HPV Vaccine to Interrupt Progression of Vulvar and Anal Neoplasia (VIVA) Trial: A Randomized, Double-Blind, Placebo-Controlled Trial

Study Consent Form

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UNIVERSITY OF WASHINGTON
FRED HUTCHINSON CANCER RESEARCH CENTER

Consent to take part in a research study:

HPV Vaccine to Interrupt Progression of Vulvar and Anal Neoplasia (VIVA) Trial: A Randomized, Double-Blind, Placebo-Controlled Trial

(VIVA Trial)

Principal Investigator: Anna Wald, MD, MPH, University of Washington / Fred Hutchinson Cancer Research Center. 206-520-4340

Emergency Number (24 hours): 206-598-0924
Call and ask for the VRC Clinician to be paged

We are inviting you to participate in a research study. The purpose of this research is to see whether the human papillomavirus (HPV) vaccine decreases the chance of having persistent HPV infection.

If you agree to join the study, you would receive either the HPV vaccine or placebo, answer questions about your health, undergo blood draws, and have vulvar or anal biopsies. To be enrolled in this study you would have to agree to an anal or vulvar screening exam that uses a special magnifying glass to examine the area where you had a prior high-grade squamous intraepithelial lesion (HSIL). If there is evidence that you may have HSIL, the physician would take a biopsy. Only those individuals without evidence of HSIL at the screening visit will be eligible for the study.

We do not know if the HPV vaccine will decrease HSIL recurrences.

You do not have to join this study. You could choose to receive standard care for HSIL surveillance. We will give you details about the purposes, procedures, risks and possible benefits related to this study. We will explain other choices that you have. We will also give you any other information that you need in order to make an informed decision about joining this study.

The following information provides a more complete description of this study. Please read this description carefully. Afterwards, you can ask questions that will help you decide whether to join the study. If you join this study, we would give you a signed copy of this form to keep for future reference.

We invite you to join this research study.

We invite you to join this research study because you have been diagnosed with either anal or vulvar HSIL. Up to 230 people will join this study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

You do not have to be in the study. You are free to say “yes” or “no”, or to drop out after joining. If you say “no,” you would have no penalty or loss of benefits. Whatever you decide, your regular medical care would not change.

Why are we doing this study?

The FDA-approved HPV vaccine (Gardasil 9) has been shown to prevent HPV infections and genital HSIL. It is not known whether the vaccine can help prevent HPV infections and genital HSIL in people who have been found to already have vulvar or anal HSIL.

We are doing this study to examine whether Gardasil decreases the chance of having persistent HPV infection. To do this, we will compare Gardasil to a placebo vaccine. A placebo vaccine is a vaccine with no active ingredients (that is, it contains only salt water). We are testing an ‘off-label’ use of Gardasil because we are using it in a population in which it is not approved for use. If you join this study, you would receive either Gardasil or a placebo vaccine.

There are two vaccine groups in this study. We will give a different vaccine to participants in each group, and compare the results. This is how we hope to find out if Gardasil reduces persistent HPV infection. In this study, we use a computer program to decide which vaccine to give. If you join this study, you would not be allowed to choose which vaccine you receive. You would have a 50/50 chance of receiving Gardasil or placebo.

After you complete all study visits (at the 42-month study point), you will be offered the opportunity to find out which vaccine group you were assigned to. If you were assigned to the placebo group, you will be offered the HPV vaccine (Gardasil 9), free of charge.

What research tests, procedures, and treatments are done in this study?

If you join this study, we would do these tests and procedures:

- **Medical History.** You would be asked questions about your general health, including personal questions about your HSIL diagnosis and treatment, and any other medical conditions and medications.

- **Medical Record Review.** We would look at your medical records to collect information about your HSIL diagnosis. We would look at information starting from your original HSIL diagnosis until the end of this research study.

- **Tissue and Pathology Reports.** We would request tissue samples and pathology reports starting from your original HSIL diagnosis until the end of this research study.

- **Physical Exam.** A physical exam would be performed at the Screening Visit. At all other visits, a physical exam would be performed only if you are having any symptoms or health problems.

- **Vital Signs.** Prior to each vaccination, we would collect your vital signs (blood pressure, pulse, and temperature). At the Enrollment Visit, we would ask you for your height and weight.

- **Questionnaire.** We would ask you to fill out four self-administered computer questionnaires during clinic visits—at Enrollment, Month 6, and Months 18, 24 and 36. Each questionnaire has personal questions about your health including health history, HSIL diagnosis including any new surgeries or treatments, medications, sexual history, and smoking history. Some of the questions may be sensitive. Questions that make you feel uncomfortable would not have to be answered.

Table of Study Visits and Procedures

			Study Month							
	Screen	**Enrollment (Month 0)**	**2**	**6**	**7**	**12**	**18**	**24**	**36**	**42**
Medical History	X	X	X	X	X		X	X	X	
Physical Exam[1]	X									
HIV Testing (if needed)	X									
Urine Pregnancy Test (if needed)	X	X	X	X						
Randomization		X								
Vaccination		**X**	**X**	**X**						
Self-Administered Questionnaire		X		X			X	X	X	
Blood Draw		X			X		X		X	
Blood Draw for DNA (optional)					X					
Oral Rinse	X				X		X	X	X	
Anoscopy/Vulvoscopy[2]	X						X		X	
Swabs for HPV	X						X	X[3]	X	
Biopsy	X[4]						X[4]		X[5]	
Telephone Follow-up Visit						X				X

[1] A physical exam would be performed at the Screening Visit. At all other visits, an exam would be performed only if you were experiencing symptoms or health problems.
[2] Anoscopy/vulvosocpy would not be performed at the visit if the procedure was done within study visit windows with a certified provider. The study staff would discuss this with you.
[3] Swabs may be self-collected by the participant, if necessary.
[4] A biopsy would be performed if a lesion is noted during anoscopy/vulvoscopy
[5] A biopsy would be performed if a lesion is noted during anoscopy/vulvoscopy. If there is no visible lesion, an optional biopsy would be performed at the site of the original tumor.

- **Blood draws.** A small amount of blood would be drawn (4-8 teaspoons) to study your immune response to HPV. We would also use some of the blood to study your DNA (genetic information). DNA collection would be optional.

- **HIV test.** A small amount of blood would be drawn (2 teaspoons) for an HIV test. This would only be done if you have never been tested or if your last test was over 6 months to 1 year ago. If the test is positive, one of the study staff would discuss this with you. You would receive individual counseling and the study clinician would refer you for proper treatment.

- **Urine Pregnancy Test.** Sexually active women of child-bearing potential would undergo a urine pregnancy test at the Screening Visit and prior to any vaccination.

- **Oral Rinse.** An oral rinse sample would be collected to test for HPV DNA. The rinse would be collected at Screening and at Months 7, 18, 24 and 36. To collect this rinse, we would ask you to gargle with mouthwash and spit into a small collection cup.

- **Vaccination.** As part of this study, you would be vaccinated with either Gardasil or placebo. You would receive three doses of the study vaccine: at Enrollment (Month 0) and again at Months 2 and 6. Neither you nor the study clinician would know which vaccine you get. After each vaccination, you would be asked to wait in the clinic for 15 minutes.

- **Vaccine Diary.** For 5 days after each vaccination, we ask that you keep track of any symptoms you may experience on a vaccine card. We also ask that you keep this card and bring it with you to your next clinic visit so that you can discuss any symptoms with your study clinician.

- **Anal Exam, Anal Swabs, Anoscopy, and Anal Biopsy for Participants with prior Anal HSIL).** We ask participants to avoid receptive anal intercourse for 24 hours prior to the clinic visit. The following procedures are conducted to detect abnormal skin cells or growths:

  For the rectal exam, the clinician inserts a lubricated, gloved finger of one hand into the anus/rectum.

  To collect skin cell samples from the anal canal, a swab (similar to a Q-tip) is inserted into the anus, rotated, removed, and the collected specimen is placed in a container.

  Anoscopy uses a lubricated plastic tube called an anoscope, which is inserted into the anus. Then, a piece of gauze moistened with acetic acid (vinegar) is placed in the anus for 1-2 minutes to enhance visualization of any abnormal areas. After the gauze is removed, the anoscope is put back into the anus. A colposcope (magnifying lens) is then used to examine the skin inside the anus. Iodine may be used to help make lesions show up.

  Anal biopsies remove pieces of anal skin about the size of a sesame seed (2-3 mm) to look for abnormal skin growth under a microscope. The study clinician may inject a small amount of local anesthesia (numbing medicine) before the biopsy.

You will receive a separate Information Sheet about anal biopsies that will include more information about the procedure. Exam and biopsy results will be shared with your primary healthcare provider.

- **Genital Exam, Vulvar Swabs, Vulvoscopy, and Vulvar Biopsy (For participants with prior vulvar HSIL).** An external genital exam would be performed. A swab (similar to a Q-tip) would be used to collect a sample of cells of vulvar skin by moving the swab back and forth along the entire area, including between the folds of the vulva.

  Vulvoscopy uses a special magnifying lens to detect the presence of abnormal skin changes. First, a piece of gauze moistened with acetic acid (vinegar) is placed on the vulva for 3-5 minutes. Then, a colposcope (a magnifying lens) is used to look for lesions.

  During a vulvar biopsy a piece of skin about the size of a sesame seed is removed to look for abnormal skin growth. A lidocaine injection (numbing medicine) is given to help prevent pain. Bleeding from the biopsy is usually minimal. We may use the medication silver nitrate to stop the bleeding.

  You will receive a separate Information Sheet about vulvar biopsies that will include more information about the procedure. Exam and biopsy results will be shared with your primary healthcare provider.

- **Complementary Anoscopy/Vulvoscopy.** For participants with HSIL at both sites (anal and vulvar) or for participants who, in the opinion of the investigator, may benefit from anoscopy/vulvoscopy, we would offer a free exam at the other site. This would occur at any visit after Enrollment depending on your schedule and our provider schedule. You would be asked questions about this other HSIL diagnosis and treatment. The results from your complementary exam would become part of the research record.

- **Biopsy Follow-up.** We would contact you 1-3 days after you receive a biopsy to make sure the biopsy site is healing. If a biopsy is taken from a lesion, the results of the biopsy would be shared with you. Results would also be shared with your healthcare provider. Any follow-up treatment would be provided by your healthcare provider.

- **Telephone Follow-up.** Follow-up by telephone interviews would take place at 12 and 42 months after enrollment. We would ask a short series of questions about any changes in your health, smoking status, and any updates on your HSIL diagnosis.

- **Study Reminders.** We would also give you a reminder (by phone, email or text, your preference) every 1-3 months after the Month 12 Visit to remind you about the study and confirm your contact information.

How long would you stay in this study?

If you join this study, you would stay in this study for 3½ years (42 months). You would receive 3 doses of Gardasil within the first 6 months (at 0, 2 and 6 months). After that, you would have follow-up visits in the clinic approximately every 6-12 months for 3 years.

The study doctors could take you out of this study at any time. This would happen if:

- They think it is in your best interest not to continue in the study.
- You not able or willing to follow study procedures.
- The whole study is stopped.

If you withdraw from the study for any reason, previously collected information would remain in the study records and would be included in the analysis of results. This information could not be removed from the study records.

What if I become pregnant?

If you become pregnant during the vaccination phase of the study, we will stop vaccinations and start them again after your pregnancy is over. We want you to stay on study for blood draws and other procedures that will not affect your pregnancy.

What are the side effects (risks)?

In this part of the consent form, we describe the side effects we expect from the tests and treatments in this study. We carefully watch everyone in the study for side effects.

If you join this study, we would tell you if we discover new side effects that could affect you. Side effects may be mild or very serious. Medicines could be given to help lessen side effects.

Blood Draw: Having blood drawn may cause some pain. You may feel faint. A bruise may form where the needle enters the vein. In rare cases, an infection may develop.

HIV Testing: Being tested and learning your HIV test results may cause you and any partner(s) stress and anxiety. If the test is negative, you might be tempted to have unsafe sex which would increase your risk of becoming infected with HIV.

Medical History & Questionnaires: Some questions asked during the study may be sensitive and embarrassing to you. You do not need to answer questions that make you uncomfortable. You may refuse to answer any of the questions.

Reproductive risks**:** The risks to an unborn human fetus from the Gardasil are not known. Women who are pregnant are not eligible to participate in this study. A urine pregnancy test will be done at the Screening Visit and prior to each vaccination. If you suspect that you have become pregnant during this study, you must notify the study clinician immediately. If you become pregnant during the study, we would ask that you remain in the study. If you become pregnant during vaccine dosing, you would receive the rest of your vaccine doses after your pregnancy.

Vaccination: Gardasil vaccination risks include a small risk of severe allergic reaction; pain, redness and/or swelling of the arm at the injection site; mild to moderate fever, nausea, dizziness, headache, or fainting. As with any drug there may be unexpected side effects. Safety of the vaccine after treatment for HSIL is unknown.

Participants with prior Anal Condition:

Anal Swabs: Putting a swab into the anus may cause some discomfort. Minor bleeding (less than a quarter of a teaspoon) rarely occurs in some people due to the insertion of the swabs. The bleeding stops almost right away.

Anoscopy: Insertion of an anoscope will likely cause some discomfort. Participants may feel pressure and the urge to have a bowel movement. Putting acetic acid (vinegar) in the anal canal rarely causes minor burning and irritation.

Anal Biopsy: Participants may have pain with the anal biopsies. Participants may have some bleeding for up to a week after biopsies, especially when they experience a bowel movement. There is a rare chance of very heavy bleeding that may require extra treatment. There is a very slight risk of infection (<1%). Participants will be instructed to contact the study clinic if they have symptoms of heavy bleeding or infection (fever, pain, redness, or swelling).

We will ask participants to refrain from receptive anal sex for 24 hours before the biopsy and to refrain from taking aspirin and ibuprofen, or medications containing these, prior to the biopsy. This will help prevent any possible increase in risk of infection or bleeding after the procedure. We will instruct participants to avoid aggressive exercise immediately after the biopsy and to not engage in receptive anal sex for one week after the rectal biopsy.

Participants with prior Vulvar Condition:

Vulvoscopy: Participants may feel discomfort during the procedure. Application of acetic acid (vinegar) for the exam may cause a burning sensation.

Vulvar biopsy: Injection of a local anesthetic prior to the biopsy maybe painful and the biopsy itself may cause pain, even with the use of an anesthetic. Biopsies may cause a pressure or tugging sensation. Bleeding and pain or irritation at the biopsy site(s) may continue for up to a week following the procedure. Although the skin biopsies are small (3-4mm), scarring may occur at the site. Participants will have to avoid sexual contact for 5 days after a biopsy, or until healing is complete.

Lidocaine (injectable, +/- epinephrine): Lidocaine administration is associated with temporary pain and burning. Allergic reactions to lidocaine may occur, even in participants with no history of allergic reactions. Examples of allergic reactions include wheezing or difficulty in breathing, light-headedness or fainting, skin rash and itching. As with any drug there may be unknown side effects. Biopsies may cause discomfort even when the area is numbed using lidocaine

Silver nitrate: Silver nitrate may be used if there is excessive bleeding after a biopsy. As with any drug there may be unknown side effects.

Monsel's Solution: Topical Monsel's solution may be used for excessive bleeding after an anal biopsy.

Oral Rinse: If an oral lesion is present when collecting the oral rinse, this may cause discomfort while using the oral mouthwash.

What are the benefits?

We do not know if Gardasil will reduce HSIL recurrences or disease progression in persons with HSIL. Although the study may not benefit you directly, we hope the information we learn will help people with HSIL in the future.

You have other choices besides this study.

You are free to choose not to participate in this study. If you choose not to participate it will not affect your other care at this clinic. You do not have to join this study. You are free to say "yes" or "no". Your regular medical care would not change if you decide to say "no".

Enrollment in this study may exclude you from other research studies.

Protecting Privacy as an Individual and the Confidentiality of Personal Information

If you join this study, some people or organizations might need to look at your medical records and research records for quality assurance or data analysis. They include:

- Researchers involved with this study.
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Research Center IRB. An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- Fred Hutchinson Cancer Research Center, and University of Washington
- US National Institutes of Health, National Cancer Institute,
- Office for Human Research Protections, and other regulatory agencies as required.
- Food and Drug Administration (FDA)

We will do our best to keep personal information confidential. But we cannot guarantee total confidentiality. Personal information may be given out if required by law. For example, work place safety rules may require health workers to contact you about lab tests. Or a court may order study information to be disclosed. Such cases are rare.

HIV is a notifiable condition. The study staff will send a report your local health department. This report will include your name, address and other information.

We will not use personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

If you join this study, information about your participation would be made part of your permanent medical record. This information would include a copy of this consent form. If you authorize others to see your medical record, they would see a copy of this consent form.

We have a Certificate of Confidentiality from the National Cancer Institute. This Certificate helps us protect the privacy of people who join this study. If you join the study, the Certificate means that generally we would not have to give out identifying information about you even if we were asked to by a court of law. We would use the Certificate to resist any demands for identifying information.

We could not use the Certificate to withhold research information if you give written consent to give it to an insurer, employer, or other person.

This protection has some limits. We would voluntarily provide your information:

- To a member of the federal government who needs it in order to audit or evaluate the research.
- To individuals at the University of Washington, the Fred Hutchinson Cancer Research Center, the funding agency, and other groups involved in the research, if they need the information to make sure the research is being done correctly.
- To the federal Food and Drug Administration (FDA), if required by the FDA.
- To someone who is accused of a crime, if he or she believes that our research records could be used for defense.
- To authorities, if we learn of child abuse, elder abuse, or if patients might harm themselves or others.

How is my genetic information protected?

A federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect genetic information about people who join research studies.

GINA restricts access to genetic information so that it cannot be used for health insurance coverage decisions. GINA prevent health insurance companies or group health plans from

- Asking for genetic information obtained in research studies, or
- Using genetic information when making decisions regarding your eligibility or premiums

GINA *does not* help or protect against genetic discrimination by companies that sell life, disability or long term care insurance.

Would we pay you if you join this study?

If you join this study and do what is necessary, you would receive payment for each clinic visit as described in the table below. If you do not complete the study, you would receive a partial payment based on the visits you complete. Parking validation or bus tickets would be provided at each study visit.

			Study Month							
	Screen	**Enrollment (Month 0)**	**2**	**6**	**7**	**12**	**18**	**24**	**36**	**42**
Payment	**$100***	**$75***	**$25**	**$25**	**$25**		**$100**	**$50**	**$150**	

*If a combined Screening & Enrollment Visit is conducted, you would receive $175 for that visit.

Payments for being in the study may be taxable. If you join the study, we would need your social security number for tax reasons.

Would you have extra costs if you join this study?

There are no extra costs for being in this study. Study drug will be provided free of charge.

What if you get sick or hurt after you join this study?

For a life-threatening problem, call 911 right away or seek help immediately. Contact your study doctor when the medical emergency is over or as soon as you can.

For all other medical problems or illness related to this research, immediately contact Dr Anna Wald or your study clinician. They will treat you or refer you for treatment.

The costs of the treatment may be billed to you or your health insurance just like other medical costs, or it may be covered by the University of Washington's (UW) discretionary Human Subjects Assistance Program (HSAP), depending on a number of factors. The researcher may request HSAP coverage by following established procedures. If you wish to request HSAP coverage yourself, contact the researcher or the UW Human Subjects Division at hsdinfo@uw.edu or 206-543-0098. You may also call collect to the UW Human Subjects Division at 206-221-5940 if you do not otherwise have access to a telephone. Ask the researcher if you would like information about the limits and conditions of the HSAP. The UW does not normally provide any other form of compensation for injury. However, the law may allow you to seek payment for injury-related expenses if they are caused by malpractice or the fault of the researchers. You do not waive any right to seek payment by signing this consent form.

You or your insurer will be billed for treatment of problems or complications that result from your condition or from standard clinical care.

You would not lose any legal right to seek payment for treatment if you sign this form.

We invite you to donate samples for other research.

After we do tests on samples in this study, some samples may be left over. We invite you to donate these leftover samples for future research. This may include genetic research.

If you join this study, you would not have to donate samples for research. You would be free to say "yes" or "no". Regular medical care would not change if you say "no."

If you donate samples, they would be stored in a secure location. If we want to use your samples for other research or share it with other scientists for research, an ethics review committee (IRB) would review the request. The IRB would decide if we need to ask you for permission to do the research.

Your donated samples would be used only for research. This research could be done by for profit companies. Researchers would not report their results to you or your doctors. The research results would not be included in medical records. The results would not affect your medical care.

Research with samples might help develop new products. If these products make money, there is no plan to share the money with the participants who donate the samples.

If you donate samples for research, you could withdraw the donation at any time by calling Dr. Anna Wald at 206-520-4340. You would have no penalty for withdrawing the donation, and regular medical care would not change. We could not return donated samples, but we might be

able to destroy the donated samples. We could keep samples if they are stored or shared without any label saying who donated it. In this case, it could still be used for research.

Future genetic research

Several generic databases are available to help researchers understand different diseases. These databases contain DNA code and medical information from participants who have various diseases.

As part of this study, we would like to release DNA code and information about your medical condition into a genetic database in order to help future research. The genetic database would not contain names, addresses, or other information that could be used to identify you.

The DNA code in a genetic database cannot be used by itself to identify any specific person. A researcher who already has DNA code about you could use information from a genetic database to learn more about you. Once we release information to a genetic database, we no longer have any control over the use of this information.

Your rights

- You do not have to join this study. You are free to say “yes” or “no”.
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we might learn new information that you need to know. For example, some information may affect your health or well-being. Other information might make you change your mind about being in this study. If we learn these kinds of information, we would tell you.
- If you join this study, you would not have to stay in it. You could stop at any time (even before you start). Your regular medical care would not change. You would have no penalty for stopping, but it would be better not to join the study if you think that you would change your mind later.

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

Your responsibilities

If you join this study, you would have some responsibilities.

- Follow the schedule of study visits and procedures.
- Prevent pregnancy.
- Tell us about side effects.

For more information

If you have questions or concerns about this study, you could talk to your doctor anytime. Other people you could talk to are listed below.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	206-520-4340 (Dr. Anna Wald) 206-520-4340 (your study clinician)
If you get sick or hurt in this study	206-520-4340 (Dr. Anna Wald)
Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center) 206-543-0098 (Human Subjects Division, University of Washington)

Emergency number (24 hours): 206-598-0924

Read each question and think about your choice. When you decide on each question, please circle **YES** or **NO**.

Do you agree to donate your leftover samples for future research? (circle one) **YES** **NO**

Is it OK if someone contacts you in the future to ask you to provide more samples? (circle one) **YES** **NO**

Is it OK if someone contacts you in the future to ask you to participate in other research studies? (circle one) **YES** **NO**

Do you agree to provide a blood sample to study your DNA? (circle one) **YES** **NO** If YES, is it OK if we send your genetic information to one or more databases for future research? (circle one) **YES** **NO**

Signatures

If you have read this form (or had it read to you), asked any questions, and agree to participate, please sign:

Participant / Printed Name, Signature, and Date

If you served as an interpreter or witness during the consent process, sign below to indicate you attest to the accuracy of the presentation to the participant and the apparent understanding of the research by the participant.

Witness or Interpreter / Printed Name, Signature, and Date

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

Person obtaining consent signature / Printed Name, Signature, and Date

Protocol: 9790