up mobile phone numbers) will be collected in addition to information on mobile phone ownership and use.

The survey will be administered electronically, or on paper if not available electronically, by a trained data collector using Qualtrics, REDCap or another offline app based on a mobile device. Surveys will be conducted in Spanish. Surveys may include open-ended questions that may be audio recorded, transcribed and translated to English for analysis and inclusion in any publications.

Activity 3: Allow review of medical records to assess follow-up and correlates of follow-up.

Activity 4: Complete a few questions about motivators or barriers to follow-up clinical evaluation.

The interview will be conducted by phone and will be administered electronically, or on paper if not available electronically, by a trained data collector using Qualtrics, REDCap or another offline app based on a mobile device. Surveys will be conducted in Spanish. The interview will include open-ended questions that may be audio recorded, transcribed and translated to English for analysis and inclusion in any publications.

Study activities with enrolled La Liga health providers and administrative staff:

- First, we will consent, screen for eligibility, and enroll approximately 18 La Liga health providers and administrative staff.
- Once health providers and staff are consented, screened and enrolled, we will work with La Liga to train midwives, nurse technicians who worked in mobile units, and colposcopists to use mIVAA (including use of the Pocket) and on research protocols including maintaining confidentiality of participant

data.

Midwives with assistance from nurse technicians

Activity 1: Use mIVAA system during VIA with consenting women
For each woman who consents to the use of mIVAA system, midwives will:

- Attempt to capture digital images of the cervix with mIVAA.
- Enter relevant clinical notes in mIVAA.
- Use mIVAA to send images of the cervix and of the VIA results form for each patient to participating expert colposcopist for evaluation of these images to evaluate the need for a management plan,
- For women with a positive VIA or suspicion of cancer, follow-up clinical evaluation with a colposcopist in a La Liga detection center will be scheduled based on feedback received from these same colposcopists as per La Liga's institutional protocols.
- For women without suspected lesions, further referrals may be made according to standard of care based on Pap results when available, and if positive.

Activity 2: Provide feedback on mIVAA through a brief survey and interviews, and/or an individual or group interview. Discussions will assess feedback and satisfaction with mIVAA. Individual or group interviews may be completed in person, by phone or by Zoom. The interviews will be audio recorded using an encrypted digital audio recorder, voice recording app on tablet or using Zoom's audio recording function.

Study staff will document in Spanish La Liga provider and staff feedback, and translate to English for analysis and inclusion in any publications. Interviews may be audio recorded, transcribed and translated.

Colposcopists

Activity 1: Use mIVAA system to access patient cervical screening documentation and communicate with midwives and staff at mobile unit.
For each patient, expert colposcopist will:

- Provide feedback on whether the patient should have a follow-up clinical evaluation.
- Rate quality of cervical image.

Activity 2: Provide feedback on the use of mIVAA through a survey, brief interviews, and/or an individual or group interview. Discussions will assess feedback and satisfaction with the mIVAA system. Individual or group interviews may be completed in person, by phone or by Zoom. The interviews will be audio recorded using an encrypted digital audio recorder, voice recording app on tablet or using Zoom's audio recording function.

Study staff will document in Spanish La Liga provider and staff feedback, and translate to English for analysis and inclusion in any publications. Interviews may be audio recorded, transcribed and translated.

Aim 2: To evaluate effectiveness of mIVAA by comparing the attendance for follow-up clinical evaluation among women screened with mIVAA compared to historical data on women referred for follow-up without mIVAA**.**

Hypothesis: Use of mIVAA will result in a 13.5% increase in the proportion of screen-positive women completing follow-up clinical evaluation, compared to situations where mIVAA is not used.

Methodology:

For this aim, we will enroll approximately 200 VIA+ women attending any one of five La Liga mobile units for cancer screening, and approximately 18 La Liga health providers and administrative staff. As per standard of care, VIA+ women would be referred for follow-up care. Improving attendance of follow-up care is a primary objective of the study.

As part of the evaluation, we will:

- Assess mIVAA for image quality, network stability, challenges with image transmission, ability and time to reach experts and receive feedback from experts (two-way communication between health providers).
- Assess provider feedback and satisfaction from the use of mIVAA
- Document timing of providing women who screen positive on VIA with colposcopist evaluation of cervical images and management plans based on digital cervical images, and follow-up appointment for confirmatory colposcopy and biopsy.
- Collect survey data from women to identify correlates of follow-up.
- Document rate of follow-up care among women who are referred for management and treatment.
- Abstract historical data from medical records including: clinical notes on Pap results; for women who screened positive on VIA, rates of attending follow-up appointments and colposcopist evaluation; and possible reasons for not attending follow-up appointments.

Study activities with enrolled women

Approximately 200 women from up to 5 mobile units who screen positive on VIA will be enrolled.

First, we anticipate that we will need to consent and screen for eligibility approximately 2,000 women getting cancer screening at La Liga mobile units in order to enroll approximately 200 women who screen positive on their VIA screening and who have consented. This estimate is based on current VIA positivity rates of approximately 10%.

Women who consent may complete the following study activities:

Activity 1: Allow mIVAA to be used as part of VIA for cervical cancer screening.

Activity 2: Complete a survey. The survey will include:

- Socio-demographic characteristics, reproductive and clinical history, knowledge of cervical cancer, social support, household decision making, experience with screening, barriers and facilitators to attending follow-up clinical evaluations, mobile phone use and feedback on the intervention.

- Contact information (including primary and back-up mobile phone numbers) will be collected in addition to information on mobile phone ownership and use.

The survey will be administered electronically, or on paper if not available electronically, by a trained data collector using Qualtrics, REDCap or another offline app based on a mobile device. Surveys will be conducted in Spanish. Surveys may include open-ended questions that may be audio recorded, transcribed and translated to English for analysis and inclusion in any publications.

Activity 3: Allow review of medical records to assess follow-up and correlates of follow-up.

Activity 4: Complete a few questions about motivators or barriers to follow-up clinical evaluation.

The interview will be conducted by phone or in person and will administered electronically, or on paper if not available electronically, by a trained data collector using Qualtrics, REDCap or another offline app based on a mobile device. Surveys will be conducted in Spanish. The interview will include open-ended questions that may be audio recorded, transcribed and translated to English for analysis and inclusion in any publications.

Study activities with enrolled La Liga health providers:

- The same providers and administrative staff who enrolled for aim 1 will continue with activities for aim 2. We will conduct a training/orientation to inform them of any changes to mIVAA and inform them of the flow of research activities for aim 2.

Midwives with assistance from nurse technicians

Activity 1: Use mIVAA system during VIA for consenting women

- Midwives and nurse technicians will proceed with usual care with all women who register for a cancer screening exam.
- Research staff will provide the nurse technician or midwife with a green card in the medical record that indicates that a woman has consented for the study. Research staff will verify that the name of the patient on the clinical history form/medical record matches the name on the consent.

If an enrolled woman screens positive on the VIA, the midwife will:

- Capture cervical images using mIVAA system.
- Enter relevant clinical notes in mIVAA.
- Use mIVAA to send images of the cervix, VIA result and clinical notes for each patient to participating expert colposcopist for evaluation of these images to evaluate the need for a management plan,
- For women with a positive VIA or suspicion of cancer, follow-up clinical evaluation with a colposcopist in a La Liga detection center will be scheduled

based on feedback received from these same colposcopists as per La Liga's institutional protocols.

If a consented woman screens negative (without suspected lesions or suspicion of cancer) on the VIA or does not have a VIA screen:

- Midwife will document on a screening eligibility form, whether or not she completed a VIA screen for the patient and the VIA result.
- Research staff will inform the woman that she is not eligible for the study, and therefore she will not continue with further activities.
- Further referrals may be made according to standard of care based on Pap results when available, and if positive.

Activity 2: Provide feedback on the use of mIVAA through a survey, brief interviews, and/or an individual or group interview. Discussions will assess feedback and satisfaction with the mIVAA system.

Study staff will document in Spanish La Liga provider and staff feedback, and translate to English for analysis and inclusion in any publications. Interviews may be audio recorded, transcribed and translated.

Colposcopists

Activity 1: Use mIVAA system to access patient cervical screening documentation and communicate with midwives and staff at mobile unit.

For each patient, an expert colposcopist will:

- Provide feedback on whether the patient should have a follow-up clinical evaluation.
- Rate quality of cervical image.

Activity 2: Provide feedback on the use of mIVAA through a survey, brief interviews, and/or an individual or group interview. Discussions will assess feedback and satisfaction with the mIVAA system.

Study staff will document in Spanish La Liga provider and staff feedback, and translate to English for analysis and inclusion in any publications. Interviews may be audio recorded, transcribed and translated.

Medical record abstraction for historical controls

For the control group, data from 200 women who received cervical cancer screening at a mobile unit prior to use of mIVAA will be abstracted from medical records to assess follow-up and correlates of follow-up.

6. Selection of Subjects:

The following groups of participants will be included in the study:

1. Health providers (for aim 1 & 2): Approximately 18 health providers and administrative staff identified in consultation with La Liga will participate in the study, based on the following eligibility criteria.

   Inclusion criteria:
   - Age 18 or older
   - Must be a health provider (Midwives, nurse technicians, expert colposcopists, etc.) or administrative staff working in La Liga clinics and/or staffing the mobile units.
   - Agree to be audio recorded

   Exclusion criteria:
   - Does not understand the study purpose and details
   - Is not willing to sign an informed consent

2. Women for Aim 1: Approximately 102 women who are screened for cervical cancer in the mobile units will be approached for participation in the study, based on the following eligibility criteria.

   Inclusion criteria:
   - Age 18 or older
   - Patients coming to the mobile unit for cervical cancer screening
   - Willing to allow use of mIVAA during screening with VIA
   - Agree to be audio recorded

   Exclusion criteria:
   - Currently pregnant
   - History of hysterectomy
   - Does not understand the study purpose and details
   - Is not willing to sign an informed consent

3. Women for Aim 2: Approximately 2,000 women will be approached for participation and consented to allow eligibility screening (eligibility criteria listed below) for participation in the study. Approximately 200 women who screen VIA+ will continue their participation in the study.

   Inclusion criteria:
   - Age 18 or older
   - Patients coming to the mobile unit for cervical cancer screening
   - Screen-positive on the VIA
   - Willing to allow use of mIVAA during screening with VIA
   - Agree to be audio recorded

   Exclusion criteria:
   - Currently pregnant
   - History of hysterectomy
   - Does not understand the study purpose and details
   - Is not willing to sign an informed consent

7. Subject Recruitment & Compensation:

This study does not include Duke University Health System (DUHS) patients.

La Liga and Duke's research staff will be trained how to recruit study participants; conduct eligibility screening; and conduct the informed consent. A study coordinator or data collector/research assistant will conduct recruitment, consenting, screening, and data collection.

For all participants (La Liga health providers, administrative staff, and women), consenting process will be conducted in a private setting prior to screening and enrollment. No identifying information will be collected prior to consent, however, we will keep a record of the number of staff and women approached and, if applicable, reasons for ineligibility or refusal when provided by the prospective participants.

Recruitment

Health providers:
The site investigator and coordinators at La Liga will identify health providers interested in participating in the study.

Women (Aim 1 & 2):
Research staff will approach women coming to the mobile unit for cervical cancer screening. Depending on the flow of patients at La Liga mobile units, on any given day, research staff will either recruit women individually or in groups. If there are multiple women waiting for their cancer screening exam, staff may introduce the study to the group of women. If there are few women waiting, staff may present the information one-on-one. Staff will describe eligibility criteria and what is entailed in participating in the study. Study staff may also use a digital presentation of the consent to be viewed on a tablet which would include the consent text and audio recording of the text. This would be help reduce the amount of time that an interested woman would need to wait. After viewing the digital presentation, staff would answer all questions and review key points with each individual woman.

Staff will consent all interested women individually and then assess eligibility based on criteria specified above.

Recruitment locations may include:

- All areas where the five La Liga mobile units conduct campaigns (San Juan Lurigancho, San Juan de Miraflores, Comas, Carabayllo, Ventanilla, Puente Piedra, among others).
- La Liga's detection centers (Pueblo Libre, Cercado de Lima)

Compensation (compensation amounts are based on Peruvian input).

In consultation with La Liga, appropriate compensation was determined for La Liga health providers and administrative staff, and for women who participate in the study. Since provider and staff participation in the study will require time beyond their work schedule they will be compensated for participation in research activities. Payment to women participants will be made in cash, given in an envelope at the end of the survey and to providers/staff deposited through the employee payroll system or through other payment process.

- Expert colposcopist will receive compensation for reviewing cervical images and clinical notes, s/20 per patient (about $6.00).
- La Liga health providers and administrative staff who complete a survey will receive s/10 per survey (about $3.00).
- La Liga health providers and administrative staff who complete in-depth interview (or group meeting) will receive s/20 per interview (about $6.00).

Since women's participation in the study will require time beyond their regular appointment for cancer screening they will be compensated for participation in research activities.

- Women who complete a survey will receive s/10 (about $3.00).

Participant (women patients, La Liga staff and health providers) names, tax information and contact information may be shared with La Liga financial staff to comply with Peruvian legal requirements for reporting compensation payments. Financial staff will maintain study participation and personal information confidential.

8. Subject's Capacity to Give Legally Effective Consent:

The study will only include participants who have the capacity to give legally effective consent. In addition, the study population does not include any minors.

9. Consent Process

The consent process will be carried out by qualified research staff hired by La Liga for this study and by research staff at Duke University. Staff will conduct the consent in a place that is away from other people so that participants' privacy can be maintained. The informed consent process will be conducted in Spanish. All details of the study will be explained to each recruited participant, including the study purpose, the selection criteria, duration of participation, risks, benefits, confidentiality and disclosure issues. We will emphasize the voluntary nature of the study, that there is no penalty for withdrawing from the study at any time, and who to call with questions and concerns. Research staff will be trained to pause and solicit questions at various points during the consent process. The informed consent process is expected to take approximately 20 minutes.

<u>Description of the consent process</u>
There are three parts to the consenting process at the time of enrollment.

1) Review of the consent content.
2) Respond to participant questions regarding the study and the consent.
3) Acquire consent with a signature from the participant.

Part 1 - Review of the content of the consent
Review of the consent will be completed in one of several ways. All participants will receive a paper copy of the consent to review. As a supplement, research staff may:

a. Meet individually with interested women or health providers and administrative staff to review the study and consent form information.
b. Provide audio recording and/or digital images and text of the written consent.

c. Present to a group of potential participants information covered in the written consent. When this would be appropriate includes if several women are waiting together at the mobile unit and are interested in the study, staff would share information regarding the study to these women together.

Part 2 - Response to participant questions regarding the study and the consent
Research staff will respond to participant question individually as well as to questions if asked during a group introduction. Regardless of how a participant reviews the consent content (Part 1), research staff will ask that all participants meet in a private setting with research staff to ask questions.

Prior to signing, participants will be given the opportunity to ask questions and have them answered to their satisfaction. They will be encouraged to take the time they need to consider study participation and to ask questions.

Women seeking cancer screening will be recruited on the same day as they come to the mobile unit and will need to be consented prior to their exam with the midwife. Therefore, in practical terms women will have limited time to consider their study participation. They will be encouraged to take the time they need and to ask questions. This protocol is necessary such that the midwife can use mIVAA at the time of the woman's cervical cancer screening. The midwife will only obtain images with mIVAA from women who have provided consent.

Part 3 - Acquire consent with a signature from the participant
Written consent will be obtained from all study participants prior to any study participation, including eligibility screening. Only those participants providing written informed consent will be enrolled in the study. For aim 2, the majority of the 2,000 women consented will not be eligible (VIA negative) and therefore will not continue their participation past the eligibility screening. Participants who are illiterate and those with minimal literacy will have the Spanish consent form verbally summarized by the study staff. The participant will provide their thumbprint on the consent. A literate witness will be asked to observe the consent form discussion and sign the consent form.

A signed copy of the consent form will be given to study participants. Participants will have contact information for the principal investigator, the study coordinator and the ethics board to contact in the event of any question or concern. A second signed copy of the signed consent will be scanned and stored electronically in research records, then saved in the patient's medical record at La Liga. Research staff will document the study consent in the medical record for each La Liga patient who is enrolled in the study. The consent form may be stored in the paper medical record at La Liga. Consent records will be maintained by La Liga.

To minimize the possibility of coercion or undue influence, participants will be informed of all aspects of the study and questions will be answered. The voluntary nature of the study will be emphasized and that the participant may withdraw at any time for any reason. Women getting cancer screening who are being consented will be told that their decision to accept or decline participation in the study will not impact their ability to receive health services provided by La Liga. Health providers and administrative staff

who are being consented will be assured that there will be no penalty or impact on their employment if they refuse to answer and/or skip any questions in the interviews.

Historical controls: For women whose records are used as a historical control, we will be unable to conduct informed consent. We will request a waiver of consent from the Duke IRB, as is required by Duke.

10. Risk/Benefit Assessment:

Risks:
There are three potential risks of the study: loss of confidentiality, discomfort with questions, and, for women at mobile units only, the unlikely risk associated with placing the Pocket, a digital image capture device, within the vaginal canal.

Loss of confidentiality
There is always risk associated with loss of confidentiality for participants in a study. However, this risk of loss of confidentiality will be minimized through rigorous training of study personnel, use of study identifiers to make data de-identified unless linked to personal identifiers, restricting access to identifiable data, and publishing only aggregate (not individual-level) statistical summaries that limit re-identification of participants.

Discomfort with questions
There is also the possibility that some questions might upset or create discomfort in participants if topics are considered sensitive. Women at mobile units may be upset by questions about personal experiences with cervical cancer screening and their belief about procedures. Research staff will look for signs of discomfort and assure participants that they are not being judged, that answers will be kept confidential, and that they can refused to answer any question.

Physical risks
For La Liga health providers and administrative staff there are no physical risks from participation in the study.

For women who get screened with mIVAA, when cervical images are captured using the mobile phone camera, there will be no physical risk. Alternate digital capture devices, such as the mobile phone, will be used from outside the vaginal opening.

For women who get screened with mIVAA, when cervical images are captured using the Pocket, there is an unlikely risk due to the use of the Pocket within the vaginal canal. The Pocket is not intended to come in contact with the vagina or the cervix rather it may touch the speculum that is used during the vaginal exam. In the event that the Pocket comes in contact with the vaginal walls, the risk of injury is unlikely since the Pocket does not emit any heat or electricity because it has no power source of its own. However, theoretically the pocket could become a conductor for an electrical charge while plugged into a laptop. That said, there are redundant safety systems in place both with the 5Volt USB cable (very difficult to get a meaningful shock from a USB) and a fused/fault interrupter on the power supply for the laptop, depending on type of laptop the current and voltage are limited by the 'brick'. The test lab that did IEC 60601 testing required listing as a possible complication of the Pocket to be electric shock because it is an electrical device. However, the risk is mitigated since the inner electronics of the Pocket are completely encased in insulating materials (e.g. ABS plastic and glass for the

window), which mitigate the risk for electric shock and vascular injury.

The device does not emit ultraviolet light and emits only visible light from 400 to 700 nm, which fulfills the ANSI/IESNA RP-27 Photobiological Safety Standards. The device is electrically isolated from the body. Heating of the tissue due to light exposure is unlikely because the heat generated by the light of the Pocket should be negligible and is less than the heat generated by conventional halogen illumination sources used in traditional clinical colposcopes. The Pocket stays under the IEC 60601 temperature limit, which for direct contact with human skin (<10 minutes duration) is to remain under 48C. In fact, the Pocket meets the more stringent criteria of remaining under 43C for direct contact with human skin for a duration of >10 minutes. Furthermore, given the short duration of use of Pocket within the vagina with each patient, we do not anticipate any adverse events.

The Pocket is an FDA approved device. The Pocket's outer shell is made out of medical grade ABS plastic. Medical grade and biocompatible adhesives (Loctite 4011) are used to seal the device and prevent infiltration of water and bodily fluids. The edges of the probe face are also chamfered to avoid a sharp edge so there should be minimal risk of abrasion caused by the probe with the pressure exerted.

Finally, the Pocket will undergo cleaning and high-level disinfection per the instructions for use prior to use in a patient. The reprocessing procedures have been validated by an independent third-party laboratory, Nelson Labs, and found to be a safe and effective way of infection control.

Benefits:
Women receiving the intervention may be referred to follow-up care sooner than those who do not receive the intervention (standard of care).

For participants who are La Liga health providers or administrative staff, there are no direct benefits for taking part in the study. However, they may feel a sense of satisfaction in helping inform a process that may improve future cancer screening and treatment programs (for the community), provide faster care to patients, improve patient follow-up care, and reduce deaths from this disease in the future.

11. Costs to the Subject:

There are no costs to the participants of this study.

12. Data Analysis & Statistical Considerations:

Sample size justification: With the proposed sample size of 200 women/group, we are powered to detect a difference of 13.5% or higher in loss to follow-up with 80% power at 5% level of significance. This difference of 13.5% corresponds to an odds ratio around 1.8, or a Cohen's h around 28%. For the in-depth interviews, sample size reflects number of interviews required to achieve saturation of themes. Namey et.al estimate that 8-16 interviews are needed to achieve 80-90% saturation, respectively.

Statistical analysis plan:
Quantitative data analysis will be conducted using STATA statistical software, SAS, JMP and/or MS Excel. Descriptive statistics will be generated to assess and quantify statistical properties of all the relevant variables (mean, median, standard deviation,

etc.). The difference in the proportion of women attending follow-up clinical visits between the two arms will be calculated to estimate the intervention effect at 5% level of significance level. Baseline covariates will be modeled using multivariable logistic regression to determine patient characteristics associated with loss-to-follow-up. Measures of predictive power (like R-square) and goodness of fit tests (like the Pearson chi-square) will be used to assess the fit of the regression model.

As part of the qualitative analysis plan, we will conduct applied thematic analysis on the observation notes and interview transcripts. Electronic files will be uploaded into QSR NVivo--software that supports coding and finer level re-coding of text data that enables researchers to explore how concepts fit by developing and modifying a hierarchical coding index. Thematic analysis will be conducted via an iterative process of data collection and analysis that utilizes four interrelated steps: reading; coding; data display; and data reduction. The team will use a codebook of a priori, structural codes based on the interview guide, and then a second round of coding, i.e. content coding, will be conducted to identify additional themes, ideas, or concepts. Twenty percent of transcripts will be coded by 2 team members, inter-rater reliability assessed, and discussions held to resolve coding discrepancies. We will create a summary of each interview and look across interviews for commonly named problems and solutions for each step of image acquisition, transfer, and interpretation.

Data will be summarized in the following areas: Core functionality (including expectations, and communication formats), data analytics, storage and availability, (3) Security, hosting and privacy, 4) Mobile delivery platform, 5) Monitoring and maintenance, 6) Hardware, equipment, power and connectivity needs.

In interviews with women in aim 1 and 2, we will assess satisfaction with the (a) overall experience, (b) timeliness of evaluation of cervical images and management, and (c) any barriers to attending future clinical visits.

Evaluation outcomes are summarized in table below.

Primary outcome - Efficacy

- Percentage of referred women who are lost to follow-up in intervention versus control arm

Secondary outcomes - Process

- Percentage of women approached who consented to participate in study
- Percentage of women approached who refused to participate in study
- Percentage of VIA screened women who are VIA+ (by study arm)
- Average # of days from screening to when a follow-up appointment is scheduled (by study arm)
- Percentage of women who were screened using mIVAA
- Percentage of mIVAA screened women with suspected cancer or pre-cancer by midwife
- Percentage of mIVAA screened women with suspected cancer or pre-cancer by expert
- Average # of days from screening to when expert enters feedback using mIVAA

- Percentage of mIVAA screened women with expert feedback within 0-7 days of mIVAA screening date
- Concordance between midwife and colposcopist on women with suspected cancer or pre-cancer as measured by:
    - Number of women screened positive by midwife
    - Number of women screened positive by expert colposcopist

System outcomes

- Average # of attempts per woman before a readable image is obtained by midwife
- Percentage of mIVAA screened women with at least 1 image rated as readable by expert
- Number of instances of mIVAA failure
- Number of instances of network failure

13. Data & Safety Monitoring:

The risks from participation in the study are considered minimal and commensurate with getting screened with routine methods of cervical cancer screening in Peru such as Pap smears. While no formal data and safety monitoring board is established for this study, study personnel will be instructed to report any unexpected and study-related adverse event to the local study PI in Peru, and Duke PI immediately.

14. Privacy, Data Storage & Confidentiality

Privacy during data collection:
Surveys and interviews will be conducted in mutually agreed upon locations where participants' privacy can be ensured.

Identifying information collected
The study will collect identifying information such as names, dates of birth, and mobile phone numbers to enable the prospective tracking of participants and pulling of medical records. In addition, for women enrolled at the mobile units, data from medical record will be abstracted to measure study outcomes. Mobile phone numbers provided by the participants will be used for any study-related communication.

The study will collect identification information only from health professionals and La Liga personnel, such as participants' names, dates of birth, and mobile phone numbers for reaching out to participants to complete study activities.

Data storage and confidentiality:
Specific actions to maintain confidentiality will include:

- All enrolled participants will be assigned study identification (ID) numbers to help protect their identity. Only study IDs will be recorded and stored alongside participants' survey responses, observation notes, audio files, interview transcriptions and medical record abstraction data.

- We will not collect DNI (Peruvian National Identification Document) or US social security numbers (SSN), except if required for payment of compensation.
- Enrollment logs, paper consent forms, a contact information logs will be the only linkages between study IDs and participants' identifiable data. Enrollment and contact logs will be stored separately from other record forms containing collected research data.
- Any data collected on paper will be stored in locked cabinets in secure offices.
- Interviews will be audio recorded on encrypted devices. When using Zoom's audio recording function, files will only be recorded to the local computer or device, not to the cloud. Audio recording files will be stored on encrypted device, Duke's box.com and/or Duke's secure servers. Identifiable information will be removed from audio-recording notes and transcriptions.
- Since this study is conducted in partnership between La Liga and Duke University, all study data collected by La Liga will be shared with Duke University. Data and files that may be shared with authorized study personnel at Duke include but are not limited to copies of study logs (including the enrollment log) to keep track of participant recruitment and study progress; eligibility screening data; scans of consent forms, interview/observation notes and other study paper documents; transcriptions of audio recordings; and data files and audio recordings.
- Electronic records containing identifiable participant data will be stored on secure applications and/or servers administered by La Liga (in Peru) and Duke University's Office of Technology Services (in the United States). Electronic records containing participant data, identified by a study ID, will also be stored on secure applications and/or servers administered by Medical Innovation & Technology (Peru). Electronic data transferred between Peru and the United States will be sent via Duke centrally administered Box account created by Toolkits; Box is HIPAA-compliant and encrypts files at rest and in transit. Permissions for the Box folder are provided centrally by Duke Office of Information Technology and approved by the study PIs. Data stored in mIVAA by MI&T will be transferred to La Liga and Duke via secure website. Data may be collected and shared via Qualtrics, REDCap or other secure and approved survey platforms/data capture system. All data will only be accessed by authorized study staff.
- La Liga health providers and administrative staff will capture and store digital images in mIVAA. Study IDs, personal health and clinical information will also be documented in mIVAA. mIVAA will be used through an App on password protected mobile devices such as a tablet(s) and/or in a browser through a web page on a mobile phone(s). Information collected and shared in mIVAA will be securely stored on servers managed by Peru-based Medical Innovation & Technology, developers of mIVAA. mIVAA data will be store in cloud storage, encrypted for MI&T's use only and transferred to La Liga and Duke via secure website. Data will be shared between La Liga health providers and administrative staff as well as research staff at La Liga and Duke. In the future, if mIVAA is linked to La Liga's electronic medical record platform (WebLiga), clinical data collected through mIVAA may be transferred to WebLiga.
- Long-term storage of data will be on a secure drive at Duke.
- To meet federal and state requirements, the research records may need to be reviewed by the Duke University Health System or a Peruvian IRB. If this information is disclosed to the external reviewers for audit purposes, it may be disclosed by them and cannot be covered by federal privacy regulations.

- Study documents and data containing identifiable information will be kept for at least six years after the study is completed. Audio files will be deleted once all analyses have been completed and published. All other data will be retained indefinitely.
- A description of this research study will be available on https://clinicaltrials.gov/ as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.
- In the informed consent, participants will be told that they will have access to results of the study that will be published in an open access journal so that all participants have access at no cost. By agreeing to be in the study, participants consent to the publication and presentation of study results.
- All the data in the study will be treated in accordance with the Peruvian Law of Data Protection Nº 29733, and all other laws and regulations that are applicable. La Liga, the coordinating center for the study, will be responsible for ensuring the protection of identifiable information.
- In publications or other materials created for study dissemination, only aggregate statistics will be reported and participants will not be named.