Informed Consent with HIPAA Authorization to Collect, Use, and Disclose Protected Health Information (PHI)

A Phase II Clinical Trial of PepCan Randomized and Double-Blinded to Two Therapy Arms for Treating Cervical High-Grade Squamous Intraepithelial Lesions

Subject Name: _____

MRN: _____

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Study Location: UAMS Obstetrics/Gynecology Clinics,
UAMS Winthrop P. Rockefeller Cancer Institute (WPRCI)

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INTRODUCTION

You are invited to take part in a research study. Subjects in the study will be women aged 18-50 years old who have human papillomavirus (HPV). HPV is known to cause cervical, vaginal, oral, and anal cancers. The study will look at how well a new therapeutic HPV vaccine designed to shrink a precancerous condition called high-grade squamous intraepithelial lesion (HSIL) works and if it is safe. This new vaccine, called PepCan, is not approved by the United States Food and Drug Administration (FDA). The vaccine will consist of a laboratory-made piece of HPV protein called E6 and yeast extract called Candin®. Since the results of the Phase I study showed that Candin by itself may be effective, you will be assigned by chance, like flipping a coin, to receive either PepCan or Candin treatment. You and the study staff (except for the pharmacists) will not know which treatment you receive until after you complete the last study visit at 12 months. There is a small chance that PepCan may not be available temporarily during the study. If this happens, it is possible to be switched from the treatment you were assigned to Candin only. You can find out after study completion. Up to 125 women will be enrolled into the study for screening, and 80 eligible women will receive one of the two treatments. An equal number of subjects will be assigned to each treatment.

This study will determine if PepCan or Candin is effective after a one-year period. This research study will also examine your body's immune system response to PepCan/Candin and how well it works to shrink HSIL. You would be eligible to enroll in the study for screening:

- If you have had a recent Papanicolaou (Pap) smear result indicating that you have HSIL or "Cannot rule out HSIL"
- If you have a biopsy-confirmed diagnosis of HSIL
- If you meet the inclusion/exclusion criteria listed below.

The presence of HSIL will be confirmed during screening and may involve performing a biopsy and imaging of the cervix. You'll be eligible to receive vaccination if the diagnosis of HSIL is confirmed.

WHO CAN PARTICIPATE IN THIS STUDY?

You will be invited to join the study if you meet these inclusion criteria and do not have any exclusion criteria:

- Inclusion Criteria
    - Had a recent Pap smear with results consistent with HSIL or "Cannot rule out HSIL" or a diagnosis of HSIL confirmed by colposcopy-guided biopsy; HSIL is classified as "cervical intraepithelial neoplasia "CIN" II, II/III, or III"
    - Untreated for HSIL or "Cannot rule out HSIL"
    - Women 18-50 years of age
    - Able to provide informed consent
    - Willing and able to comply with the requirements of the protocol

- Exclusion Criteria
    - History of disease or treatment that has caused your immune system to not work very well, such as cancer, HIV, organ transplant, and autoimmune diseases

- Being pregnant or attempting to become pregnant within the period of study participation
- Breast feeding or planning to breast feed within the period of study participation
- Allergy to *Candida* antigen
- History of severe asthma requiring emergency room visit or hospitalization within the past 5 years
- History of invasive squamous cell carcinoma, or cancer of the cervix
- History of having received PepCan
- If in the opinion of the principal or other investigators, it is not in the best interest of the patient to enter this study.

You will be eligible to receive the study vaccine if the biopsy taken at the Screening Visit showed HSIL, you have acceptable laboratory test results, and your vital signs are within the defined ranges. Otherwise, you will exit the study.

If you already were diagnosed with HSIL on biopsy at an outside institution, you can still enroll in this study as long as you fulfill other criteria. The duration between the day your biopsy was taken and the first vaccine injection day cannot be more than 60 days.

WHAT WILL HAPPEN

- Inclusion/exclusion criteria will be reviewed by telephone or in person.
- If you are age 18-24, the most recent recommendations released by the American Society of Colposcopy and Cervical Pathology (ASCCP) will be carefully explained to you.
- After the study has been explained to you, you will be asked to provide informed consent.
- You'll be asked to provide your name, date of birth, ethnicity and contact information, so that UAMS may make an appointment for you.
- A Screening Visit appointment will be made in one of the UAMS Gynecology Clinics or in the UAMS Winthrop P. Rockefeller Cancer Institute (WPRCI).

Screening Visit (Gynecology Clinics or UAMS Winthrop P. Rockefeller Cancer Institute)

- You'll be asked to fill out "Subject Contact Information" form and "Screening Visit Questionnaire" which will gather information such as your contact information, education level, employment, number of children, smoking history, and use of birth control.
- You'll be asked to provide medical history including drug allergies and current medications.
- Vital signs will be obtained and physical examination will be performed.
- If you can have children, the risks involving becoming pregnant will be discussed, and you'll be asked to specify which birth-control method you will be using during the study.
  - Examples of ways you can prevent getting pregnant include pills, patches, rings, implants, shots, double-barrier methods (condoms and spermicide), abstinence, or vasectomies of your male partner combined with another birth-control method.
- You will be asked if you would like the study to provide birth control. The study will offer the following options at no cost:
  - Sprintec is an oral contraceptive. It will be available throughout the study.

  - Low-Ogestrel is also an oral contraceptive. It will be available throughout the study for subjects who need to be taken off Sprintec for medical reasons.
  - Depo-Provera is a contraceptive given as a shot every 3 months. It will be available throughout the study.
  - Liletta is an intrauterine device (IUD) contraceptive. This device must be placed during the first 3 months of participation. It will only be available during the first 3 months. An exception would be allowed if an existing IUD were removed during one of the study visits. In this situation, the IUD may be replaced with Liletta throughout the study.
    - The study will cover the cost of the IUD, placement of the IUD within the first 3 months of study participation (with the exception of replacing an IUD removed during study visits), and removal of the device during your study participation, but not afterwards.
- Cervical cells will be obtained by Pap smear for HPV and bacterial testing.
- Colposcopy may be performed, and a doctor may take piece(s) of your visibly abnormal cervical tissue (biopsies) and possibly scrapings (endocervical curettage); additionally, if no lesions are visible, a doctor may take cervical tissue (biopsies) in four different areas on your cervix. Colposcopy may be performed in the operating room (OR) if medically necessary. If the colposcopy is performed in the OR, a COVID-19 test may be required per hospital policy prior to this intervention.
  - The colposcopy procedure is a simple, 10- to 15-minute pelvic exam and biopsy that is painless and performed in the clinic. You will be positioned on the examination table like you are for a Pap smear, and an acetic acid (such as common table vinegar) will be placed on the cervix. Your physician will use a colposcope (a large, electric microscope that is positioned approximately 30 cm from the vagina) to view your cervix. A bright light on the end of the colposcope lets the physician clearly see the cervix. Your physician may take images of the cervix and will take tissue samples from the abnormal areas and these samples will be sent to the pathology lab for further evaluation.
- Two to three tubes of blood (about 2 tablespoons total) will be drawn for clinical testing.

You'll be contacted with the results, and will be informed whether you'll be eligible for vaccination. If you are eligible, Vaccination Visits will be scheduled. If you are found to be ineligible, an optional follow-up visit can be scheduled at the Gynecology clinic for you to receive biopsy results and instructions from the physician about follow up care.

Vaccination Visit 1 (UAMS Winthrop P. Rockefeller Cancer Institute)

- You'll be asked about any medication changes.
- You'll be asked to take a urine pregnancy test.
- Vital signs, height, and weight will be obtained before vaccine injection.
- Eight to ten tubes of blood (up to 7 tablespoons total) will be drawn for clinical and immunology testing. The blood may be used to study how your white cells are reacting to HPV, to allow them to grow in a laboratory, for tissue (HLA) typing, genetic testing of your immune cells and related genes, and other similar tests. In addition, the blood may be used for other testing to see if the vaccine worked in your body by examining proteins and other types of specialized cells.
- PepCan or Candin will be injected in your skin usually in one arm but can also be given in one leg.

- After resting for at least 30 min after the injection, vital signs will be obtained.
- You'll be offered a dose of ibuprofen or naproxen. You do not have to take it, but it might help limit possible reactions that may occur.
- You'll be given a "Subject Diary" to fill out for at least 7 days following the injection, or for as long as you have any reaction at the injection site or other symptoms.

Vaccination Visit 2 (UAMS Winthrop P. Rockefeller Cancer Institute)

- You'll be asked to turn in the completed "Subject Diary" or verbally recall any reactions to the previous vaccination.
- You'll be asked about any medication changes.
- You'll be asked to take a urine pregnancy test.
- Vital signs will be obtained before vaccine injection.
- Eight to ten tubes of blood (up to 7 tablespoons total) will be drawn for immunology testing. The blood may be used to study how your white cells are reacting to HPV, to allow them to grow in a laboratory, for tissue (HLA) typing, genetic testing of your immune cells and related genes, and other similar tests. In addition, the blood may be used for other testing to see if the vaccine worked in your body by examining proteins and other types of specialized cells.
- PepCan or Candin will be injected in your skin usually in one arm but can also be given in one leg.
- After resting for at least 30 min after the injection, vital signs will be obtained.
- You'll be offered a dose of ibuprofen or naproxen (e.g., Advil® or Aleve®). You do not have to take it, but it might help limit possible reactions that may occur.
- You'll be given another "Subject Diary" to fill out for at least 7 days following the injection, or for as long as you have any reaction at the injection site or other symptoms.

Vaccination Visit 3 (UAMS Winthrop P. Rockefeller Cancer Institute)

- You'll be asked to turn in the completed "Subject Diary" or verbally recall any reactions to the previous vaccination.
- You'll be asked about any medication changes.
- You'll be asked to take a urine pregnancy test.
- Vital signs will be obtained before vaccine injection.
- Eight to ten tubes of blood (up to 7 tablespoons total) will be drawn for clinical and immunology testing. The blood may be used to study how your white cells are reacting to HPV, to allow them to grow in a laboratory, for tissue (HLA) typing, genetic testing of your immune cells and related genes, and other similar tests. In addition, the blood may be used for other testing to see if the vaccine worked in your body by examining proteins and other types of specialized cells.
- PepCan or Candin will be injected in your skin usually in one arm but can also be given in one leg.
- After resting for at least 30 min after the injection, vital signs will be obtained.
- You'll be offered a dose of ibuprofen or naproxen. You do not have to take it, but it might help limit possible reactions that may occur.

- You'll be given another "Subject Diary" to fill out for at least 7 days following the injection, or for as long as you have any reaction at the injection site or other symptoms.

Vaccination Visit 4 (UAMS Winthrop P. Rockefeller Cancer Institute)

- You'll be asked to return the completed "Subject Diary" or verbally recall any reactions to the previous vaccination.
- You'll be asked about any medication changes.
- You'll be asked to take a urine pregnancy test.
- Vital signs will be obtained before vaccine injection.
- Eight to ten tubes of blood (up to 7 tablespoons total) will be drawn for immunology testing. The blood may be used to study how your white cells are reacting to HPV, to allow them to grow in a laboratory, for tissue (HLA) typing, genetic testing of your immune cells and related genes, and other similar tests. In addition, the blood may be used for other testing to see if the vaccine worked in your body by examining proteins and other types of specialized cells.
- PepCan or Candin will be injected in your skin usually in one arm but can also be given in one leg.
- After resting for at least 30 min after the injection, vital signs will be obtained.
- You'll be offered a dose of ibuprofen or naproxen. You do not have to take it, but it might help limit possible reactions that may occur.
- You'll be given another "Subject Diary" to fill out for 7 days following the injection, or for as long as you have any reaction at the injection site or other symptoms.

6-Month Visit (6 months after Vaccination Visit 4; Gynecology Clinics and/or UAMS Winthrop P. Rockefeller Cancer Institute)

- You'll be asked to return the completed "Subject Diary" or verbally recall any reactions to any of the previous vaccinations.
- You'll be asked about any medication changes.
- Vital signs will be obtained and physical examination will be performed.
- Cervical cells will be obtained by Pap smear for Pap smear, HPV and bacterial testing.
- Colposcopy will be performed, lesions will be described and recorded and may be imaged. If there is a suspicion of progressive disease, a doctor may take piece(s) of your cervical tissue (biopsies) and possibly scrapings (endocervical curettage). Colposcopy may be performed in the operating room (OR) if medically necessary. If the colposcopy is performed in the OR, a COVID-19 test may be required per hospital policy prior to this intervention.
- Eight to ten tubes of blood (up to 7 tablespoons total) will be drawn for clinical and immunology testing. The blood may be used to study how your white cells are reacting to HPV, to allow them to grow in a laboratory, for tissue (HLA) typing, genetic testing of your immune cells and related genes, and other similar tests. In addition, the blood may be used for other testing to see if the vaccine worked in your body by examining proteins and other types of specialized cells.
- If your Pap smear and/or pieces of your cervix are suspicious or consistent with HSIL and if you decide not to come back for the 12-Month Visit, optional LEEP visit may be offered to you if a study doctor thinks that would be beneficial.

12-Month Visit (6 months after 6-Month Visit; Gynecology Clinics and/or UAMS Winthrop P. Rockefeller Cancer Institute)

- You'll be asked about any medication changes.
- You'll be asked to fill out a "12-Month Visit Questionnaire" which will gather information such as your contact information and social security number for study participation reimbursement, as well as your experience while participating in the study.
- Vital signs will be obtained and a physical examination will be performed.
- Cervical cells will be obtained by Pap smear for HPV and bacterial testing.
- Colposcopy will be performed, lesions will be described and recorded and may be imaged. A doctor will take piece(s) of your visibly abnormal cervical tissue (biopsies) and possibly scrapings (endocervical curettage) to assess your response to the vaccine. If no lesions are visible, a doctor will take cervical tissue (biopsies) from the area(s) where cervical tissue (biopsies) with HSILs were taken prior to vaccination or from area(s) without any known abnormalities so at least 4 areas are tested. Colposcopy may be performed in the operating room (OR) if medically necessary. If the colposcopy is performed in the OR, a COVID-19 test may be required per hospital policy prior to this intervention.
- Eight to ten tubes of blood (up to 7 tablespoons total) will be drawn for clinical and immunology testing. The blood may be used to study how your white cells are reacting to HPV, to allow them to grow in a laboratory, for tissue (HLA) typing, genetic testing of your immune cells and related genes, and other similar tests. In addition, the blood may be used for other testing to see if the vaccine worked in your body by examining proteins and other types of specialized cells.

You will be informed of the colposcopy results from this visit. If there is no evidence of remaining HSIL upon biopsy, you will have completed the study. If you are found to still have HSIL, you can discuss with your study physician and choose to 1) to have LEEP performed as part of the study or 2) to complete the study and be followed by a gynecologist.

The latest recommendation from the ASCCP does not endorse performing LEEP in young women ages 18-24 after diagnosis of CIN II on biopsy. For CIN III, LEEP is recommended. This should be taken into consideration in your decision to enroll in this study and at the time of the above choice.

Optional Follow-up Visit (Gynecology Clinics and/or UAMS Winthrop P. Rockefeller Cancer Institute)

- Physician will discuss with you the follow-up schedule of repeat Pap/colposcopy for the next year, and appointments will be scheduled.
- Depending on the results of the prior blood test, eight to ten tubes of blood (up to 7 tablespoons total) will be drawn for further immunology testing.

Optional LEEP Visit (Gynecology Clinics and/or UAMS Winthrop P. Rockefeller Cancer Institute)

- Loop electrical excision procedure (LEEP) biopsy will be obtained.
    - The LEEP procedure takes about 20-30 minutes and is performed in the clinic. You will lie on the exam table with your feet in the stirrups. A colposcope will be used to guide the

physician to the abnormal area. An electrosurgical dispersive pad will be placed on your thigh. The pad is a gel-covered adhesive electrode, which provides a safe return path for the electrosurgical current. A single-use, disposable loop electrode will be attached to the generator hand piece by the physician. Your cervix will be prepared with solutions that enable the physician to more easily see the extent of the abnormal area. Imaging of your cervix may be performed. A local anesthetic will be injected into the cervix; the electroloop will be generated and the wire loop will pass through the surface of your cervix. After the lesion is removed, the physician will use a ball electrode to stop any bleeding that occurs; he/she may also use a topical solution to prevent further bleeding. You can leave the physician's office soon after the procedure. LEEP may be performed in the operating room (OR) if medically necessary. If LEEP is performed in the OR, a COVID-19 test may be required per hospital policy prior to this intervention.

- Depending on the results of the prior blood test, eight to ten tubes of blood (up to 7 tablespoons total) will be drawn for further immunology testing.
- Depending on the results of the prior test, cervical cells will be obtained by Pap smear for HPV and bacterial testing.

Optional LEEP Follow-up Visit (Gynecology Clinics and/or UAMS Winthrop P. Rockefeller Cancer Institute)

- You will be seen back in the clinic several weeks after the LEEP so the Physician can make sure your cervix is healing well, to discuss results, and to make a plan of follow-up care.
- In the event of inconclusive (unclear) LEEP results, a repeat LEEP will be offered if a study physician determines it to be medically necessary.
- You would remain in the study until all LEEP follow-up visits are complete.
- Depending on the results of the prior blood test, eight to ten tubes of blood (up to 7 tablespoons total) will be drawn for further immunology testing.

Other Optional Follow-Up Visits (Gynecology Clinics and/or UAMS Winthrop P. Rockefeller Cancer Institute)

- You may request a follow-up visit or may be asked to come back for a follow-up visit after being informed that you are not eligible for vaccinations or after exiting the study early for any reason.
- Depending on the results of the prior blood test, eight to ten tubes of blood (up to 7 tablespoons total) will be drawn for further immunology testing.
- You may also be asked to come back for a follow-up visits for the following reasons:
  - For evaluation of side effects or complications.
  - To pick up oral contraceptives, receive Depo Provera injections, or have an IUD placed or removed
  - For diagnostic assessment or surgical intervention during your participation in the study if it is related to the study and medically necessary including, but not limited to, colposcopy or LEEP performed in the operating room (OR), hysterectomy due to invasive cervical cancer, cone biopsy or medical imaging such as ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) scan. For any procedures performed in the OR, a COVID-19 test may be required per hospital policy prior to intervention.

- Surgical intervention required after your study participation has ended will not be covered by the study.

Visit Durations

- The Screening Visit, 6-Month, 12-Month, and LEEP Visits are expected to take about 90 minutes, but may be longer on busy clinic days.
- Vaccination Visits 1-4 and any Optional Follow-up Visits are expected to take about 60 minutes each.

Visit Windows

- The Vaccination Visit 1 should be scheduled as soon as possible after the Screening Visit but they cannot be more than 60 days apart.
- Vaccination Visits 1-4 should be scheduled at a 3-week interval. You do have a 7-day time frame before or after your appointment if you are not able to make the scheduled 3-week appointment.
- The 6-Month Visit should be scheduled 6 months after the last vaccination. You do have a 2-week time frame before or after your appointment if you are not able to make the scheduled 6-Month appointment.
- The 12-Month visit should be scheduled 6 months after the 6-Month Visit. You do have a 2-week time frame before or after your appointment if you are not able to make the scheduled 12-Month appointment.
- The entire study will last about 16 months.
- If you do not keep your appointment during the time required, you may be taken out of the study.

Other

- The investigator or sponsor may terminate the study at any time without your consent.
- You may be removed from the study if you do not follow study instructions, you become pregnant, there is a suspicion your HSIL may have progressed into cancer, or if it is not in your best interest to continue.
- You will be informed of any new significant findings that may affect your willingness to continue.
- Clinically relevant research results, including individual research results, collected during the study using standard tests/procedures may be provided to your at your request in accordance with UAMS Department of Health Information Management policies and requirements. However, research information and results obtained using research-only tests are not considered standard-of-care and, therefore, will not be released to you.
- You will not be notified about the results of the study. However, we may publish the results in an academic journal. (What we publish will not include anything that can identify you.)

RISKS AND DISCOMFORTS

HSIL progression

- Whether or not you decide to participate in the study, there is a risk that the HSIL may progress and develop into invasive cervical cancer, which may require a hysterectomy (removal of the uterus and/or ovaries) or other treatment. You may be removed from the study if there is a clinical suspicion that the HSIL has progressed into invasive cervical cancer, such as persistent vaginal bleeding. This is so you can receive the appropriate work-up and treatment for it. In the rare instance you are diagnosed with invasive cervical cancer during your participation in the study, you may be given the option to receive a hysterectomy prior to being removed from the study if a study physician determines it to be medically necessary. You would remain in the study until the follow-up visit after the hysterectomy is complete.

Colposcopy, LEEP procedures

- The possible risks of the colposcopy procedure are not common, but may include bleeding or infection at biopsy site(s). Minor discomfort may be experienced with endocervical curettage and biopsy.
- The possible risks of the LEEP procedure are mild pain or discomfort, mild cramping, and light bleeding. Other, less likely possible risks include difficulty in getting pregnant or potential for preterm birth or having a low birth weight baby.
- After LEEP procedure, the incidence of preterm delivery is known to increase from 4.4 to 8.9 percent.

Vaccine Injection

- The possible risks of injection of the study drugs are bleeding, infection, large immune response, pain, and scarring. These risks will be minimized by the presence of licensed medical personnel who will be present during and give the injections. Large local immune reactions of red and puffy skin will be treated with ice pack and a cream that is applied to that area of skin. If a large immune reaction occurs, you will be treated immediately by trained personnel. Any vaccine may potentially cause a life-threatening systemic reaction, rarely resulting in death. The reaction is called anaphylaxis. Anaphylaxis is a sudden, severe, potentially fatal allergic reaction that can involve various areas of the body (such as the skin, respiratory tract, gastrointestinal tract, and cardiovascular system). Symptoms can occur within minutes or up two hours after contact with an allergy-causing substance, but in rare instances may occur up to four hours later. Symptoms of an anaphylactic reaction may begin with a tingling sensation, itching, or metallic taste in the mouth. Other symptoms can include hives, a sensation of warmth, asthma symptoms (shortness of breath and/or wheezing), and swelling of the mouth and throat area.
- Adverse events are undesirable side effects that may occur. Adverse events or risks that also may occur include nausea, flu-like syndrome, fever, headache, chills, and muscle aches. Most of these side effects can be limited by taking ibuprofen or naproxen with your vaccinations. In our earlier preliminary study, the most common reaction seen in most vaccine recipients was injection site reaction (redness, itching, swelling) both immediate and delayed (occurring $\geq$24 hours after injection).
- The possible risks of taking ibuprofen or naproxen are in rare instances: difficulty breathing; swelling of your face, lips, tongue, or throat; and in some people: gastrointestinal problems; rash or other skin problems; kidney problems; or heart problems.

- This particular treatment or procedure may involve risks, which are currently unforeseeable, to the subject, embryo, or fetus if the subject is or may become pregnant.

Blood Draw

- The risks of drawing blood include temporary discomfort from the needle in your arm, bruising, swelling at the needle site and, in rare instances, infection.

Possible Loss of Confidentiality

- The risks of loss of confidentiality include your information being released to people who are not authorized to access your information. To minimize such event, your results will be protected and handled as confidentially as possible within the law, including the results of genetic testing, which would reveal a portion of your genetic make-up. All results will be stored and published using coding consisting of numbers.

Other Risks

- The risks of the treatments given in this clinical trial to unborn children are unknown. If you become pregnant due to not complying with using contraceptive methods or due to failure of contraceptive methods, you may be taken out of the study.
- Participation in this study may involve risks that are currently not known.

GENETIC STUDIES

As part of this study, white cells from your blood samples may be tested for tissue (HLA) types and immune cell genes, as well as other studies. The samples will be assigned a number instead of your name. The number will be linked to your name but the code will be stored under lock and key in the laboratory of the principal investigator.

Genetic Testing Risks

- With genetic testing of your tissue, there is a potential risk of loss of confidentiality. Genetic testing involves unique risks such as psychological and social risks and the risk of re-identification. Social risks include being stigmatized, discriminated against, labeled, or having difficulty obtaining employment or insurance. There is a risk that someone could trace the information back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, because your samples will be coded (without your name or identifying information), but the risk may change in the future as people come up with new ways of tracing information.
- Every effort will be made to protect your confidential information, but this cannot be guaranteed. The genetic information obtained as a result of your participation in this research will not be included in your medical record. Information from which you may be personally identified will be maintained in a confidential, secure location in Dr. Nakagawa's laboratory, accessible only by authorized members of the study team, and will not be disclosed to third parties except as described in this consent form, with your permission, or as may be required by law.
- The genetic testing will be done for research purposes only, and we do not plan to return any genetic results to you or your doctor.

- The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:
  - Health insurance companies and group plans may not request genetic information from this research;
  - Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premiums;
  - Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.
  - GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

In order to participate in the study, you need to allow your blood samples to be genetically tested.

QUESTIONS

If you have questions during the study about the research, you should contact Dr. Nakagawa at 501-217-0630. You may contact the IRB at (501) 686-5667 regarding a research-related injury, with questions regarding your rights as a research subject, or to discuss any problems or concerns about the research. Also, you may call this number if you are unable to reach the Investigator or you wish to speak to someone not directly related to this study.

LEGAL RIGHTS

You do not waive any legal rights to which you are otherwise entitled to by signing the consent form. You may also refuse to participate without loss of benefits.

TREATMENT FOR INJURY

In the event you are hurt by being in this research, treatment will be available. This treatment may include first aid, emergency treatment and/or follow-up care. This treatment may be billed to you or your insurance company in the normal manner. Normally, no other form of compensation is available. If you think you have been hurt by this research, let the study Investigator know right away by calling Dr. Nakagawa at (501) 686-8635 during the day or (501) 217-0630 after hours.

BENEFITS

There may be no benefit to you from participating in this research. It is possible that the vaccine treatment may benefit you by clearing your cervical dysplasia. Information to be obtained in this study may be of benefit to humankind in the future if it helps to develop a new therapeutic vaccine to prevent cancers caused by HPV, including cervical cancer.

ALTERNATIVE TREATMENT

If you do not participate in this study, you will still be able to receive the current standard of care. Please feel free to talk to your doctor about your choices.

COST

No cost is charged to you or your insurance for research tests and procedures. Optional LEEP performed at UAMS during your participation in the study and any optional follow-up visits will be paid for by the study. In the rare instance you develop invasive cervical cancer and require a hysterectomy during your participation in the study, the hysterectomy and any optional follow-up visits will be paid for by the study. For any study-related procedures performed in the OR, the study will pay for the cost of mandatory pre-operative COVID-19 testing at UAMS while institutional COVID-19 precautions are in effect. LEEP and other procedures performed outside of UAMS or after your participation in the study has ended will not be paid for by the study. You and/or your health insurance will be required to pay for those services, supplies, procedures and care that you continue to require for your routine medical care during this study (meaning the procedures and services you would have had even if you were not in the study). You will be responsible for any co-payments and/or deductibles as required by your insurance for such routine medical care. Before you agree to be in this study, you should contact your health care payer to see if your plan will cover the costs required as part of your participation.

REIMBURSEMENT

You will be given $300 compensation by check or gift card if you are eligible for the vaccinations and after completing the study. You will not receive compensation if you are not eligible for the vaccinations. If you were removed from the study early (after completing at least one vaccination visit) because of experiencing toxicity (certain bad side effects) or if you have signs of advancing disease and require treatment, you will receive $300 after completing the “Early Termination Questionnaire.” If you exit the study early for any other reason, such as withdrawing from the study or being taken out by Dr. Nakagawa for non-compliance, or if the study is suspended or discontinued for reasons not involving you, you can receive a partial payment after completing the “Early Termination Questionnaire”. You will be paid $50 per visit for each of the Vaccine Visits, the 6-Month Visit, and the 12-Month Visit. There will be no payments for the Screening Visit and Optional LEEP or Follow-up Visits. In order to receive a payment, you’ll be asked to provide your social security number so UAMS can comply with the applicable laws and regulations. While attending visits, parking will be provided for you at no cost.

In addition, if you travel more than 50 miles in one direction to come for appointments, you may be eligible to receive a per-visit travel stipend. The stipend will be based on miles traveled as verified by Google Maps, MapQuest, or other internet mapping software package.

Stipends will be:

- $40 for those traveling more than 50 but less than 100 miles
- $60 for those traveling more than or equal to 100 but less than 150 miles
- $80 for those traveling more than or equal to 150 but less than 200 miles
- $100 for those traveling more than or equal to 200 miles.

The stipend will be available on the dates of appointments in the form of a pre-loaded gift card.

In accordance with the United States IRB tax guidelines, UAMS has implemented new requirements for payments received for participation in a clinical trial. Payments paid to an individual per calendar year (January-December), equal to or greater than $600, are considered income and are taxable. UAMS requires a W-9 to be on file for all clinical trial subjects regardless of the amount of payment. If your payments were equal to or greater than $600 in that calendar year, UAMS will send you a 1099-MISC form to file with your taxes. Your name, address, and social security number are needed to process these payments. The 1099-MISC will be sent in January of the following year as required by the IRS. If your payments were not greater than $600 in the calendar year, you will not receive a 1099-MISC form and you will not have to file this on your taxes.

If you are a recipient of Social Security Income (SSI), Social Security Disability Income (SSDI) recipient, or other income based assistance programs, the additional income from this study will increase your yearly income and possibly making you ineligible for these benefits. Please contact your Social Security Office or your financial advisor if you have any questions.

PREGNANCY DURING THE STUDY

The risks of the treatments given in this clinical trial to unborn children are unknown. Should you become pregnant during the study period, the study sponsor will ask you to agree to the collection, storage and use of data about the pregnancy, birth and health of your baby. Please feel free to discuss any questions you might have with Dr. Nakagawa.

The only purpose of collecting, storing and using the data is to evaluate if the use of PepCan or Candin has any effect on the pregnancy and subsequent health of babies born by mothers who have been exposed to PepCan or Candin.

CONFIDENTIALITY

You have a right to privacy. All records are confidential; however, there are risks of loss of confidentiality due to the nature of research. Every effort will be made to keep your information confidential; however, this cannot be guaranteed. By signing this form you are allowing your records (including information that identifies you) to be made available to qualified personnel on Dr. Nakagawa's study team, and for the Food and Drug Administration, the Office for Human Research Protections, the University of Arkansas for Medical Sciences IRB, and other institutional oversight offices. The results of this study may be published in a scientific journal or book. Your name or any information to identify you would not be used. Records will be kept regarding your participation in the study. The records will be made available for review only as required by the Food and Drug Administration under the guidelines established by the Federal Privacy Act and the UAMS Institutional Review Board.

By law, the study team must release certain information to the appropriate authorities if at any time during the study there is concern that abuse has possible occurred or you disclose a desire to harm yourself or others.

HIPAA RESEARCH AUTHORIZATION

As part of the research study in which you are consenting to participate, we need to collect health information that identifies you. We may collect demographic data (such as date of birth, address, social security number for reimbursement purposes), health and medical history (including doctor's notes and clinic records), records from your study visits, and laboratory and test results. We will only collect information that is needed for this research. For you to be included in this research, we need your permission to collect, create, and share this information with the research team.

By signing this form, you are giving us permission to create, collect, use, and share your health information as described above. Your information could be shared with the groups listed above and institutional review committees whose job is to ensure we are protecting your information correctly. Any records or information released might be redisclosed by the person receiving them and will not be covered under the federal privacy laws.

You do not have to sign this form. However, if you decide not to sign this form, you cannot participate in the research study. If you sign this form, but decide later that you no longer want us to collect or share your information, simply send a letter to Dr. Nakagawa at 4301 West Markham Street, Slot 502, Little Rock, AR 72205. If you do revoke your permission, you cannot continue to participate in the research. However, in order to maintain the reliability of the research, we may still use and share your information that was collected before the principal investigator received your letter withdrawing the permissions granted under this authorization. All clinical information will be available to you as standard of care medical information. Research information collected during the study is not considered standard of care and, therefore, will not be released to you.

This authorization to collect, use, and share your health information expires at the end of the research. If you decide not to sign this form or change your mind later, this will not affect your current or future medical care at the University of Arkansas for Medical Sciences.

CONFLICT OF INTEREST DISCLOSURE

This research study is designed to test a product invented by Dr. Nakagawa. UAMS and Dr. Nakagawa are entitled to a share of royalties received from the sale of this product. The financial value of this interest might be affected by the results of this study. This means that UAMS and Dr. Nakagawa could gain or lose money depending on the results of this study.

CLINICALTRIALS.GOV REGISTRY

This study will be registered with Clinicaltrials.gov. A description of this clinical trial will be available on http://www.clinicaltrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this web site at any time.

FUTURE USE OF REMAINING SAMPLES

After we complete our tests, we would like to save any leftover samples for future research studies on HPV. Your blood and cervical cell samples will be frozen and stored with a number assigned to them instead of your name. The blood and cell samples may be stored indefinitely until needed for a future research study. The number will be linked to your name, which means you can withdraw your leftover blood and cell samples at any time. If at any time you would like to withdraw your stored sample, please write Dr. Nakagawa at 4301 West Markham Street, Slot 502, Little Rock, AR 72205.

You may agree to participate in this research study, but refuse to allow your samples to be stored for future research. Please **initial** the appropriate box.

Initials: _____ Date: _____ ***I AGREE*** *to have my leftover samples stored for future research.*

Initials: _____ Date: _____ ***I DO NOT AGREE*** *to have my leftover samples stored for future research.*

WHETHER OR NOT TO PARTICIPATE

Your participation is VOLUNTARY. You may refuse to participate or decide to withdraw from the study at any time. You may refuse to participate in the study without loss of benefits to which you are otherwise entitled. If you choose to quit the study, there will be no prejudices against you for other studies or care at UAMS. You may stop being part of the study by simply informing Dr. Nakagawa or a Study Coordinator.

Dr. Nakagawa or other study investigator (physician) may terminate your participation in this study at any time after he/she has explained the reasons for doing so. Reasons for termination may include your safety, not following appointment scheduling, not being able to contact you, among others.

I have read the above statements and have been able to ask questions and express concerns, which have been satisfactorily responded to by the study team. I understand the purpose of the study as well as the potential risks and benefits that are involved. I hereby give my informed and free consent to be a subject in this study. I have been told that I will be given a copy of this consent form.

MY SIGNATURE INDICATES THAT I HAVE DECIDED TO TAKE PART IN THIS STUDY.

Printed Name of Subject	Signature	Date

Printed Name of Person Obtaining Consent	Signature	Date