Closing the gap between identification and treatment of cervical abnormalities in Lima, Perú through integraton of pocket colposcopy, telemedicine and visual counseling

Document Date: 10/10/2023

NCT05340322

Randomized Controlled Trial for the evaluation of pocket colposcopes and visual counseling for improvement in follow-up and treatment of HPV positive women in Peru: HOPE treatment trial.

I. BACKGROUND

Globally each year, there are approximately 570,000 new cases of invasive cervical cancer (CC) and 300,000 cervical cancer-related deaths. More than 90% of those deaths occur in low- and middle-income countries (LMICs)[1]. The discovery of the human papilloma virus (HPV) as the etiological factor for CC has opened up several opportunities for prevention, screening, and therapy[2]. Currently, there are HPV vaccines available (Gardasil, Gardasil 9, and Cervarix) which are prophylactic in nature and derived from adjuvanted L1-based virus-like particles of HPV, and these have proven to be very safe and efficacious in preventing cervical cancer[3]. However, vaccine coverage is still limited, especially in those countries with the higher burden of disease[4]. Cytology-based detection programs have failed to reduce the incidence of CC in most countries since they are complex to implement adequately, and the cytological method, the Papanicolaou (PAP), has limited sensitivity and low reproducibility. New screening strategies have appeared, especially for LMICs. Visual inspection with acetic acid (VIA) for example, uses 5% acetic acid applied to the cervix. With this procedure, the abnormal epithelium (dysplastic) turns white and can be detected with the naked eye. However, the sensitivity of VIA is similar to a Pap smear and varies among evaluators[5,6]. Most CC cases are caused by persistent infection with high-risk human papillomavirus (hr-HPV) and disease progression from HPV infection to micro-invasive cervical cancer is typically slow (over a decade or more)[7,8,9]. Another alternative for the screening recommended by the World Health Organization (WHO) is the detection of hr-HPV DNA starting at age 30 and regularly afterwards ever three to five years[1,10,11]. Studies have shown that molecular HPV tests are more effective than VIA and PAP.[12,13] Some countries, such as Australia, with well-established high-quality Pap smear programs have changed their programs to molecular HPV testing.

There have been significant global efforts to ramp up screening rates to facilitate early identification of cervical cancer and its precursors. However, screening is not enough. The traditional approach for following up screen-positive woman includes a visit to a referral setting to undergo a confirmatory test which typically needs to be performed by

an expert gynecologist, who will visualize the cervix directly (VIA), or, if available, with a colposcope, which is an expensive low-power microscope. If an abnormality is found, it is biopsied and submitted for pathology. A positive diagnosis is available weeks later and requires yet another visit for treatment. Unfortunately, in LMICs, there are often not enough expert gynecologists, colposcopes, or treatment equipment, and a woman may come for the first visit, but may not necessarily understand the importance of returning for results or completing the treatment cascade. In these cases, the opportunity of saving her from cervical cancer is lost.

Recognizing these barriers, WHO has endorsed recommendations for a simple screen-and-treat strategy, acknowledging that increased access to treatment with simpler protocols may result in overtreatment. In May 2018, WHO Director-General, Dr. Tedros Ghebreyesus, announced a call to action to eliminate cervical cancer globally[14]. However, unless we can ensure we have the means for accurate screening, affordable treatment, technology that does not require an expert gynecologist, and education for women that engages them in the process so that they understand the importance of completing the treatment cascade, we will not succeed in the goal of elimination.

In this study, we propose the implementation of a new low-cost technology, the Pocket Colposcope, as a tool to improve the diagnostic capabilities for cervical cancer screening and treatment of non-expert health providers in Peru, coupled with improved counseling to enhance the women's experience during the examination and to increase adherence to the completion of care.

1.1 Cervical Cancer in Peru

Peru is a Latin American country with a population of 32 million, of which approximately 11 million are women 15 years and older. In Peru, one woman dies every five hours from cervical cancer. Annually, it is estimated that at least 4,100 women are diagnosed with cervical cancer, 50% of which die due to late diagnosis[15]. According to international sources, cervical cancer ranks as the second most frequent cancer among Peruvian women. This data is based on the cancer registry, which mainly collects data from Lima, Peru, the capital city. Unpublished data from the Ministry of Health (MOH) shows that outside of Lima, cervical is the most frequent and fatal cancer in women. It is estimated

that 6.6% of women in the general population have HPV16/HPV18 and at least 66% of invasive cancers are attributed to these forms of HPV.

In 2011, HPV vaccination efforts for young girls between the ages of nine to eleven began. However, only in 2016 did coverage increase substantially.

Most of the screening for cervical cancer in Peru has been done historically by cytology (Pap smears) at health centers free of charge. In a study that we conducted in 20 cities in Peru, including upwards of 6,000 women between the ages of 18 and 29, we found that only 30.9% had ever had a PAP, with even lower rates in the rainforest and mountainous regions[16]. These data are consistent with other reports of only 53.9% of women between 25 and 59 years of age who report having had a PAP in the last three years[15]. There are also data on the gaps in the delivery of results and the follow-up of positive cases: only 25% of women with PAP abnormalities would receive adequate and timely management[17]. This same study showed that the PAP had a sensitivity of just 42.5% to detect Carcinoma, which embodied another serious problem: the low sensitivity of PAP which could be explained by the multiple steps in the processing of samples for this test that can fail. Another study in Peru showed that fear and embarrassment of being "examined and exposed", along with lack of knowledge were the main barriers identified for not getting Pap smears[18].

1.2 HOPE: A new model for cervical cancer screening in Peru

With funding from Grand Challenges Canada in 2015, we started the implementation and evaluation of the viability and performance of a new model for the detection of CC in Peru. HOPE included participation of women of the community as agents of change (the HOPE Ladies), the use of self-sampling with molecular hr-HPV-testing (CareHPV®), and the use of technology to ensure results reached women (SMS, internet) and that treatment was provided. This was a proof-of-concept grant with a duration of eighteen months. There were more than 2,000 tests distributed free-of-charge and at least two-thirds of the women had never had a PAP screening. Self-sampling was very well accepted. Most women (74.2%) were satisfied or very satisfied with the program. The majority (68%) preferred self-sampling over physician-sample collection at the health center. Almost all (96.9%) said they would choose to participate in the same program again and 99% said

that they would recommend the program to a friend[19]. HPV Positive women were referred for treatment to the health center, and the main limitation was the lack of a health center equipped and with personnel trained to offer treatment. For the study, we were able to implement treatment for cervical cancer at the Ventanilla local network by training a colposcopist and by donating a colposcope and equipment for cryotherapy.

1.3 New guidelines for cervical cancer screening in Peru and the National Plan for Cervical Cancer 2017-2021

After national and international consultations in 2016, the new "Guidelines for Prevention and Management of Cervical Cancer" were released by the MOH[20]. These guidelines summarized international experiences and the local findings with HOPE, and they incorporated screening with VIA and HPV molecular testing, self-sampling between other things. In 2017, the MOH published the National Plan for Prevention and Control of Cervical Cancer in Peru 2017-2021. The plan included an assessment of the current situation, the needs and gaps, and a plan for procurement of HPV tests, colposcopes, cryotherapy equipment, additional equipment for surgical procedures, training of professionals, and implementation of an information system for around $30 million over the course of the five year period. With funding from the Binational Plan: Peru-Ecuador in early 2018, the implementation of HPV self-testing started in the north of Peru on the border between the two countries. More than 8,000 women were screened, and screen-positive women were treated.

Unfortunately, the MOH now is focusing only on training of health professionals to perform VIA screening.

1.4 HOPE Peru: Women helping women fight cervical cancer

Based on the success of HOPE, we applied for additional funding to continue improving this model. In hopes of securing sustainability, we proposed the creation of the first Peruvian public health social enterprise aiming to improve access to healthcare technologies for communities with the involvement of women from the communities. HOPE's first project seeks to market the HPV self-testing (CareHPV®), to gain commitment, and to promote a culture of cervical cancer prevention. The tests will be sold to high-income women to create a sustainable platform to offer free testing to women with

less resources involving training of community women (as the “HOPE Ladies”). The project is based on four key pillars: (1) the use of molecular HPV tests for screening, with better sensitivity and affordability than PAP tests; (2) the use of self-collected vaginal samples, which offers an opportunity to increase screening coverage; (3) community women teaching other women about cervical cancer and how to apply the HPV self-test; and (4) use of affordable technology and development of an informatics platform to collect data for the distribution of molecular HPV screening tests, results, follow-up of women screened, and the transmission of reminders through text messages (SMS) for clinic visits, along with an internet information platform and hot-line. Additionally, HOPE is promoting the concepts of timely detection and saving another life through the purchase of a kit, since for each test sold, we will be able to reach a woman who otherwise would not likely be tested for cervical cancer.

The distribution model relies on “HOPE Ladies”, women from marginalized communities who disseminate information on HPV door-to-door in their communities, and then provide screening kits for convenient and relatively comfortable self-testing for free or at a semi-subsidized price, depending on the region. The HOPE Ladies receive an incentive for every test distributed. This project is in the phase of transition to scale and has received funding for Grand Challenges Canada for up to 1 million CAD for the next three years, for which it required matching funding. So far, HOPE has received funds from Fogarty NIH, the Center for Global Health, the University of Manitoba, Crowdfunding, United for Health Innovation (UfHI), Global Coalition Against Cancer, and Qiagen.

In the social component, women are referred to the MOH health centers. We are coordinating with the MOH and regional governments to train health professionals on HPV testing and cervical cancer screening according WHO guidelines. HOPE aims to scale up progressively across the country over the next three years, but we need to address the limitation of an inadequate number of trained professionals and health centers with capacities to manage women who have been screened and are HPV positive.

1.5 New technologies to improve cervical cancer see-and-treat strategy

a. Screening: Pocket Colposcope

The Point-of-Care Pocket Colposcope was designed as a portable, cost-effective alternative to high-end colposcopes used in hospital settings. Rather than requiring high-resolution cameras and optics as in the high-end colposcopes, the pocket colposcope's design enables insertion with a speculum to take close-up images of the cervix (three centimeters rather than thirty centimeters) which provides images of comparable quality for a fraction of the cost. Stakeholder interviews and surveys in a variety of countries were administered to ensure that the technology was a good fit in a multitude of contexts. By bringing the ability to perform colposcopy exams to a primary care setting, we are creating an avenue for access to cervical cancer screening for women in LMICs who are most vulnerable to this preventable disease.

The Pocket Colposcope currently has FDA 510k clearance and is actively used around the globe. We are in the process of manufacturing the device at a larger scale with intentions of obtaining a CE mark for global acceptance.

b. Treatment: Thermocoagulation

In the 1990's Peru was one of the first countries to introduce cryotherapy for treatment of pre-cancerous lesions of the uterine cervix; as part of that experience many challenges and limitations were found with cryotherapy. It was wrongly assumed that procurement and distribution of the gas refrigerant could be easier than having a electricity-powered medical device, but the experience in Peru and globally shows that gas is usually expensive with limited availability in gas plants located in very few sites in the country, and transportation of the gas tanks is challenging. Additionally, cryotherapy units could be obstructed during the procedure, and the final temperature in the cryo tip is very variable.

In recent years the global attention turned to thermal-coagulation, an electricity-powered device used for 50 years in United Kingdom and some countries in Asia; the cure rates of thermal ablation in those settings is around 90%, better than cryotherapy, and comparable to LEEP. In addition, the thermal ablation units can be powered with rechargeable batteries similar to cell phones, and very light for transportation (1 Kg) and they do not need any supplies to work. In May 2019 the WHO approved the new guidelines for use of thermal ablation, recommending thermal ablation for the treatment of pre-cancerous lesions of the uterine cervix.

II. AIMS

The continuum of care is one of the main challenges to ensure effective actions against cervical cancer. We are proposing to leverage what we are doing within the project “HOPE Peru: Women helping women fight cervical cancer” and improving treatment at the health center for those women found to be HPV(+). Our goal is to demonstrate that the combination of HPV self-sampling with the participation of community women, the Pocket colposcope and the thermocoagulator will yield a high proportion of HPV positive women who complete treatment and follow-up care.

Main Aim

To perform a demonstration trial on the feasibility of HPV self-sampling as a way to mobilize women to get to the next level of care and the feasibility of a “see and treat” strategy in a community health setting and the effectiveness of the Pocket colposcope and the thermocoagulator to improve the rates of treatment and follow up care to women who have a positive HPV results.

Specific Aims

Aim # 1: To assess the proportion of HPV positive women who go to a health center for treatment, are examined with the Pocket Colposcope and if required, received Thermocoagulation.

Aim # 2: To assess the proportion of HPV positive women that receive treatment and a 6 month follow up visit.

Aim #3: To evaluate feasibility, acceptability, and ease of use of the Pocket colposcope

Aim #4: To assess the costs, cost-effectiveness, and population health impact of using the pocket Colposcope, and thermocoagulator for cervical cancer treatment.

III. LOGIC MODEL AND FRAMEWORK

Currently, the MOH does not have a follow-up system to track and secure a successful progression of women with a positive screen test to the subsequent steps in the cervical cascade of care. This study will provide the MOH with direct insight into how cervical cancer treatment is offered in standard practice and what can be improved to facilitate the progression along the cascade with the introduction of new technology and counseling.

The cascade of care (also known as the "continuum of care") is a concept used to describe the patient's pathway within the process of receiving care for a disease[23]. The most successful example of its application is within HIV care, and has also been used for TB, hepatitis C infection, other STIs, and more recently, non-communicable diseases such as diabetes. It is increasingly considered a valuable tool for scientific and public health evaluations and interventions; however, it has not been consistently applied to other conditions that might benefit from its use. As we have seen, unless we ensure that every woman at high-risk for cervical cancer, and every woman found to be HPV (+) receives the care she needs, investments in screening are largely lost.

Framework

a. "The Continuum of Care" construct

The construct of the continuum of care derives from the models used in the 1980s and 1990s to understand systems of care within STI and TB. However, only in 2014 did it become more popular in public health research and program evaluation due to its effectiveness in identification of gaps within HIV care and in proposing global goals for controlling the HIV epidemic. Its usefulness mainly lies on the visual representation of the model as a bar graph where eat bar represents the proportion of persons completing each step along the continuum of care of a disease (prevention, diagnosis, linkage to treatment, adherence to treatment or retention, and successful treatment). This bar graph thus helps to identify the losses occurring at each step of the continuum of care[23]. The use of continuum models that reflect longitudinal rather than cross-sectional data may be particularly important for understanding chronic conditions.

The specificities of the continuum, such as the starting point, the endpoint, the steps being considered, or the denominators used for each step, are not clearly defined, and usually vary according to the disease or condition being studied.

In this study, the construct of the continuum of care will be applied for the evaluation of losses within the process of linkage to treatment after a woman receives a positive results from HPV screening until she receives her treatment and has her six month follow-up visit. We will also include the addition of the time required for transitions from one step to the next, and we will track cases to analyze causes of loss within the care cascade, as done in other settings[24].

IV. METHODOLOGY

4.1 Study Design

This is a demonstration/implementation trial.

4.2 Study Setting

The study will be conducted in the Cajamarca region of Peru. The department of Cajamarca is located in the Andean region, at a distance of 856 km from the city of Lima, the capital of Peru. It has 13 provinces and 127 districts, and its provinces are: Cajabamba, Cajamarca, Celendín, Contumazá, Cutervo, Chota, Hualgayoc, Jaén, San Ignacio, San Miguel, San Marcos, San Pablo, and Santa Cruz. It has an area of 33,317 $km^{2.}$ This surface represents 2.6% of the national territory. We aim to work on one of the provinces, which will be chosen in coordination with the Directorate of Health of Cajamarca.

4.3 Study population and sample size

Our main aim is to increase the proportion of women HPV(+) who complete treatment. From previous data collected in the region of Callao, we have found that only around 30% of women found to have an abnormal high-grade PAP completed treatment in 2014, we will explore if there is data available in Cajamarca to calculate comparative historical information regarding rates of treatment of women with positive screening tests.

Power Calculations: With an overall testing population of 10,000 women, assuming 10% HPV positivity, there will be approximately 1,000 HPV positive women. Assuming an uptake rate of 80%, the effective sample size will be 800 HPV(+) women for follow. This will provide us with a precision of 3.5% or better for the estimation of the proportions to be estimated in the two primary outcomes[27]. We are planning to include 10 to 12 health centers in the region, with around 60-80 women HPV(+) to be seen and followed in each center.

4.4 Selection criteria for women

Women between the ages of 30-49 will be offered the HPV self-sampling at the semi-subsidized price. This is the screening age recommended in Peru in the National

Guidelines[20]. The exclusion criteria for the testing will be women with history of hysterectomy or pregnant.

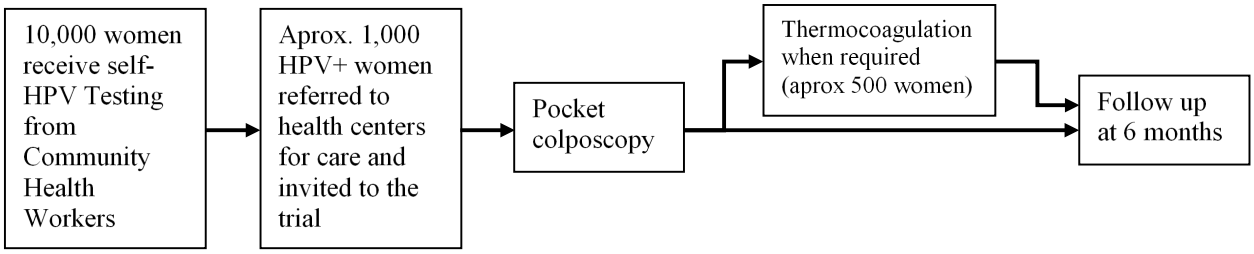
4.5 Data collection

Part of the data will be collected directly on the HOPE informatics platform: system in β version currently in use for the collection of data of logistics of the HPV test distribution, processing, and results. As part of the project we will develop fields for the follow-up of each woman so we will be able to collect the specific data on times. The data for follow-up will be collected directly from the medical records.

For the surveys and qualitative data collection, data will be collected and analyzed accordingly.

Costing data will be collected as part of the baseline data collection and during the implementation. At the end a costing evaluation and cost-effectiveness analysis will be performed

4.6 Study design



10,000 women with HPV self-testing, HPV+ women will be assigned geographically to the centers for management.

V. STUDY PROCEDURES

5.1 Initial Activities

5.1.1 Seek ethical approval of the protocol by Cayetano Heredia University

5.1.2 Initial and working meetings

We will perform a stakeholder assessment at the national and regional level to guide the future meetings and activities within the project. The meetings will be held with the key authorities of the most relevant institutions related with public health and cervical cancer at the national level and with the Regional Authorities of Health in Cajamarca. We will have an initial visit to Cajamarca to define the area where the study will be implemented. It will be important to start sharing the scope of the study and to collect suggestions and contributions. Then meetings will be scheduled throughout the study to report on progress and achievements as the implementation of the intervention evolves to prepare for scaling up and sustainability of the model.

5.1.3 Start the approval process for the entrance of the Pocket colposcope in Peru for research purposes (DIGEMID-INS)

5.1.4 Interview and hire personnel for the study.

5.2 Preparatory activities

5.2.1 Collection of baseline data

We will be collecting baseline data of the health centers and surrounding areas in Cajamarca to plan the future activities. We will collect information about (a) cervical screening in Cajamarca (numbers, providers, supplies, costs, rates of treatment etc.); (b) processes related to cervical cancer screening at health establishments.

5.2.2 Procurement of Thermocoagulators and other supplies

5.2.3 Pocket Colposcope

The Pocket Colposcope currently has 510k clearance and the Center for Global Women's Health Technologies is working with local manufacturing companies in the US to prepare an appropriate shipment.

5.2.4 Software improvement for the Pocket Colposcope

A software for image acquisition and telemedicine capabilities will be implemented. We plan to collect inputs and outputs and to use artificial intelligence to map the relationships between the inputs that lead to health disparities.

5.2.5 Adaptation/Enhancement of the HOPE platform

We will assure that the indicators pertinent to the project will be captured. We will also develop a module for follow up of the cases.

5.2.6 Development of training manuals, videos and other materials for providers who will use the pocket colposcope and the thermocoagulator. These materials should be easily accessible for providers in low-resource clinics.

5.3 Implementation of the local laboratory in Cajamarca for the processing of the HPV tests.

The staff of the DIRESA laboratory will be trained in the processing of HPV tests. We will provide the necessary equipment, implement a quality control system, and set up a connection to the HOPE digital platform.

5.4 Designation of health centers to participate in the trial and training of health providers at Health Centers (intervention and control)

Providers will need to be trained about the study protocol, the national guidelines for cervical cancer, the use of the thermocoagulator, visual counseling, and pocket, and the deployment of equipment.

5.5 Identification and recruitment of women leaders (HOPE Ladies)

Through key informants, data will be collected on groups and activities of women in the community that will allow us to identify potential female “leaders”. The field coordinator will meet in different places (mothers clubs, wawawasi, health center, municipality, etc.) with these women and they will be introduced to the HOPE model and invited to participate. The leaders will receive training specifically on cervical cancer, HPV testing, importance of treatment and for those HOPE ladies in the intervention areas they will learn about the visual counseling. As per the HOPE model, the HOPE Ladies will receive a small incentive (around $1) for each HPV test process from a woman they contacted.

We hope to recruit between 2-4 HOPE Ladies per catchment area of a health center with approximately 24-48 women leaders in total among the 10-12 health centers. We will assess knowledge and address myths about cervical cancer, and we will build strategies to improve the coverage in the community. We will use the materials, contents, and methodology that we have already developed, piloted, and used to train and coach the HOPE Ladies.

5.6 Initiation of the trial, distribution of collection kits to HOPE Ladies, collection of data, and visits to health centers by local monitors

5.7 Data collection and analysis

For the demonstration trial we will collect process information about the distribution of HPV tests and basic information from women who participate in the HPV self-sampling as age, history of previous paps. For the HPV (+) women coming to the centers we will collect data on dates, procedures and results of procedures performed (pocket colposcopy, thermocoagulation, other procedures as leep/hysterectomy). To maintain the confidentiality of the information, we will use codes and keep protected health information separate from the rest of the study data. At the end of the study, personal identifiers will be destroyed. The data will be stored in a specially developed database. The information from the source documents will be reviewed and encrypted. We will use descriptive analysis of the data (process and outcomes) and comparisons with historical information if available and appropriate.

5.9 Process and Impact Measures

Activity	KPI Metric	How to measure metric
Conduct a **baseline** KAP survey of a sample of providers regarding HPV tests and cervical cancer management	Survey performed	Report of survey results
Conduct a baseline assessment of health centers	Assessment performed	Report of assessment

in the Andean Region where we will be working		
Implementation of local laboratory with capabilities to process HPV testing	1 laboratory implemented for HPV testing	Visit Report
Identification of rural health clinics in Andean region of Peru and provision of appropriate equipment (pocket colposcope, thermocoagulators)	# of health clinics (10-12) # of innovations deployed #thermocoagulators deployed (#10-12) # pocket colposcopes deployed (10-12)	Visit reports
Send staff to train HOPE Ladies in the rural regions chosen	# HOPE Ladies trained and registered	HOPE informatics platform
Preparation of tools for the use of pocket colposcope and thermocoagulator	manual of use of pocket colposcope and thermocoagulator finished in Spanish. Video tutorial for the use of pocket colposcope	Reports Tools ready
Send staff to train health providers in the use of pocket colposcope and thermocoagulators	# of health providers trained on the use of pocket colposcope # of health providers using pocket colposcope # of providers using thermocoagulator	Reports
Provide 10,000 HPV self-sampling kits for HOPE ladies to distribute	# of HPV tests distributed to HOPE ladies # of HPV tests correctly returned # of HPV tests processed # of HPV tests positive # of women who receive HPV positive results	HOPE informatics platform

Facilitate women HPV (+) to get treatment at Health centers	% of HPV (+) women coming to the health center for treatment	Monitors/hope ladies HOPE informatics platform
Health centers giving treatment and F/U to HPV (+) women	-% of HPV (+) women completing treatment -% of HPV (+) women completing F/U at 6m	Monitors/ review health centers records (check list) HOPE informatics platform
Conduct a **post-study** evaluation (qualitative, quantitative) of providers to evaluate acceptability and ease of use (pocket colposcope)	# of providers who indicate they would use the Pocket/thermocoagulator regularly for cervical cancer diagnosis/treatment or found it useful	Report of results
Measuring Efficiency	-Average time to come for treatment -Average time to complete treatment	Monitors/ review health centers records (check list) HOPE informatics platform
Cost-effectiveness	Complete cost of care cascade Patient level cost Monthly budget Cash on hand Co-funder contribution Personel	Report

**PC + TC = Pocket Colposcopy + Thermocoagulator*

VI. ETHICAL CONSIDERATIONS

The study will be presented for IRB approval by Cayetano Heredia University and Duke University.

VII. TIMELINE

Timeline	Year 1												Year 2											
	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
	AGO	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JULY	AGO	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JULY
Prepare all the docs for IRB, and obtain approvals	☒	☒																						
Send docs for RCT and Obtain approval from National Institute of Health for the use of Pocket colposcope in trial and facilitate shipment to Peru			☒	☒	☒																			
Initial coordinations with Regional government/approvals		☒	☒																					
Hiring/training team		☒																						
Identify and visit 10-12 health centers in Andean Region to be included in the trial		☒	☒	☒																				
Conduct baseline data collection in each center (2 days observation workflows, costing) Interview personnel about barriers for cervical cancer screening, potential solutions etc			☒																					
Procurement of additional supplies/materials/equipment missing at health centers for see/and treat				☒	☒																			
Integration of mhealth software platform with HOPE platform			☒	☒	☒																			
Procurement of thermocoagulators				☒	☒																			
Shipment of pocket colposcopes to Peru (needed to start the training)						☒																		
Prepare/Print educational materials for IVA, Pocket colposcope, thermocoagulator,			☒	☒	☒																			
Training and implementation of health centers: Controls IVA/thermocoagulator Intervention Pocket colposcope/thermocoagulation/ethical issues consents etc.						☒	☒																	
Procurement of HPV equipment				☒																				
Procurement of HPV tests (10,000 total , but we have to buy it in batches)				☒								☒												
Identification and training of women from the community (HOPE Ladies) who will promote and distribute HPV testing					☒	☒	☒																	
Periodic meetings/communications with authorities MOH (including report of final findings)			☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
HOPE Ladies start promotion and distribution of HPV self-sampling							☒																	
Implemented centers working								☒																
10,000 women had a HPV self-sampling performed - 2400 HPV positive women																								
Collect data on costing in centers								☒	☒	☒	☒	☒	☒	☒	☒	☒	☒							
Complete data collection of women HPV positive									☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	
Data analysis of trial and final report									☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Economic analysis performed																								☒
Dissemination meeting with stakeholders, local research teams, providers, national authorities to present results								☒																☒
Obtain local registration from DIGEMID in Peru for Pocket colposcope (preparing for scale-up)								☒																☒
Preparation of Manuscript with trial results								☒																☒
Presentation of results in international congress								☒																☒

VIII. REFERENCES

1. WHO | Cervical cancer [Internet]. WHO. [cited 2019 Jun 11]. Available from: http://www.who.int/cancer/prevention/diagnosis-screening/cervical-cancer/en/

2. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999 Sep;189(1):12–9.

3. HPV vaccines: Global perspectives: Human Vaccines & Immunotherapeutics: Vol 13, No 6 [Internet]. [cited 2019 Jun 11]. Available from: https://www-tandfonline-com.offcampus.lib.washington.edu/doi/full/10.1080/21645515.2017.1289301

4. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob Health. 2016;4(7):e453-463.

5. Chen C, Yang Z, Li Z, Li L. Accuracy of several cervical screening strategies for early detection of cervical cancer: a meta-analysis. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2012 Jul;22(6):908–21.

6. Sritipsukho P, Thaweekul Y. Accuracy of visual inspection with acetic acid (VIA) for cervical cancer screening: a systematic review. J Med Assoc Thail Chotmaihet Thangphaet. 2010 Dec;93 Suppl 7:S254-261.

7. Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003 Feb 6;348(6):518–27.

8. Schlecht NF, Kulaga S, Robitaille J, Ferreira S, Santos M, Miyamura RA, et al. Persistent Human Papillomavirus Infection as a Predictor of Cervical Intraepithelial Neoplasia. JAMA. 2001 Dec 26;286(24):3106–14.

9. Gravitt PE, Winer RL. Natural History of HPV Infection across the Lifespan: Role of Viral Latency. Viruses [Internet]. 2017 Sep 21 [cited 2019 Jun 11];9(10). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5691619/

10. Sawaya GF, Kulasingam S, Denberg TD, Qaseem A, for the Clinical Guidelines Committee of the American College of Physicians. Cervical Cancer Screening in Average-Risk Women: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2015 Jun 16;162(12):851.

11. Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE. Human papillomavirus testing in the prevention of cervical cancer. J Natl Cancer Inst. 2011 Mar 2;103(5):368–83.

12. Denny L, Kuhn L, Hu C-C, Tsai W-Y, Wright TC. Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. J Natl Cancer Inst. 2010 Oct 20;102(20):1557–67.

13. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. HPV screening for cervical cancer in rural India. N Engl J Med. 2009 Apr 2;360(14):1385–94.

14. WHO | WHO Director-General calls for all countries to take action to help end the suffering caused by cervical cancer [Internet]. WHO. [cited 2019 Jun 11]. Available from: http://www.who.int/reproductivehealth/call-to-action-elimination-cervical-cancer/en/

15. HPV INFORMATION CENTRE [Internet]. [cited 2019 Jun 13]. Available from: https://hpvcentre.net/datastatistics.php

16. Paz Soldan VA, Lee FH, Carcamo C, Holmes KK, Garnett GP, Garcia P. Who is getting Pap smears in urban Peru? Int J Epidemiol. 2008 Aug;37(4):862–9.

17. Almonte M, Ferreccio C, Winkler JL, Cuzick J, Tsu V, Robles S, et al. Cervical screening by visual inspection, HPV testing, liquid-based and conventional cytology in Amazonian Peru. Int J Cancer J Int Cancer. 2007 Aug 15;121(4):796–802.

18. Paz-Soldán VA, Nussbaum L, Bayer AM, Cabrera L. Low knowledge of cervical cancer and cervical pap smears among women in Peru, and their ideas of how this could be improved. Int Q Community Health Educ. 2010 2011;31(3):245–63.

19. Morán F, Cárcamo C, Valderrama M, García PJ. Preferencias y satisfacción hacia un programa de tamizaje con pruebas autoadministradas de detección del virus de papiloma humano. Rev Peru Med Exp Salud Pública. 2017 Jun;34:228–32.

20. Resolución Ministerial N° 1013-2016-MINSA [Internet]. [cited 2019 Jun 13]. Available from: https://www.gob.pe/institucion/minsa/normas-legales/191413-1013-2016-minsa

21. Resolución Ministerial N° 440-2017-MINSA [Internet]. [cited 2019 Jun 13]. Available from: https://www.gob.pe/institucion/minsa/normas-legales/189456-440-2017-minsa

22. Plan Binacional Perú-Ecuador [Internet]. [cited 2019 Jun 13]. Available from: https://planbinacional.org.pe/

23. Perlman DC, Jordan AE, Nash D. Conceptualizing Care Continua: Lessons from HIV, Hepatitis C Virus, Tuberculosis and Implications for the Development of Improved Care and Prevention Continua. Front Public Health. 2016;4:296.

24. Austad K, Chary A, Xocop SM, Messmer S, King N, Carlson L, et al. Barriers to Cervical Cancer Screening and the Cervical Cancer Care Continuum in Rural Guatemala: A Mixed-Method Analysis. J Glob Oncol. 2018 Jul;4:1–10.

25. Carrillo JE, Carrillo VA, Perez HR, Salas-Lopez D, Natale-Pereira A, Byron AT. Defining and targeting health care access barriers. J Health Care Poor Underserved. 2011 May;22(2):562–75.

26. EAST: Four Simple Ways to Apply Behavioural Insights [Internet]. [cited 2019 Jun 14]. Available from: https://www.bi.team/publications/east-four-simple-ways-to-apply-behavioural-insights/

27. Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. Int J Epidemiol. 1999 Apr;28(2):319–26.

28. WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care Is Safer Care. Geneva: World Health Organization; 2009. 2, Patient empowerment and health care. Available from: https://www.ncbi.nlm.nih.gov/books/NBK144022/

29. Guiterriez, Karla. Studies Confirm the Power of Visuals in eLearning. SHIFT eLearning. 2014 Jul 8. Available from: https://www.shiftelearning.com/blog/bid/350326/studies-confirm-the-power-of-visuals-in-elearning

30. Dwyer, Francis. "Edgar Dale's Cone of experience: a quasi-experimental analysis." International Journal of Instructional Media, vol. 37, no. 4, 2010, p. 431+. Academic OneFile, http://link.galegroup.com.proxy.lib.duke.edu/apps/doc/A273786647/AONE?u=duke_perkins&sid=AONE&xid=7ff3e0e3. Accessed 20 June 2019.