MsFLASH NETWORK PROTOCOL 5
INFORMED CONSENT

Consent to be part of a research study:

Study Title:	MsFLASH 5: The Vaginal Health Trial – Effects of Vaginal Estradiol Tablet and Moisturizing Gel on Postmenopausal Vaginal Symptoms
Lead Researcher:	<<Insert Site PI, Credentials, Department, Address, Telephone Number>>
Emergency Contact:	<<Insert Local Physician>> <<Local Phone>>

We are inviting you to be in a research study. The purpose of this study is to better understand how well vaginal estrogen and a vaginal moisturizer work to decrease uncomfortable vaginal symptoms related to menopause.

If you agree to join the study you will be randomly assigned to one of three treatment groups: vaginal estrogen tablet plus vaginal placebo gel (inactive), vaginal moisturizing gel and vaginal placebo tablet (inactive), or vaginal placebo tablet and vaginal placebo gel (both inactive). You will use your study treatment for 12 weeks: the tablet daily for the first two weeks and then two times a week, the gel three times a week during the whole study. During those 12 weeks you will have 3 clinic visits. At each clinic visit you will fill out questionnaires, and have a pelvic exam. During the pelvic exam we will collect vaginal swabs, vaginal fluid, a vaginal biopsy and a rectal swab. You will have blood drawn at 2 clinic visits. At home, you will self-collect vaginal swabs, weekly or daily.

We do not know whether the vaginal estrogen tablet or the vaginal moisturizing gel is better to decrease uncomfortable vaginal symptoms related to menopause. We do not know if vaginal estrogen or a vaginal moisturizer will decrease your particular vaginal symptoms related to menopause. Both treatments may cause side effects.

Following is 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 will 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 vaginal symptoms related to menopause. Up to 320 women 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 join this 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 and you could choose to receive standard methods to treat vaginal symptoms related to menopause.

We will give you details about the purposes, procedures, risks, and possible benefits related to this study below. 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 choice about joining this study.

Why are we doing this study?

After menopause, many women have bothersome symptoms in the vaginal area, such as dryness, itching, irritation, soreness, or pain with intercourse. These symptoms can cause distress, interfere with daily life, and decrease quality of life long after other menopause symptoms end. We want to know how well some common vaginal preparations work to decrease these symptoms.

In this study we want to measure the effectiveness of a hormone-containing vaginal tablet and a non-hormone containing vaginal gel in decreasing vaginal discomfort due to menopause. We are studying a vaginal tablet containing the estrogen hormone, estradiol, called Vagifem®, which is a popular prescription treatment for the relief of vaginal symptoms. This tablet is placed in the vagina with an applicator. We are also studying Replens®, a currently available over-the-counter vaginal moisturizing gel that is placed in the vagina with an applicator. We hope to learn which treatment works better for women with uncomfortable vaginal symptoms related to menopause. There is no single standard recommended treatment for vaginal symptoms related to menopause, so we will compare each product to a placebo, or inactive, substance.

Blood, vaginal and rectal specimens will be collected and saved (with your permission) to assist with our understanding of the biology of vaginal symptoms.

There are 3 groups of participants in this study. We will give different treatments to different groups, and compare the results. This is how we hope to find out how well estrogen tablets and moisturizing gel work to decrease vaginal symptoms related to menopause.

If you join this study you will not be allowed to choose the treatment group that you are assigned to. We use a computer program to assign both a study bottle of tablets and a tube of gel to you. You will have a 1-in-3 chance of receiving a vaginal estrogen tablet (plus a placebo gel), a 1-in-3 chance of receiving the vaginal moisturizing gel (plus a placebo tablet), and a 1-in-3 chance of receiving a placebo tablet and a placebo gel (see table below). The computer program holds the information on whether you were given active or placebo medication; neither you nor the study doctors or the study staff will know which treatment group you are assigned to. If necessary, site staff can request this information.

Group	Tablet	Gel
1	Vagifem	placebo
2	placebo	Replens
3	placebo	placebo

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

If you choose to join the study, these are the procedures, treatments and tests that would occur:

Study medication:

At your initial clinic visit, we will provide a personalized study calendar to help you remember when to take each medication.

- Weeks 1-2: Each day, we ask that you use the vaginal tablets in the morning. We will ask you to use the gel at night, three times a week. Both the vaginal tablets and the vaginal gel have an applicator to help you put them in the vagina.
- Weeks 3-12: We ask that you use the tablet two times each week, and the gel three times a week, but not to use both medications on the same day.

Clinic visits (Screening/enrollment, week 4, week 12):

- Visit: We anticipate that each clinic visit will take a total of 1-1.5 hours
- Questionnaires: We will ask you to fill out questionnaires at each clinic visit. These include questions about overall health, including your vaginal symptoms, feelings, sleep, pain, bodily functions, and sexual activity. You can fill this out before your clinic visit if you wish.
- Self-collected vaginal swab: We will provide detailed instructions. In a private space, you will insert a small cotton-tipped swab about an inch into the vagina to collect vaginal fluid.
- Collection of blood: We will draw about 2 tablespoons of blood at each the baseline and week 12 clinic visits.
- Pelvic exam & vaginal swabs: A speculum will be placed in your vagina, and 3 vaginal swabs will be collected.
- Vaginal cytobrushes: A small brush will be used to brush the vaginal wall to obtain vaginal cells.
- Vaginal lavage: While the speculum is in place, about 2 tablespoons of salt solution will be placed in the vagina to wash the walls of the vagina and cervix and then the fluid will be collected again, using a sterile eyedropper.
- Vaginal biopsy (optional): While the speculum is in the vagina, the vaginal wall is numbed with a spray of a medicine like Novocaine, then an instrument will be used to remove a small piece of tissue (about the size of a grain of rice) from your vagina. Any bleeding from the biopsy site is stopped with pressure and a medicine called silver nitrate. This will take about 5 extra minutes during your pelvic exam.
- Rectal swab: The clinician will moisten a small cotton swab and place it into the rectum, turn it once and remove it.

At-Home Activities:

- Diary: This is a form asking about vaginal symptoms, use of the study medications, sexual activity, and other vaginal product use. We ask that you complete this daily for 7 days at the beginning, for 7 days before the Week 4 visit, for 7 days before the Week 12 visit, and once weekly during the remaining weeks of the study.

- Self-collected vaginal swabs - You will collect vaginal swabs (like the ones during the clinic visits) in the privacy of your home. We will ask you to do this daily for the first 7 days of the study, for 7 days before the Week 4 visit, and for 7 days before the Week 12 visit. Swabs will be collected once weekly during the remaining weeks of the study.

Phone Calls:

- During follow-up phone call(s) we will check to see how you are doing with the study gel and tablets, ask about symptoms or health problems you may have had since we last spoke with you, and remind you of upcoming appointments. Phone calls will occur on a scheduled basis during weeks 1, 3, 7 and 11, and at other times if we do not receive samples or diary entries from you.

How long will I be in this study?

Your participation should last about 12 weeks from the day you sign this consent form.

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 are 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 are the possible risks or discomforts?

Ultra-Low Dose Estrogen Tablet: The estrogen vaginal tablet used in this study (Vagifem®) is not an experimental drug. It has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of vaginal symptoms. No serious adverse events have been observed in any previous studies of Vagifem®. There is a small risk of having a reaction to using Vagifem®. The most common side effects (each seen in 5-8% of women using Vagifem® compared to 0-3% of women not using Vagifem®) include back pain, diarrhea, genital yeast infections, and genital itching.

Standard-dose estrogen pills taken orally for **longer** periods of time, **usually years,** and in doses 100 times greater than the vaginal tablet we are evaluating have been studied in large groups of women (tens of thousands). These studies of standard dose estrogen have shown an increase in the risk of stroke (a little over 1 in 1,000 per year), blood clots in the leg or lung (less than 1 in 1,000 per year) and gallbladder problems (approximately 3 in 1,000 per year) in post-menopausal women. Standard-dose estrogen taken without progesterone, as in our study, did not increase the risk for heart attacks or breast cancer in these large studies.

Because the estrogen used in this study is ultra-low dose and is absorbed through the vagina, the risks for any of these problems is very small. There are no published reports of these problems in women who have taken Vagifem®, and these problems have not been reported to the FDA or to the company that makes Vagifem®.

Non-Hormonal Moisturizing Gel: No serious adverse events from the use of Replens® have been observed. Potential side effects include vaginal discharge and odor.

Other Risks or Discomforts:

- Questionnaires: You may feel uncomfortable answering questions that seem sensitive and personal, including questions about your feelings, bodily functions, or sexual activity. You can skip any question that you don't want to answer.
- Blood draw: There are minor risks when having blood drawn. You may feel pain from the needle or get a bruise. In rare cases, people may faint, or feel faint, or the site of the blood draw may get infected.
- Self-collected vaginal swab: Placing a dry cotton swab into the vagina may be slightly irritating. We will teach you techniques that moisten the swab to minimize any discomfort. Introducing a cotton swab into the vagina should not increase risk of vaginal or urinary tract infection.
- Rectal swabs: Placing a cotton swab into the rectum may be slightly irritating.
- Pelvic exam, vaginal swabs and cytobrushes: Conducting a pelvic exam may be uncomfortable. We will do our best to minimize any discomfort by choosing smaller speculums and using lubricants.
- Vaginal biopsy (optional): A biopsy may cause pain that occurs at the time of the biopsy, like a pinch that tends to be short-lived. There can be mild bleeding that resolves with pressure and medication. Infection occurs in <1% of women and would be treated with antibiotics.
- Unknown Risks: It is always possible that using vaginal medication could have unknown risks. During the study, we may learn something new about the medications or their side effects. We will tell you as soon as possible if we find new information that might change your mind about being in this study.

What are the possible benefits of the study?

Being in this study may or may not help you. You may be diagnosed with a vaginal infection that you otherwise would not have known about – if this happens, you will be referred to your regular provider for treatment. There is no guarantee that your symptoms will improve. You could receive a prescription for Vagifem® or buy Replens® at the drugstore without participating in this study. Some women find that being monitored closely helps them better manage their symptoms. We hope that information from this study will help us better provide care in the future for women with genital symptoms after menopause.

What other choices do I have if I do not participate?

It is possible that you would benefit from other treatments. Vaginal estrogen is the standard treatment for post-menopausal symptoms of genital irritation. All other FDA approved estrogen formulations contain more estrogen than the tablet used in this study. If your symptoms are determined not to be due to menopause, additional diagnostic testing may be needed. You may discuss this evaluation and the risks and benefits of other treatments for vaginal symptoms with your doctor. If you join this study, we ask that you not take any other treatments for vaginal symptoms while you are in the study.

Will you pay me to be in this study?

As a token of our appreciation for your time and effort, you will be paid between $150-300 if you complete all study activities. This includes $25 upon completion of each of the 3 study visits, $50 for each of 3 (optional) vaginal biopsies, and $75 at study completion. You will be paid for each part of the study you complete, even if you do not complete all activities.

Will I have to pay for anything?

No. The study tablets and gel, all tests and physical examinations required for this study, and parking at the clinic are free of charge.

Will the study provide me with routine preventative care?

No. We recommend that you receive routine screening and prevention care such as mammograms and pap smears with a primary care provider or gynecologist.

What if I have a medical emergency or get sick or hurt during this study?

If you have a medical emergency during the study, you should go to the nearest emergency room or dial 911. Be sure to tell the doctor or medical staff that you are in a research study being conducted at <<Insert Local Institution Name>>. Ask them to contact << Insert "Emergency Contact" Local Physician Name and Local Phone Number from page 1>> for further instructions and information about your care. Note that this emergency contact information is also available on the first page of this document.

If you are hurt or get sick and think this is related to the study, please call << Insert "Emergency Contact" Local Physician Name and Local Phone Number from page 1>>. You may also choose to seek treatment outside of this clinic or contact your own doctor. Please tell study staff right away if you are admitted to the hospital for any reason during the study.

You or your insurance company will have to pay for medical care or hospitalization. There are no funds to pay you for a research-related injury, added medical costs, loss of a job, or other costs to you or your family.

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

Who can see or use my information? How will my personal information be protected?

Your information will be kept confidential. We will store the personal information in locked file cabinets and secure computer files. Only staff who need to contact you or track your information will have access to your name or other information that can identify you. This information will not be on any research data or published reports about the study. We will assign a code number to your information, and only your assigned number will be in the information sent to a central study database. Some people or organizations may need to look at your study records for research, data analysis, or to make sure the study is done safely and legally. They include:

- Researchers involved in this study, as well as researchers at the MsFLASH clinical centers (Group Health Research Institute and University of Minnesota) or the data coordinating center at Fred Hutchinson Cancer Research Center. Samples will also be sent to

investigators at Massachusetts General Hospital for analyses. However, they will not have access to any information that can directly identify you.

- Institutional Review Boards (IRBs), including the IRBs at <<Site>> and Fred Hutchinson Cancer Research Center, the data coordinating center for the study. An IRB is a group that reviews the study to protect your rights as a research participant.
- U.S. National Institutes of Health, Office for Human Research Protections, and the Food and Drug Administration.

These people are interested in study data, not your personal information. 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, workplace 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.

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.

Will you keep my information if I am found to be ineligible for the study?

If at any time during the screening process you are found to be ineligible for the study, we will not retain your name or other identifiable information in our database. We will retain data that describes why you were not eligible for the study, but this information will not be linked with your name or other identifiable information.

Will the study keep the biologic samples collected?

Any samples and data collected as part of the study will only be identified by a number, and will not have any information identifying that they came from you. Once the study is over, the code linking your identifying information to that number will be destroyed and there will be no way to know where data or a sample came from. These samples, such as blood, vaginal swabs, vaginal fluid, and rectal swabs could continue to be used for additional studies about the causes and treatments for vaginal discomfort in menopause. You may choose whether to allow use of your samples for future research. We are taking vaginal samples to allow us to study the effects of these treatments. We will look at how vaginal bacteria, the vaginal lining, and the vaginal immune system change with the study treatments. This will help us figure out the causes of vaginal discomfort. Any such use would require approval from an Institutional Review Board.

Your rights

- You do not have to join this study. You are free to say yes or no. Your regular medical care will not change.
- If you join this study, you do not have to stay in it. You may stop at any time. There is no penalty for stopping. If you want to withdraw from this study please contact your MsFLASH clinical center.
- If you get sick or hurt while 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. Other information might make you change your mind about being in this study. If we learn these kinds of information, we will tell you.

Who can I call with questions or concerns?

If you have questions, concerns, or complaints about this study, please call the lead researcher at the number on page 1 of this form. You may also call any other member of the study team. If you want to talk to someone who doesn't work on the study, please call the Institutional Review Office at <<Insert Local Phone Number>> and ask to speak to <<name>>. You may also call this number if you have questions about your rights as a research participant.

The checkboxes below refer to the optional vaginal biopsy procedure:

☐ I do give permission to perform the vaginal biopsy.
☐ I do NOT give permission to perform the vaginal biopsy.

Name of Subject (Please Print)	Signature of Subject	Date

The checkboxes below refer to permission to save blood, vagina, and rectal specimens:

☐ I do give permission to save my blood, vagina and rectal specimens.
☐ I do NOT give permission to save my blood, vaginal and rectal specimens.

Name of Subject (Please Print)	Signature of Subject	Date

Subject's Statement

By signing below, I indicate that I have read this consent form. I willingly agree to take part in this research study. If I change my mind later, I may leave the study at any time. If I have questions in the future, I may contact the Principal Investigator or any other study staff.

Name of Subject (Please Print)	Signature of Subject	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.

Name of Person Obtaining Consent (Please Print)	Signature	Date

FHCRC IRB Approval
NOV 01 '16 AUG 19 '17
Consent Released Date Consent Expiration Dat