Study Protocol: NCT05551949

Study title: Mechanisms of Successful Vaginal Estrogen Prophylaxis for Postmenopausal Women With Recurrent Urinary Tract Infections: Urogenital Microbiota and Host Immune Responses

PI: Victoria Handa, MD

Date of this consent form: December 19, 2022

If appropriate for this study, a scanned copy of the signed consent form should be uploaded to the participant's Epic/EMR record.

Patient I.D. plate

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: **Mechanisms of Successful Vaginal Estrogen Prophylaxis for Postmenopausal Women with Recurrent Urinary Tract Infections: Open Label Clinical Trial**

Application No.: **IRB00314740**

Principal Investigator: **Victoria L. Handa, MD**
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You are being asked to join a research study. Participation in this study is voluntary. Even if you decide to join now, you can change your mind later.

1. Research Summary (Key Information):

The information in this section is intended to be an introduction to the study only. Complete details of the study are listed in the sections below. If you are considering participation in the study, the entire document should be discussed with you before you make your final decision. You can ask questions about the study now and at any time in the future.

This study is for postmenopausal women who experience recurrent urinary tract infections (UTIs).

For many women with recurrent urinary tract infections, vaginal estrogen is recommended to reduce or prevent infections. You are being asked to join this study because you have recurrent urinary tract infections and your doctor or nurse practitioner has recommended vaginal estrogen for you as part of standard care. For this study, the vaginal estrogen ("estradiol") will be a tablet that you put into your vagina. If you join the study, the estrogen tablets will be provided for you at no cost for a total of 24 weeks.

The purpose of this study is to learn more about the effect of vaginal estrogen on the woman's vagina and urinary tract. The study team will collect vaginal swabs and urine from women who join this study. These specimens will be collected two times: (1) before estrogen is started and (2) after about 12 weeks of the estrogen regimen. The specimens will be collected when you come to a routine clinic visit.

We will also want to know whether you have urinary infections while you are using vaginal estrogen. We may ask you questions about infections or check your medical record for infection treatments. We will be interested in whether you have any infections during the 24 weeks of the estrogen regimen.

After the 24 weeks are done, you might decide to continue the vaginal estrogen tablets. Your doctor or nurse practitioner can give you a prescription so that you can continue the same regimen but you would no longer be in the research study.

All women enrolled in this study will be receiving estrogen, which is commonly prescribed in clinical practice. Vaginal estrogen is currently recommended by the American Urologic Association as a best practice for preventing recurrent UTI. You may feel uncomfortable when providing the vaginal and urine samples. There is a risk that information about you may become known to people outside of this study. You will not receive any direct benefits from the study (other than helping to advance science).

2. Why is this research being done?

This research is being done to learn more about the effect of vaginal estrogen on the woman's vagina and urinary tract.

Are there any investigational drugs/devices/procedures?

No. Vaginal estrogen treatments (including vaginal tablets as well as vaginal creams and rings) are approved by the Food and Drug Administration (FDA) for the treatment of "menopausal vaginal atrophy" (vaginal problems related to menopause) but not approved for use in urinary tract infections (UTI). However, vaginal estrogen used during this study (vaginal estradiol) is commonly prescribed by doctors and nurse practitioners to treat women after menopause.

Who can join this study?

Women 55 years or older with recurrent urinary tract infections and who have been recommended to use vaginal estrogen may join.

Potential participants with a current urinary tract infection or who have received antibiotics in the prior 2 weeks, may have to wait to join this research study.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

- You will complete a brief questionnaire including questions about urinary symptoms.
- At your visit today or a future visit (but before you start the estrogen regimen), we will collect vaginal and urine specimens:
    - During a gynecologic examination, we will collect swabs from the vagina.
    - We will ask you to provide a urine specimen. During your clinic visit, if we use a catheter to obtain a urine specimen, we use the urine collected with the catheter.
- After we collect those specimens and swabs, you will be provided with a 12-week supply of vaginal estrogen tablets.
- You will be asked to come back for a second visit after you have been using the vaginal estrogen for approximately 12 weeks. At the 12-week visit:
    - We will discuss whether you have had any urinary tract infections during the study period.
    - You will complete a brief questionnaire including questions about urinary symptoms.
    - We will collect the same types of specimens.
    - You will receive a second 12-week supply of vaginal estrogen tablets.

- You will come back for a third and final visit after you have been using the vaginal estrogen for a total of 24 weeks. At the 24-week visit:
  - We will discuss whether you have had any urinary tract infections during the study period.
  - You will complete a brief questionnaire including questions about urinary symptoms.
  - If you want to continue using the vaginal estrogen, your doctor or nurse practitioner can give you a prescription.
- During the study period, we will ask you to tell us if you have a urinary tract infection. In addition, we will also look at your medical records to see if you have been treated for an infection during the study period.

The biospecimens you provide for this research study (vaginal swabs and urine) will be sent to the lab and then stored in the freezer. The biospecimens will be then analyzed for the "microbiome" (the type of bacteria living in the woman's body) and "inflammatory mediators" (chemicals produced by the immune system). Other types of analysis might be performed as well, such as to better understand the types of bacteria and their functions. We will compare the "before" and "after" specimens to see how estrogen effects the "microbiome" and "inflammatory mediators". As the study goes on, we will also compare women who stop having urinary infections to those who continue to experience infections. We believe that this comparison will help scientists better understand how vaginal estrogen works to reduce infection.

Will research test results be shared with you?
This study involves research tests that we do not expect will be useful for your clinical care. We will not share these results with you.

How long will you be in the study?
You will be in this study for 24 weeks (approximately 6 months).

Contacting you about possible future research
If you join this study, the research team might want to contact you in the future (possibly to ask you to join additional research). Will you allow this research team to contact you about future research?

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

4. What happens to data and biospecimens that are collected in the study?

If you join this study, your data and biospecimens will be used to answer the research question and your data will be used to publish the findings of this study. Biospecimens may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person.

You will not own the data and/or biospecimens collected from you as part of this research study. If researchers use them to create a new product or idea, including those that may have commercial value, you will not benefit financially from those efforts.

Johns Hopkins researchers and their collaborators may use the data/biospecimens collected in this study for future research purposes and may share some of the data/biospecimens with others.

Because science constantly advances, we do not yet know what future use of research data or biospecimens may include. This future research may be unrelated to the current study and may include outside collaborators.

Sharing data and/or biospecimens is part of research and may increase what we can learn from this study. Often, data/biospecimen sharing is required as a condition of funding or for publishing study results. It also is needed to allow other researchers to validate study findings and to come up with new ideas. Your data and/or biospecimens may be shared with researchers at Johns Hopkins and other institutions, for-profit companies, sponsors, government agencies, and other research partners. Your data and/or biospecimens may also be put in government or other databases/repositories.

We (Johns Hopkins) will do our best to protect and maintain your data/biospecimens in a safe way. One of the ways we protect data/biospecimens is by limiting the uses of the information and the type of information that is shared, especially your personal information. This may occur through data/specimen sharing agreements and review by oversight groups within Johns Hopkins.

If data/biospecimens are used or shared with types of information that may be likely to identify, you such as your name, address or medical record number, further institutional review and approval would be required. In these cases, Johns Hopkins will review whether additional consent from you is required. Generally, if your data/biospecimens are used/shared without any personal identifiers or with information that is less likely to identify you (such as the date of a procedure), further review and approval is not needed.

Data/biospecimen sharing could change over time, and may continue after the study ends.

The use and sharing of your data and biospecimens is required for participation in this research study. If you are not comfortable with the use and sharing of your data/biospecimens in future research without further consent, you should not participate in this study.

Genomic Data Sharing

Genomic studies, including genome-wide association studies (GWAS), examine genetic differences in the entire human genome (the complete set of human genes) and the association between these genetic differences and health conditions.

As part of this study, we will collect information about your health and your individual genes. This information will be sent to a National Institutes of Health (NIH) designated data repository that includes genomic and other data from studies funded by the NIH.

The aim of collecting this information is to look for genetic connections that may:

- Increase the likelihood of getting a certain disease (such as asthma, cancer, diabetes, heart disease or mental illness) or a condition (such as high blood pressure or obesity);
- Affect the progress of a certain disease or condition;
- Affect treatments (medicines, etc.) that work for certain diseases in some people, but not in others.

We or our collaborators will remove direct personal identifiers (such as your name or date of birth) and instead code your information before sending it to the repository**.** The NIH will never receive this code or the personal identifiers we have removed.

The repository is a controlled-access repository. This means that your individual de-identified data is only available to researchers who apply to the NIH. The NIH will review data requests for scientific merit and for methods to protect data and methods to ensure data will be used for the approved purpose. We will not always know what types of health-related research will be done with the data that are sent to the repository. Information from Johns Hopkins participants that is sent to the repository will only be shared with researchers at other not-for-profit organizations (for example, other academic institutions).

Genomic summary results (GSR) data for non-sensitive studies may be made available by NIH without controlled-access. GSR data does not include information about you as an individual, but consists of statistical information calculated using your data combined with data from other people.

5. What are the risks or discomforts of the study?

The vaginal estrogen used in this study is the same treatment that gynecologists and urologists typically recommend to reduce recurrent urinary tract infections.

This estrogen treatment is considered “low dose” and is expected to cause minimal or no increase in blood estrogen levels. Therefore, the treatment used in this study is not expected to have risks or benefits beyond the vagina. For example, you should not expect improvement in hot flashes. Similarly, there are no scientific data suggesting that low-dose vaginal estrogen is linked to cancer risk or circulatory diseases. However, the FDA labeling (package insert) for low-dose vaginal estrogen does not distinguish between low-dose vaginal estrogen and high dose or “systemic” estrogen products. Based on the FDA package insert, side effects in women receiving this regimen may include back pain, diarrhea, and vaginal itching/irritation. Please notify study personnel if you experience persistent back pain, diarrhea, or vaginal itching/irritation. Also, please notify study personnel if you experience vaginal bleeding while using vaginal estrogen tablets.

This study includes obtaining vaginal swabs during a pelvic examination. While the pelvic examination is uncomfortable for some women, obtaining swabs for this research is not expected to add any risks or discomforts.

During your clinic examination, your doctor or nurse practitioner may obtain a urine specimen with a catheter (a tube placed briefly into your urinary tract during the examination). In most cases, the catheter is part of routine care for women with recurrent urinary tract infection. While the catheterization may be uncomfortable for some women, obtaining this additional urine specimen is not expected to add any risks or discomforts.

Finally, although we follow precautions to protect your health information, there is the risk that information about you may become known to people outside this study.

6. Are there benefits to being in the study?

There is likely to be no direct benefit to you from being in this study. However, if you take part in this study, you may help others in the future.

7. What are your options if you do not want to be in the study?

You do not have to join this study. You can use vaginal estrogen without joining the study. If you do not join, your care at Johns Hopkins will not be affected.

8. Will it cost you anything to be in this study?

You will receive estrogen at no charge during the time that you are on the study. You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet. This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research and that will be paid for by the study (no cost to you).

It may also include the following, if applicable for the study:

- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

9. Will you be paid if you join this study?

You will receive a total of $100. You will receive $50 at the end of the first 12 weeks of the study and a second $50 payment at the conclusion of the study. If you cannot complete the study (such as due to medication intolerance), you will be paid when you leave the study, which includes a return for specimen collection at that time.

10. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, Johns Hopkins may use or share your health information that it has already collected if the information is needed for this study or any follow-up activities.

11. Why might we take you out of the study early?

You may be taken out of the study if:

- You fail to follow instructions.
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, Johns Hopkins may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

12. How will your privacy be maintained and how will the confidentiality of your data be protected?

HIPAA Authorization for Disclosure of Protected Health Information

What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Johns Hopkins Medicine and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive, or use your private health information include the researchers and their staff who may be a part of Johns Hopkins Health System, Johns Hopkins University or the Johns Hopkins Applied Physics Laboratory. Additionally, we may share your information with other people at Johns Hopkins, for example if needed for your clinical care or study oversight. To improve coordination of your research and clinical care, some information about the study you join will be included in your electronic medical record.

By signing this form, you give permission to the research team to share your information with others outside of Johns Hopkins. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team.

We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

How will your information be protected?
To protect your privacy and confidentiality, data will be managed on a secure system. All collected specimens will be labeled with the participant's study number. We will keep track of your study number in a log that we maintain at the research office. No one who analyzes your specimen will know your name or medical record number. The log that links each participant to the assigned study number will be kept electronically in a protected database.

Only the study team will have access to these data. No identifiable information will be stored on private devices or directly on computers or other electronic devices. Paper documents containing your information (such as signed consent documents) will be uploaded electronically but the original hard copies will also be retained in accordance with institutional policy.

13. Will the study require any of your other health care providers to share your health information with the researchers of this study?

As a part of this study, the researchers may ask to see your health care records (from your other health care providers) related to treatment for urinary tract infections that occur during the study. If you go to a non-Johns Hopkins facility for treatment of a urinary tract infection, we may ask you to help us obtain those records.

14. What treatment costs will be paid if you are injured in this study?

Johns Hopkins does not have a program to pay you if you are hurt or have other bad results from being in the study. However, medical care at Johns Hopkins is open to you as it is to all sick or injured people.

The costs for any treatment or hospital care you receive as the result of a study-related injury that are not covered by a health insurer will be billed to you.

By signing this form, you will not give up any rights you have to seek compensation for injury.

15. What is a Certificate of Confidentiality?

Your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

16. What other things should you know about this research study?

During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.

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. If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

What is the Institutional Review Board (IRB) and how does it protect you?
This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB can help you if you have questions about your rights as a research participant or if you have other questions, concerns or complaints about this research study. You may contact the IRB at 410-502-2092 or jhmeirb@jhmi.edu.

What should you do if you have questions about the study?
Call the principal investigator, Dr. Handa, at 410-550-0336. If you wish, you may contact the principal investigator by letter. The address is on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-502-2092.

If you have an urgent medical problem or think you are injured or ill because of this study, call 911 or go to your local emergency department. You should also call Dr. Handa, at 410-550-0336 during regular office hours and at 410-550-0100 after hours and on weekends. If this doctor is not available, the operator will page the "on call physician."

17. What does your signature on this consent form mean?

Your signature on this form means that you have reviewed the information in this form, you have had a chance to ask questions, and you agree to join the study. You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

Signature of Participant	(Print Name)	Date/Time

Signature of Person Obtaining Consent	(Print Name)	Date/Time

I have received the separate Insurance and Research Participant Financial Responsibility Information Sheet.

Signature of Participant, LAR or Parent/Guardian	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR AND A COPY MUST BE GIVEN TO THE PARTICIPANT. IF APPROPRIATE FOR THIS STUDY, A SCANNED COPY OF THE SIGNED CONSENT FORM SHOULD BE UPLOADED TO THE PARTICIPANT'S EPIC/EMR RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

DOCUMENTATION OF PHYSICIAN/MID-LEVEL PROVIDER CONSENT PROCESS

My signature below indicates that I have discussed the risks, benefits, and alternatives, answered any questions, and believe the participant is able to make an informed choice to join the study.

_____

Signature of Physician/Mid-Level Provider (Print Name) Date/Time

_____

Signature of Participant (Print Name) Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR AND A COPY MUST BE GIVEN TO THE PARTICIPANT. IF APPROPRIATE FOR THIS STUDY, A SCANNED COPY OF THE SIGNED CONSENT FORM SHOULD BE UPLOADED TO THE PARTICIPANT'S EPIC/EMR RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).