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Evaluation of the Liger Medical Thermocoagulator for treatment of cervical intraepithelial lesions in Honduras.

Study Sponsor: PATH

Principal investigator (PI): Silvia de Sanjose, MD, PhD
PATH
2201 Westlake Ave, Suite 200
Seattle, WA 98121
Phone: 206-285-3500
Email: sdesanjose@path.org

Local Principal Investigator: Manuel António Sandoval Lupiac, MD
ASHONPLAFA
Ave. Principal entre Colonia Rubén Darío y Alameda
Tegucigalpa, HONDURAS
Phone: +504 9985-9669
Email: MSandoval@ashonplafa.org

Co-investigator Jacqueline Figueroa, MD
Secretaría de Salud de Honduras
Sub Secretaría de Regulación
Dirección General de Regulación Sanitaria
2 Calle, Avenida Cervantes
Tegucigalpa, HONDURAS
Phone: +504 3190-7159
Email: jacqueline_figueroan@yahoo.com

Collaborating Institutions: Ministry of Health, Honduras

ASHONPLAFA (Honduras)

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Protocol Summary

Title:	Evaluation of the Liger Medical Thermocoagulator for treatment of cervical intraepithelial lesions in Honduras.
Principal investigator:	Silvia de Sanjose, MD, PhD
Local Principal investigator and Co-investigator:	Manuel Sandoval, MD Jaqueline Figueroa, MD
Description of study design:	This is a descriptive/prospective study to determine the short-term safety and acceptability of thermal coagulation for treatment of cervical lesions, as well as to observe rates of disappearance or persistence of lesions after thermal coagulation. HPV and Visual Inspection with Acetic Acid (VIA)-positive women who are eligible for ablative treatment will be offered thermal coagulation to treat their lesions. Women will be followed-up 12 months after treatment to evaluate cure rates.
Study purpose and objectives:	***Study purpose:*** The goal of the study is to demonstrate whether thermal coagulation for the treatment of cervical intraepithelial lesions is acceptable and safe; and to observe rates of lesion disappearance or persistence after thermal coagulation, at four government health facilities in Honduras. ***Primary objective 1:*** To evaluate the experience of pain and other factors influencing acceptability of thermal coagulation among women receiving this treatment. ***Primary objective 2:*** To evaluate short-term safety of thermal coagulation treatment. ***Secondary objective 1:*** To observe the 12-month rates of disappearance or persistence of CIN2-3 lesions after thermal coagulation. ***Secondary objective 2:*** To explore potential factors associated with treatment failure. ***Secondary objective 3:*** To improve the analytical capability of the Duke Pocket Colposcope software.
Study population:	320 women aged 30-49 years
Number and location of study sites:	Four government health facilities in the Región Metropolitana de Tegucigalpa of Honduras.
Study duration:	Approximately 18 months, from March 2018 through December 2019.
Estimated time to complete enrollment:	Enrollment in the study is anticipated to be completed within 6 months of study initiation.
Participation duration:	Participants will be enrolled for ~13+ months.

Description of agent or intervention:	Two (2) devices will be used in this study: 1. HTU-110 Thermocoagulator (Liger Medical, LLC) *2.* Pocket Colposcope (Duke University)

List of Abbreviations and Operational Definitions

AE	Adverse Events
ASCO	American Society of Clinical Oncology
CIN	Cervical intraepithelial lesions
CRF	Case report form
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
LEEP	Loop Electrosurgical Excision Procedure
MOH	Ministry of Health
PI	Principal Investigator
SAE	Serious adverse events
SOP	Standard operating procedure
VIA	Visual Inspection with Acetic Acid
WHO	World Health Organization

1.0 Background and Rationale for the study

Background

Cancer of the cervix is the second leading cancer in women in the developing world. It is estimated that over 500,000 new cases and over 270,000 deaths occur every year. Developing countries are the most affected and account for over 85% of these deaths [1, 2]. The crude incidence rate of human papillomavirus (HPV) related cancers is 25.1 cases per 100,000 women in Honduras, with approximately 991 new cases and 417 deaths reported annually [3].

There are two key prevention opportunities for cervical cancer: 1) primary prevention via HPV vaccines administered before sexual debut; and 2) secondary prevention by cervical screening and treatment of precancerous lesions among women who are already sexually active and much less likely to benefit from the current HPV vaccines [4, 5]. In developing countries such as Honduras, historically there has been a lack of appropriate screening, detection and treatment methods for precancerous cervical lesions. Efforts over the past decade or so have advanced screening technologies for low-resource settings so that these are more accessible in developing countries. In particular, more affordable HPV DNA tests are now available for cervical cancer screening. According to a recent review, implementation of HPV testing in pilot cervical cancer screening programs in Nicaragua, Mexico and Argentina was highly effective, feasible and acceptable [6]. As a result, six countries in Latin America (Argentina, El Salvador, Guatemala, Honduras, Mexico and Nicaragua) have incorporated HPV testing in their national cervical cancer screening programs [6].

However, improvements in treatment technologies, a key component of an effective screening and prevention program, have lagged behind. Treatment options for developing countries must be low-cost, effective, and adaptable for areas with limited resources in terms of infrastructure and health providers.

For the treatment of precancerous cervical lesions in low-resource settings, WHO recommends cryotherapy [7], an ablative procedure where cervical intraepithelial lesions (CIN) are destroyed using freezing employing compressed refrigerant gas. This method is easy to use, is acceptable to women and providers, has few side effects (pain, vaginal discharge), and does not have adverse effects on fertility [8]. However the cost of refrigerant gas and transport, the unreliable supply and quality of refrigerant gas in low-resource settings, and the large, heavy storage tanks that are difficult to transport [9, 10] present significant barriers for utilizing this treatment method [11].

A recent situational assessment of the availability of gas for use in cryogenic procedures in Uganda, a country with low resources, found that 60 percent of clinics providing screening and cryotherapy procedures for women with precancerous cervical lesions, have significant problems with the procurement of refrigerant gas, and may go for several months to a year without supply. The assessment found that a quarter of the facilities were not offering treatment services, mostly due to unavailability of gas. In Honduras as in other low-resource settings, PATH has observed similar barriers to the provision of cryotherapy. These barriers have been mitigated due to the efforts of another PATH cervical cancer project being implemented in Honduras including in study areas. When cryotherapy cannot be performed due to non-functional medical equipment or lack of critical supplies such as the gas, opportunities for treatment may be missed. Thus, alternative non-gas treatment technologies such as thermal coagulation may offer a more feasible treatment option for women with precancerous lesions in such settings.

Use of Thermal Coagulation Therapy for CIN

Thermal coagulation (also known as 'cold coagulation') applies a heated probe (100-120°C) to the tissue to be treated in order to destroy the abnormal cells. Recently published guidelines from the American Society of Clinical Oncology (ASCO) states that thermal coagulation is an option for ablative treatment [12]. Thermal coagulation has been used in the United Kingdom for several decades for the treatment of precancerous lesions of the uterine cervix, and literature states that the rates of lesion disappearance with thermal coagulation are as good or better than those achieved by conventional cryotherapy [13-16]. Studies utilizing thermal coagulation treatment have been limited in other developed and developing country settings. A recent meta-analysis found that cure rates were 95% among CIN2-3 patients from 13 developing and developed countries treated with thermal coagulation [9]. Similar results have been documented in developing countries: 3-6 month cure rates in a screen and treat program in Malawi were 94% [10]; 84% among both HIV-infected and uninfected women in Nigeria [17]; and more than 80% at 6 months to 1 year among HIV-infected women in India [18]. Moreover, this procedure was demonstrated to be safe with little or no adverse events, quick, and preserved fertility [10].

Acceptability of thermal coagulation

Studies on women's experience of and acceptability of thermal coagulation indicate the treatment method is acceptable and well-tolerated by women. Among 714 CIN2-3 patients in Scotland randomized to treatment with thermal coagulation or CO_2 laser, patients treated with thermal coagulation reported lower pain scores and only 8% requested local analgesia during treatment, as compared to 21% in the

laser treatment group [19]. In a double-blind placebo-controlled trial also conducted in Scotland, treatment time was found to be significantly shorter among patients treated with thermal coagulation (median: 3 minutes) as compared to those treated with CO_2 laser (median: 12 minutes) [20]. The majority of the studies in a meta-analysis on the efficacy of thermal coagulation reported that local analgesia was not needed during treatment [9], and in findings from a recent USA randomized placebo-controlled trial without local anesthetic, 44.7% of patients who received thermal coagulation treatment reported mild or no pain at the most [21]. Studies of acceptability in low and middle-income countries are more limited. According to providers in Zambia, women undergoing thermal coagulation reported almost no pain to the providers and, as compared to cryotherapy, providers perceived greater acceptability of thermal coagulation therapy among women [10]. In a study among HIV-infected women in India, thermal coagulation was well-tolerated without anesthesia and was considered safe to administer in an out-patient setting [18].

Hence, more studies are needed to evaluate the success and acceptability of thermal coagulation as an option for treating precancerous cervical lesions, especially in low-resource settings where there are inherent challenges to provide timely and successful (in terms of lesion disappearance) treatment to women with CIN lesions. Such studies, especially in low-resource settings, will be particularly useful to inform country decision making with respect to treatment options for women with CIN.

Devices used in this study

Liger Thermocoagulator HTU-110

Thermocoagulator HTU-110^{TM}, manufactured by Liger Medical, LLC, is a battery-powered thermal coagulation device designed for low-resource settings given it does not rely on a consistent electrical supply, a known continual challenge in such settings. The device is capable of performing approximately 30 treatment procedures per fully-charged battery. The device requires about one minute per treatment: a warm-up time of approximately 10 seconds, and a 40-second application at 120 ^{o}C. To completely charge the battery packs, they are placed in the A/C charging base for approximately 5 hours. The device comes with 2 lithium-ion battery packs and a charging base with A/C adaptor; hence one battery can charge while the other is in use. The device received Class II FDA clearance for marketing in the United States in 2016 for ablative treatment, a similar classification as cryotherapy devices. Bench data reports submitted by Liger Medical, LLC for this application state that testing demonstrates that the HTU-110

functions by the same heating method and at the same temperature and time constant as the WISAP thermal coagulator device that is currently on the market and widely used as a standard of care treatment. Thereby Liger Medical, LLC states that their device will provide at least the same clinical results [22, 23]. To date the Liger Thermocoagulator has been used in pilot studies in India with approximately 20 patients, as well as in Democratic Republic of Congo and Zambia on approximately 150 patients. No adverse events have been reported and initial reports from health providers anecdotally report that it is easier to use and works better than other devices on the market. A study comparing the Liger Medical device and standard cryotherapy is planned in Zambia for 2017, sponsored by the International Agency for Research on Cancer, University of North Carolina and Liger Medical, LLC.

Pocket Colposcope

The Pocket Colposcope is an investigational device developed at Duke University (Durham, North Carolina). The device is the shape and size of a tampon, and is inserted into the vagina through the speculum to capture images of the cervix. It does not come into direct contact with the vagina or cervix. The Pocket Colposcope utilizes a LED ring to provide illumination that is comparable to commercially available colposcopes. The device uses less electrical power, is more portable and is projected to be available at much lower cost. The device is currently being used in clinical investigations in four international study sites: (1) Durham, North Carolina USA (2) Lima, Peru (3) Nairobi, Kenya and (4) Moshi, Tanzania. The device has undergone four generations of development [24, 25], which were tested in the aforementioned sites since 2014 with over 450 patients. The device received Class II FDA clearance for marketing in the United States in 2018 for gynecological examination, a similar classification as other colposcopes. In this study, the Pocket Colposcope and photos taken with the device will not be used for clinical care.

The study will obtain approval from the appropriate regulatory body in Honduras to use these devices in the study.

Rationale for study

Currently there are limited available and reliable treatment options in Honduras and other developing country settings for women with precancerous cervical lesions. Experience and research with thermal coagulation in such settings is also limited. Thermal coagulation offers an alternative ablative procedure to cryotherapy with comparable cure rates, and devices such as the Thermocoagulator HTU-110 may

potentially overcome the barriers frequently experienced by low resource settings. In this study, we plan to use the Thermocoagulator device for the treatment of precancerous cervical lesions among women aged 30-49 at four government health facilities in Honduras, to assess its safety and acceptability (primary objectives). Since in this study we are not comparing thermal coagulation treatment with another treatment such as cryotherapy, we will not be able to directly measure effectiveness of treatment by the Thermocoagulator device. However, we will be able to observe the outcome of lesion disappearance or persistence rates after thermal coagulation which is an important indicator of treatment success, and to explore treatment failure rates due to user error (secondary objectives).

Exploration of reasons for treatment failure

As mentioned above, ablative treatment (cryotherapy and thermal coagulation) for cervical precancer has been documented to result in lesion disappearance. Treatment failure can posited as due to 1) Characteristic of the lesion – e.g., the precancer does not respond to the treatment [26], 2) Equipment failure – For example, blockage of the gas [27] and 3) User error – For example, the provider incorrectly assigns the patient for ablative treatment. While equipment failure has been studied in some depth [28], reasons for user error have not been systematically explored or documented.

To explore potential reasons for treatment failure in this study, we will use the Pocket Colposcope to take photos of cervices at study enrollment and at the one-year follow-up visit, and conduct analysis of the photos at the end of the study.

Additionally to above, the Duke University developers of this device plan to use de-identified photos and corresponding diagnosis information to improve the analytical capability of the device software e.g., and ultimately doctors in developing countries, to identify women for treatment.

2.0 Study objectives

The goal of the study is to demonstrate whether thermal coagulation using the Thermocoagulator HTU-110 device for the treatment of cervical intraepithelial lesions is acceptable and safe, as well as to observe rates of lesion disappearance or persistence after thermal coagulation, at four government health facilities in Honduras.

Primary Objective:

The primary objectives are:

a. To evaluate the level of pain experienced by patients and other factors influencing acceptability of thermal coagulation among patients that received this treatment.
b. To evaluate the short-term safety of thermal coagulation treatment.

Secondary Objectives:

The secondary objectives of this study are as follows:

a. To determine the 12-month rates of CIN2-3 lesion disappearance as compared with persistence after thermal coagulation using the Thermocoagulator HTU-110 device.
b. To explore potential reasons for treatment failure, and explore options for improving the diagnostic capacity of evaluators in developing countries.
c. To improve the analytical capability of the Pocket Colposcope software.

3.0 Methods

3.1 Study design

Study Location

This descriptive study will be conducted at four government health facilities in Honduras. This will include urban and peri-urban health facilities, located in Región Metropolitana de Tegucigalpa that spans an area of 8,619 km^2 and has a population of 352,784 women of reproductive age (15-49 years). This region is part of the government cervical cancer screening program that conducts HPV testing, and has trained personnel with capability to conduct Visual Inspection with Acetic Acid (VIA), collect biopsy specimens, and conduct thermal coagulation treatment as well as cryotherapy. Cryotherapy will be available at each study health facility to women who decline to participate in the study. We expect the different locations of these health facilities within Tegucigalpa will capture some of the diversity of the target population e.g., in terms of socio-economic status and culture in Honduras.

Sample Size and Methods

Objective 1 - Based on previous studies, acceptability related to pain and mild bleeding from the thermal coagulation procedure and the proportion of minor adverse events (e.g., vaginal discharge longer than one week) are estimated to be 90% and 25%, respectively. In this study, we are assuming 85% acceptability and no more than 15% minor adverse events. We calculate that a sample size of 320 women

who are HPV positive, VIA positive, and eligible for ablative treatment will provide a 95% confidence interval to adequately estimate an acceptability proportion of 85% (CI 95%: 80.6–88.7) and an adverse event proportion of up to 15% (CI: 95%: 11.3–19.4) with 80% and 99% power, respectively, and an alpha of 0.05.

Objective 2 - Literature suggests a typical 12-month cure rate for treatment of CIN2-3 lesions in HIV-negative women is 90% using thermal ablation [29]. With a minimum sample size of 70 women, we would have more than 80% power to detect a success rate of 90% or better (CI 95%: 80.0–96.0) for the outcome of lesion disappearance after thermal coagulation treatment.

From the 320 women needed for Objective 1, we estimate that: 1) between 15–20% of women with positive HPV and positive VIA are determined to have CIN2-3 lesions; 2) loss to follow-up may be 10–15%. (While current dropout rates are approximately 40%, we anticipate a lower loss to follow-up rate due to study efforts to follow-up women).

Thus, we expect approximately 64 women will have CIN2-3, of whom 10 may be lost to follow-up. This would leave 54 women with CIN2-3 to observe CIN2-3 lesion disappearance after thermal coagulation treatment with a power of >65%.

For quality control (QC) purposes, the study will also evaluate the 12-month cure rate among an additional 10% sample of women who receive treatment with thermal coagulation who are biopsy-negative or with a CIN1 diagnosis. Among the 320 women needed for Objective 1, we estimate that 80% will be biopsy-negative or have CIN1 lesions or less. Thus, after accounting for 10–15% loss to follow up, we plan to follow up an additional 60 women at 12 months.

Statistical Analyses

Data will be entered into a Microsoft Excel database with built-in validation rules to minimize data entry errors. Descriptive statistical analysis, including calculating point estimates, distribution, and frequencies of responses, will be used to summarize and characterize the study population. For some secondary endpoints, Chi-square tests will be employed to make comparisons between groups.

Women who complete treatment but not the 1-year follow-up visit will be included in the analysis of pain and acceptability, but will be excluded from the analysis of lesion persistence or disappearance. The sample size takes into account 10-15% of women lost to follow-up. The study staff will be responsible for

contacting women for follow-up visits until the end of the study. We believe this will improve on the follow-up rate. We will be able to conduct some analyses even with a certain percentage of women lost-to-follow-up participants after each study visit.

Primary endpoints

a. Level of pain women experienced during the thermal coagulation procedure will be calculated by the number and percent of women indicating minimal to worst possible levels of pain using the Wong-Baker FACES® pain rating scale. Women's acceptability will also be assessed by asking if they would recommend the Liger Thermocoagulator treatment to a friend or relative who needed similar treatment as well as reasons for her response.
b. Short-term safety will be calculated as the number of women with each type of adverse event (numerator), divided by the total number of women treated (denominator). These are adverse events that WHO specifies as short-term safety concerns for ablative treatment and include: minor bleeding minor bleeding requiring packing or suturing; major bleeding requiring hospitalization/blood transfusion; major infections requiring hospital admission and antibiotics; damage to other organs or other surgery required such as injury to bladder or urethra; and major infections requiring hospital admission and antibiotics and pelvic inflammatory disease.

Secondary endpoints

a. To calculate rates of disappearance of lesions, we will include women with histologically-confirmed CIN2-3 lesions. The 12-month rate of disappearance of CIN 2-3 lesions will be calculated by dividing the number of eligible women who had no evidence of CIN 2-3 at 12 months after undergoing thermal coagulation for the treatment of their CIN2-3 lesions (numerator), divided by those women evaluated at 12 months (denominator). Analysis will include considering potential confounding factors such as clinic and provider as well as drop-out rates. Chi-square or Fisher's exact test will be used to confirm whether there are differences in rates by these potential confounding factors. Similar analyses will be performed for women in the QC group, dividing the number of women with no evidence of CIN 2-3 at 12 months who were biopsy-negative or CIN1 at baseline (numerator) by the number of women evaluated at 12 months who were biopsy-negative or CIN1 at baseline (denominator). We will compare these results to the lesion disappearance rate in the CIN2-3 group and expect that the

percentage of women with no detectable lesion in the QC group will be superior or equal to that observed among women with CIN2-3 at baseline.

b. Analysis of cervical photos will be a qualitative comparison of the characteristics of the uterine cervix and the pre-cancerous lesions at Visit 1 (enrollment) in women whose treatment resulted in disappearance of lesions and women with persistent pre-cancerous lesions after 12 months. The evaluation will examine what features or cervical conditions prior to treatment might be related to disappearance or persistence of lesions, such as shape of the cervix, size and location of the lesions, etc. Chi-square or Fisher's exact test will be used to confirm whether there are any differences by these features.

c. Improvement of the analytical capability of Pocket Colposcope software will be conducted by Duke University, including calculation of the percentage of women with concordant diagnoses by the Pocket Colposcope and the end evaluation (histology or Pap or HPV) divided by the total number of diagnoses.

3.2 Research Participants

The target population for this study is women in Honduras 30-49 years who have HPV and VIA positive results and are eligible for ablative treatment.

The inclusion and exclusion criteria for women are as follows:

Inclusion Criteria:

Women will be included in the study if they are:

- Aged 30 to 49 years.
- HPV and VIA positive.
- Eligible for ablative treatment using WHO Guidelines [30].

*The lesion covers <75% of the cervix, the lesion does not enter the endocervical canal, the entire lesion can be visualized and covered by the Liger Medical Thermocoagulator probe, and there is no suspicion for invasive cancer.

Exclusion Criteria:

Women will be excluded from the study if they:

- Are pregnant or less than 3 months post-partum

- Are not HPV and VIA positive
- Do not have a cervical lesion that qualifies for ablative treatment
- Have a bleeding disorder or taking anti-coagulant medication.
- Do not give informed consent; or unable to provide the consent.

Pregnant women will be excluded from this study. If a woman becomes pregnant during the study, she will be referred to OB/Gynecology for proper follow-up and will exit the study. Women who are 3 months postpartum are eligible for the study as this is considered a safe interval to begin screening and treatment.

3.3 Study procedures

Usual care

Under usual care for cervical cancer screening in the public system in Honduras women undergo HPV testing at health facilities offering that cervical cancer screening; test results are usually available within 1 month. Per national guidelines: women with negative HPV test results are advised to get rescreened in 5 years. All women with HPV positive test results are referred for triage by VIA, which is the current standard of care in Honduras for this step. VIA involves examining the cervix for precancerous epithelium (using a vaginal speculum and a source of light) one minute after application of 5% acetic acid, which makes abnormal cells turn white. Results are available immediately and are explained to women. Women with abnormal/acetowhite VIA results and whose lesions qualify for ablative treatment as determined by the provider are offered cryotherapy treatment and followed-up with an appointment in 1 month and another in 1 year. During both of these appointments, the patient is examined by pelvic exam and VIA. HPV testing, colposcopy and biopsy may be done if available. The patient is given a written referral slip with the date of her next appointment. There are no national guidelines or norms informing colposcopists to biopsy women who do not have a visible lesion identified during colposcopy evaluation.

Study Visit 1

Day 1 +7 days: Enrollment into study; Treatment using thermal coagulation (Length of visit: 1-2 hours)

Screening for Eligibility: Women with positive HPV and VIA test results and who qualify for ablative treatment will be invited to participate in the study during the triage visit described above by health

provider, using the Recruitment Script for Doctors. If a woman is interested in learning more about the study, a study staff will use the Recruitment Script for Study Staff to tell them more about the study.

Consent: If the woman is interested in joining the study based on interview questions for eligibility, she will be taken through the consent process and women who consent will then be assessed for pregnancy using a urine pregnancy test. Women who are pregnant or who choose not to join the study will be referred for standard of care based on their pregnancy result and need for CIN treatment. For women who remain eligible and have consented to participate in the study, the research staff will fill out information on the Data Collection Form for the enrollment visit based on the woman's eligibility and screening information.

Baseline interview/Cervical photographs: After the baseline interview if women choose, a health provider will take 1 or more digital photos of the cervix using the Pocket Colposcope. Duke University staff will train study staff in the particular usage of this specific device. The training will emphasize that the doctor cannot use the Pocket Colposcope photos to evaluate or treat the woman.

Biopsies: Then the health provider will take one or more directed biopsy/ies of any abnormal/acetowhite lesions as detected by VIA for diagnosis.

Thermal coagulation: After this, the health provider will perform thermal coagulation treatment on the woman. Analgesia (topical lidocaine and NSAIDS/AINES) will be available to women during treatment and post-treatment for pain management. These will be offered to women following standard of care procedures and treatments. The technique for treatment by thermal coagulation is similar to cryotherapy (the standard of care treatment) in that a probe-like device is applied to the surface of the cervix to freeze (cryotherapy) or heat (thermal coagulation) the lesion. In addition the health provider will be trained by the Local Principal Investigator or qualified designee to perform thermal coagulation based on the VIA evaluation per standard of care.

Post-treatment Counseling/Interviewing: The health provider or study staff will give counseling about post-treatment care.

After treatment with thermal coagulation, a study staff will interview each woman about her experience with the treatment, including pain (if any) experienced during the procedure. In addition, women will be

asked what other discomfort she had during or after the treatment. These questions will be used to better understand acceptability of the treatment to women.

Scheduling Follow-up: Study staff will then give women an appointment to return in 1 month for an exam and to receive her biopsy results. This first study visit will take approximately 1-2 hours. Women will be instructed to come back to the clinic earlier than the one month visit if they experience any complications, which will be reviewed with women before they leave.

Study procedures are shown in Figure 1.

Study Visit 2
Day 30 +/- 5 days: 1 month follow-up visit (Length of visit: 1 hour)

If women do not show up for their follow-up visit, study staff will contact them to remind them using the Follow-up Script.

Review of Biopsy Results: At the one-month follow-up visit, study staff will meet and explain to women their biopsy results.

Pelvic Exam: At this visit a health provider will also conduct a pelvic examination for returning women to assess short term safety outcomes per WHO guidelines for ablative treatment. This is visualization and palpitation of the cervix, uterus and pelvic area to assess for any complications, infections, etc. that the woman experienced after treatment. If the woman experienced any problems from the treatment during the time before this visit, the study staff will collect the information from the woman, adverse events report or health facilities records as needed and record the information to the study data collection form.

1. A convenience sample of 60 women with negative or CIN1 diagnoses will be scheduled for a follow-up visit 12 months from the date of receipt of treatment as a quality check to ensure no evidence of CIN2-3 at 12 months. All biopsy negative and CIN1 women will be invited to continue in the study as part of the quality control group until the sample size is reached. Women with negative or CIN1 diagnoses who do not wish to continue the study and women with negative or CIN1 diagnoses who attend Visit 2 after the sample size of 60 is reached will exit the study and be advised to be screened again in 1 year per national guidelines.

2. Women diagnosed with cancer or suspicious of cancer will also exit the study and be referred for further management and treatment (LEEP, hysterectomy, radiation, and chemotherapy), as deemed appropriate by the provider at the health facility and local guidelines.
3. Women with biopsy result of CIN2-3 will be scheduled for a follow-up visit 12 months from the date of receipt of treatment.

Study Visit 3
Day 358 +/- 7 days: HPV sample collection visit (Length: 30 minutes)

The goal of the HPV sample collection visit is to collect a specimen to be tested for the presence of HPV infection prior to the 12-month follow-up visit. Prior to specimen collection, the woman will be taken through an addendum consent process, where she will go through the updated study procedures with the study nurse and provide informed consent. This visit may take place in a woman's home, where she will self-collect a vaginal specimen with a collection kit provided by the nurse per standard care, or in a clinic. If a woman refuses to self-collect a sample, a provider will collect a sample for the HPV test.

Study Visit 4
Day 365 +/-14 days: 12-month follow-up visit (Length: 1 hour)

The goal of the follow-up visit is to provide a rigorous check for persistent CIN2-3 lesions. A health provider will re-evaluate all women with CIN2-3 lesions who were treated by thermal coagulation and the convenience sample of biopsy-negative and CIN1 women who were treated by thermal coagulation. The general approved standard for biopsy in the United States do not recommend nontargeted biopsies, or biopsies on women with "a completely normal colposcopic impression (i.e., no acetowhitening, metaplasia, or other visible abnormality)." [31] At this visit, biopsies will be taken only from women with a positive visual evaluation.

Prior to initiating clinical procedures at Visit 4, women will be asked questions regarding possible pregnancy per standard practice, including the date of her last menses. If pregnancy is suspected, a pregnancy test will be done. In the event of a pregnancy, the woman will receive care for her pregnancy per standard practice and undergo procedures 1–3 below, however, no biopsies will be taken. If a lesion is observed in a pregnant woman, the physician will determine her course of treatment per standard care. In most cases, treatment can safely wait until after the birth of the baby.

Procedures for Visit 4 are as follows:

1. Women will receive their HPV test result.
2. The study doctor will take 1 or more digital photos of the cervix using the Pocket Colposcope, as done in Visit 1. The doctor will not use the Pocket Colposcope photos to evaluate or treat the woman.
3. The study doctor will perform a visual inspection with acetic acid (VIA). Women with a positive visual evaluation will have directed biopsies from any visible lesion.
4. Women who are HPV-positive and visual evaluation–negative will receive a standard Pap test.
5. Women who are HPV-negative and visual evaluation–negative will exit the study. Follow-up will be recommended according to standard of care instructions.

Study Visit 5
Day 393 +/-5 days: Results from 12-month follow-up visit (Length: 30 minutes)

The purpose of Visit 5 is to provide women their 1-year biopsy or Pap results and instruct them on follow-up.

1. Women will return for their Pap or biopsy results in about one month and will be referred, as appropriate, for return screening or treatment according to the standard of care.
2. Women will then exit the study.

Treatment at the 12-month follow-up period, if needed, will be paid for by the study.

At the end of this study visit, all remaining women participating in the study will be considered to have completed the study. At any point during the study women may choose to exit the study and receive standard of care treatment as described earlier. Study staff will ensure that relevant study results for each woman are included into women's medical records when the participants complete the study to enable continuity of care.

Specimen handling

Biopsy specimens will be collected and stored per standard practice (formalin at room temperature). All collected biopsy specimens will be labeled and identified by a unique study identification number and will be accessible only to study staff. All collected biopsy specimens will be handled and stored securely at all four health facilities in Honduras or the ASHONPLAFA office and transferred once a week to an internationally validated pathologist in Tegucigalpa, where they will be evaluated. In accordance with local clinical practices, biopsy specimens collected through this study will be retained in a secure location

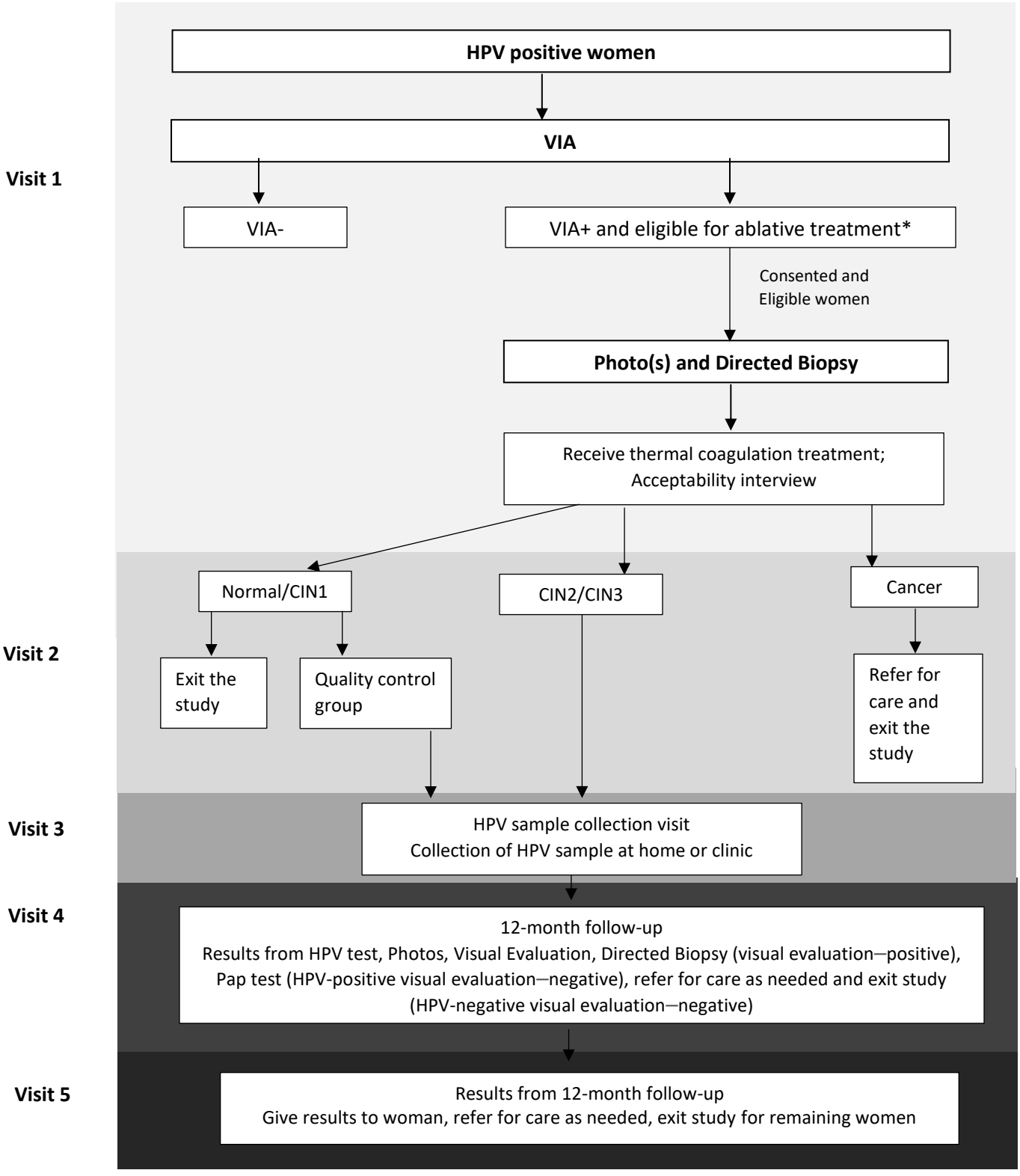
at the pathology lab for 1 year, in Tegucigalpa. Biopsy specimens will only be used for this study and not for other future studies.

Pap specimens will be stored following standard practice. Specimens for HPV testing will not be stored and will be discarded after testing per standard practice.

TABLE OF STUDY PROCEDURES

Study Procedures	Visit 1 (D1 + 7 days)	Visit 2 (D30 +/- 7 days)	Visit 3 (D358 +/- 7 days)	Visit 4 (D365 +/- 14 days)	Visit 5 (393 +/- 5 days)
Recruitment	X				
Consent	X				
Urine pregnancy test (after consent)	X				
Baseline interview	X				
Cervical photo (if agreed)	X			X	
Cervical biopsies	X			X	
Thermocoagulation treatment	X				
Post-treatment counseling/interview	X				
Scheduling 1-month follow-up visit	X				
Pelvic exam for ablative results		X			
Review of biopsy (Visit 1) and other test results (Visits 3 and 4)		X			X
Schedule follow-up visit for CIN 2-3 and quality control group of CIN1 and biopsy negative		X			
End of study for remaining negative women or CIN 1 dx; end of study/referral for suspected cancer		X			
HPV sample collection			X		
Visual evaluation				X	X
Biopsies as indicated				X	
Referral for next follow-up and end of study for HPV-negative visual evaluation–negative women				X	
Referral for next follow-up and end of study for all remaining women					X

Figure 1: Study procedures flow diagram for women with positive (abnormal) HPV cervical cancer screening results



*eligibility as determined by ASCO guidelines

Training

A qualified physician will train health providers at VIA screening sites how to collect biopsies and administer thermal coagulation therapy. Training will be conducted over 2 clinical days and will be supervised by the PI.

PATH will train all study staff regarding ethical study code, conduct and procedures.

Device training will include the following topics:

- Checking device before use and activating
- Thermal coagulator – how to identify cervical tissue that has been correctly ablated/treated
- Pocket Colposcope – how to make sure photos have been taken, labelled and saved correctly
- Battery charging
- Cleaning and disinfection
- Regular maintenance and inspection
- Potential complications, trouble-shooting

4.0 Ethical aspects and consent process

The study team will obtain approval from appropriate regulatory bodies in Honduras prior to beginning the study.

4.1 Recruitment

The health provider conducting the VIA screening of HPV+ women will identify women who are qualified for ablative treatment. The provider will ask if the woman is interested to learn more about the study (Appendix B). If interested, a study staff member will provide more information about the study and invite them to participate in the study via a Recruitment Script for Research Study Staff. The Recruitment Script will include asking study-eligible women about their menstrual history and whether or not they are or may be pregnant.

4.2 Consent process

Study staff will obtain written informed consent from women who are eligible for the study.

Only women who voluntarily give written informed consent (Appendix D) will be enrolled into the study in a private setting. A study staff member will explain all aspects of the study to the potential participants, emphasize that participation in this study is voluntary, and that a participant's care will not be affected by her decision to participate or not in the study. Women will be asked to read the consent themselves and

be encouraged to ask questions of the study nurse. If a woman is unable to read the consent and requires it to be read to her, a literate, impartial witness will serve as a consent witness to ensure that the participant understands the study information, including risks and benefits. Once all the woman's questions have been answered satisfactorily, women will be given the opportunity to choose to participate. The study staff will ask several questions to confirm the woman's understanding of the purpose of study and key information about the study. If the woman demonstrates her understanding of the study and agrees to participate, she will be asked to sign, or give her thumbprint if she is unable to sign. Women will sign two identical consents and will be given a copy of one of the consents to take home. It will be emphasized that women who decide not to participate in the study will receive their treatment according to the standard of care protocol established by the MOH.

At Visit 3, a study staff member will explain all updated aspects of the study to the participants during an additional consent process and ask the woman to sign or thumbprint (if unable to sign) the addendum consent form (Appendix G). If a woman is unable to read the consent and requires it to be read to her, a literate, impartial witness will serve as a consent witness to ensure that the participant understands the study information, including risks and benefits. If it is not possible to ensure the presence of an impartial witness to serve as a consent witness in a woman's home if she is unable to read the addendum consent form, the woman will be scheduled to come in to the clinic for Visit 3 where an impartial witness will be available.

4.3 Risks

Thermal coagulation has been shown to be safe in several studies with low potential for serious adverse events. In a 2014 meta-analysis by Dolman et al [9], the authors state that this method "constitutes a safe and acceptable procedure, as side-effects among analyzed studies were infrequent and of low or moderate severity". The side effects of thermal coagulation are similar to that of cryotherapy. Bench data [Liger Clinical Report] demonstrate that the expected risks using the Liger Thermocoagulator are no more than other ablative treatment methods and instruments. Hence, we do not anticipate greater risks for women receiving treatment via the Liger Thermocoagulator aside from the expected risks from thermal coagulation treatment.

Anticipated risks during thermal coagulation treatment include the following:

- Women may feel mild pain or discomfort during the procedure.
- Women may experience vaginal discharge or bleeding after treatment with thermal coagulation.

Rarer but more serious risks of thermal coagulation treatment include:

- Heavy bleeding
- Infection
- Injury to bladder or urethra
- Accidental burns to vagina

Currently photos of the cervix are used during colposcopy evaluation in some private practice settings, but not utilized in the public system in Honduras for diagnosis or treatment. Photos are not used in the USA for diagnosis or treatment for cervical cancer. The Pocket Colposcope is anticipated to add no or minimal risks to women as it is minimally invasive and use of this device does not involve direct physical contact with the vagina, cervix, or external genitalia. Handling of the Pocket Colposcope will follow the standard of care protocol for reusable medical devices.

Anticipated risks of the cervix photo include the following:

- Women may feel uncomfortable having photos of their cervices taken.

4.4 Mitigation of Risks

The following steps will be taken to minimize potential risks:

- Highly skilled and trained gynecologists will perform thermal coagulation treatment, take photos with the Pocket Colposcope, and conduct the gynecological procedures in the study. They will have experience conducting other ablative treatment e.g., cryotherapy. As mentioned, cryotherapy is currently the standard of care treatment and thermal coagulation mainly differs from cryotherapy by delivering heat rather than freezing to the cervix.
- Prior to study start, each thermal coagulation device will be tested e.g., on chicken breasts, to ensure each device is fully functional.
- Study doctors will be trained to be able to identify what correctly conducted ablation looks like on a treated cervix as well as what it looks like when not correctly done. They will also be trained to report problems with conducting the treatment in the interest of correctly understanding or improving the treatment.

- Local and Seattle PIs as well as Duke University staff will attend the study training and initial participant enrollment to monitor early use of devices and conduct of treatment by study doctors. Study doctors will be observed and re-trained as needed during the initial training period. If a study doctor demonstrates repeated problems in administering thermal coagulation or use of the Pocket Colposcope, they will be replaced.
- The study will have a back-up unit available in the case of malfunction or failure of a device. Malfunction or failure will be reported to local and Seattle PIs so trouble-shooting and/or device replacement can be done. Duke University will be contacted for technical assistance on the Pocket Colposcope. Device malfunction will be recorded in the data collection form.
- Study staff will advise women on potential complications and what to do if they experience these after treatment, including the importance of contacting study staff and not delaying to seek medical attention if they are concerned.
- Women will be given the option to participate in the study but not have photos of their cervix taken.
- Study doctors will be trained not to use the Pocket Colposcope for treatment decisions.
- The 12-month follow-up serves as a rigorous check to ensure that women who have persistent lesions or worse will be identified and appropriately referred for additional treatment.

4.5 Benefits

There may or may not be any benefit to women participating in this study. This is the first time thermal coagulation will be used in Honduras. All women who participate in the study will receive cervical precancer treatment with either thermal coagulation or standard of care (cryotherapy) for their visible acetowhite lesions. Previous studies have shown less pain and discomfort with thermal coagulation. However, at this early stage with thermal coagulation in Honduras, this cannot be known. Because biopsies are not normally part of the standard of care for cervical lesions, women participating in the study may benefit from more specific diagnosis based on biopsy results, while also being subjected to the increased, although minimal, risks of biopsies.

Not specific to study participants, the evidence about the feasibility and acceptability of thermal coagulation therapy in Honduras may contribute to knowledge and decision-making regarding use of thermal coagulation therapy in Honduras more broadly.

The use of cervical photos will not benefit women in this study directly. However, use of the photos for evaluation of factors associated with treatment failure and software improvement for the Pocket Colposcope may contribute to treatment improvements for cervical precancer in Honduras and more widely.

5.0 Study and safety monitoring

PATH staff in Seattle and partners in Honduras will monitor the study. PATH staff will have regular telecommunication and/or email communication with the Honduras study team at least every two weeks during enrollment and follow-up. In addition, PATH staff will visit the study sites at the start and during the study as necessary to:

- Verify compliance with human subjects and other research regulations and guidelines, including adhering to confidentiality guidelines during all study related procedures.
- Observe trained study staff to ensure that informed consent is obtained and documented in compliance with the study protocol.
- Assess adherence to the study protocol and study-specific procedures.
- Confirm the quality and accuracy of data collected at the study sites, and data entered into the study database, including the validation of data reported on data collection forms.

  At any time during the study if any of the following events occur, the study will be paused to investigate these events thoroughly:
  - Excessive bleeding (more significant than a menstrual period for more than 2 days) occurring in 2 or more participants.
  - Infection or burns (requiring hospitalization or treatment) occurring in 2 or more participants.
  - Pain at level 5 or more reported by more than the expected number (10%) of participants.
  - Note: Excessive discharge is difficult to define and distinguish from the discharge that is routinely expected; it would not be considered a health threat so will not require a pause in the study.

  These numbers are based on the limited reports of such events in published literature [9, 10].

If the study is paused due to any events above, the next steps would be to review the collected data and adverse events reports, and evaluate the cause of the adverse events (listed above). If the adverse events are determined to be due to provider error, re-training would be done, and the provider carefully observed as they conduct treatment after re-training. If the adverse events are due to problems with one specific study thermal coagulation device, treatment with the device in question would be halted, and monitor all future participants for similar issues.

5.1 Managing and reporting adverse events

In this study, an adverse event (AE) is any untoward or undesirable event experienced by a participant regardless of whether the event is expected or related to the participant's involvement in the research.

A serious adverse event (SAE) is any untoward medical occurrence or effect that involves:

- Death
- A life-threatening condition (participant at immediate risk of death)
- Persistent or significant disability/incapacity
- In-patient hospitalization or prolongation of existing hospitalization
- A congenital anomaly or birth defect
- An important medical event that may jeopardize the participant or may require intervention to prevent one of the outcomes listed above.

Staff finding out about any SAE must report the event to the Study PI either via phone or email within 24 hours of finding out about the event, even if study staff consider the event not related to the study or are unsure about relatedness to the study.

The Study PI will notify involved Ethics Committees according to reporting guidelines using the PATH Incident Report Form as well as in accordance with study Standard Operating Procedures (to be developed by study team). An initial notification can be made followed by a completed report form as soon as possible, but at latest within three calendar days of the initial notification. The completed form will detail relevant aspects of the adverse event/s, relationship to the study (related/ unrelated), action/s taken and event outcomes. If applicable, hospital case records and autopsy reports should be obtained.

Any relevant information that becomes available after the SAE report form has been sent (outcome, precise description of medical history, results of the investigation, copy of the hospitalization report)

should be forwarded as soon as possible to the Study PI. Confidentiality guidelines should be adhered to when forwarding this information.

5.2 Managing and reporting unanticipated problems or protocol deviations

In this study, an unanticipated problem is any incident, experience or outcome (physical, psychological, economic, or social) that potentially places the participants or others at greater risk for harm.

A deviation from protocol is any change in the study procedures that does not follow the approved written study protocol.

Staff are required to report any unanticipated problems or deviations to protocol that occur during the study to the Study PI within 24 hours of learning about issue. Within 72 hours, the Study PI will notify involved Ethics Committees in accordance with their reporting requirements.

5.3 Study costs

Study participants will not need to pay to participate in the study. Participants will not incur cost to participate in the study beyond what they would normally incur when they go for screening and treatment for lesions. The study will provide a nominal amount ($5 USD or 100 HNL) for participant transportation for Visits 2, 3, 4, and 5 of the study.

5.4 Care for injury

In the event of an injury resulting from study procedures, study participants will be referred to government health facilities with greater capacity for appropriate medical treatment and follow-up following the standard of care per Honduras guidelines, which will be paid for by the study. The study will not be responsible for any non-research related injuries or any health care services sought or received in private clinics. Study doctors together with the local PI and Honduras MOH co-investigator (both OB-GYNs) will determine if the problem is study-related. The Seattle PI may also weigh in.

5.5 Compensation

Participants will not be reimbursed for any lost wages due to participation in the study.

6.0 Confidentiality and data management

Confidentiality

All study staff will take training for study confidentiality as follows: Study staff will maintain all information collected by the study as confidential. Only study staff will have access to data and personal

identifying information that identifies study participants, and access to the secure rooms, computers, and/or files where these are stored. Only study identification numbers will be used to label study records, photos, and specimens. These measures will help ensure protection of confidentiality while permitting clinical management.

Linking documents connecting the participant's name and other identifying information to the study identification number will be maintained for quality control and follow-up purposes. Linking documents and other personal information will be destroyed as soon as possible within three years after study activities have been completed e.g., after all study data has been verified and cleaned and/or necessary follow-up has been conducted.

Study reports and presentations will not contain any personal identifying information of any study participant.

Data Collection, Management and Storage

Trained study staff will collect data from study participants into paper Study Case Report Forms (CRFs). Data collected will include women's socio-demographic information, VIA and biopsy procedures, results, short term safety findings (1 month after treatment), follow-up information, and post-treatment questions to assess the level of the pain experienced during the procedure, and any other comments and/or concerns experienced (Appendix E). The CRFs and digital cervical photos will not contain the participants' names or any other identifying information but will be labeled with the study identification number. These documents will be filed as part of the study records.

Data from the CRF and monitoring visits will be entered into the study database by trained study staff and maintained in a secure, password protected online electronic data management system, and the study coordinator will oversee data collection and storage including the completion of data forms, data entry and confidentiality of study data on a regular basis.

Clinical Information from the study that is relevant to women's continuity of care will be entered into each women's health facility records when women exit the study. The study coordinator will ensure that study records are maintained and stored securely throughout the study. In accordance with funder's requirements, de-identified data will be made available in a data repository. De-identified digital photos and corresponding diagnoses information will be shared with Duke University for improvement of the

Pocket Colposcope device software. Study records such as linking documents will be retained for 5 years after the end of the study and then destroyed.

7.0 Institution and Investigator responsibilities

Roles and responsibilities for the partnering institutions and investigators are described below:

PATH

PATH will provide overall management and oversight of the study. This will include developing the study protocol, obtaining needed ethical approvals at PATH as well as monitoring the implementation of the study, data collection and data analysis. PATH will also:

- Oversee all in-country study coordination
- Manage delivery and logistics of Liger Medical devices and Pocket Colposcopes
- Manage and store study data forms and consent forms
- Train providers on how to use the Liger Medical device for thermal coagulation therapy and Pocket Colposcope
- Disseminate results to the study partners.

In addition, PATH will train two or three study personnel for each site, who will be responsible for determining study participant eligibility, obtaining consent, filling in the study CRF, making appointments for follow-up visits and contacting women by phone or in-person to remind them of their upcoming visits. The study personnel will receive a half-day training on how to conduct consent, as well as how to fill in the study CRF.

Honduras study team

Honduras study team will:

- Safeguard the rights and safety of all study participants
- Follow the protocol; report deviations or concerns to the study team
- Delegate study tasks to team members who are qualified by education, training and experience to complete those tasks. Maintain a roster of study team staff and delegated activities.
- Report AEs and unanticipated problems in the established timeframes to the required institutions
- Determine study eligibility of participants and obtain consent
- Complete the study CRF accurately

- Complete all study records so that they are accurate, reliable, contemporaneous, and attributable to the person making the entry, with corrections clearly shown and not obscured.
- Make and remind study participants of follow-up appointments
- Provide thermal coagulation therapy and take images with Pocket Colposcopes
- Manage any medical needs of the study participants by evaluating, treating or referring to competent care.
- Ensure data collection and data entry

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Appendices

A. Recruitment Script: Doctor

B. Recruitment Script: Research Study Staff

C. Eligibility Checklist

D. Consent Form

E. Data Collection Form

F. Follow-up Script

G. Addendum Consent Form