Sublingual Estradiol Versus Oral Estradiol in Transgender Women

Informed Consent Form V2.0, Approved 08Jun2020

NCT04036500

EFFECTIVE

6/8/2020

MCW/FH IRB

Medical College of Wisconsin and Froedtert Hospital
INTRODUCTION TO THE INFORMED CONSENT

Name of Subject: _____

Sublingual Estradiol Versus Oral Estradiol in Transgender Women

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You are invited to take part in this research. You can decide whether to take part in this project or not. You are free to say yes or no. If there is anything that you do not understand, please ask questions.

Definitions

Estradiol – Estradiol is a form of estrogen, a sex hormone that helps regulate many processes in the body. In estrogen therapy for transgender individuals, it is used for its feminizing effects in male-to-female (MTF) patients.
Sublingual Administration – A way to take a drug that involves holding a tablet under the tongue and letting it dissolve.
Oral Administration – A way of taking a drug that involves swallowing a tablet whole
Metabolism – Drug metabolism describes how a body interacts with a drug. Many parts of the body, such as the liver, are involved in metabolizing drugs. This may include anything from changing the structure of the drug to make it more active, to breaking down the drug so it can be removed from the body.
Percutaneous Intravenous Catheter – This refers to an "IV" that is inserted into a vein, usually in the arm, that will allow us to draw blood samples.

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Purpose

This project is being done to learn more about sublingual estradiol compared to oral estradiol. Understanding the differences in absorption and metabolism based on these routes of administration will help us to design future studies on the safety and efficacy of both methods for transgender individuals.

Length

- You will be in this research project for two full days, which will be about one week apart
- Each of the two days requires about an 8-hour time commitment

Procedures

If you choose to participate, you will be asked to spend approximately 8 hours in the Adult Translational Research Unit on two different days, about one week apart. You will be assigned to a suite where you can do activities such as eat, watch TV, or read during the course of the 8 hours. During that time, we will be drawing blood at various points to study blood estrogen levels over time.

List of visits:

- Screening and Information Visit
  - Total Number: 1
  - Total Time: 30 min
- Oral Estradiol Visit
  - Total Number: 1
  - Total Time: 8-9 hours
- Sublingual Estradiol Visit
  - Total Number: 1
  - Total Time: 8-9 hours

Procedures that will occur at various visits:

Invasive Procedures

- You will have 7 blood draws taken at hours 0,1,2,3,4,6,8 on each of the two days.

Non-invasive Procedures

- Vitals will be taken at the beginning of each visit (blood pressure, pulse, respiration rate, height, weight)
- You will be provided estradiol 1 mg ORALLY after time 0 blood draw on day 1.

Risks

This is a brief list of the most commonly seen side effects. The ***full consent form*** after this introduction contains a more complete list of potential research risks.

Estradiol risks:

There are few risks associated with taking estradiol in such a short-term dosing schedule (two days, one week apart). However, the risks of systemic estradiol include:

- Swelling
- Hypertension
- Blood clots
- Headache
- Mood changes
- Skin rash
- Weight gain
- GI disturbance

Blood Draw risks:

Risks or discomforts from having your blood drawn include:

- Bruising or hematoma
- Infection from blood draw
- Pain from percutaneous intravenous catheter

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- You will be provided estradiol 1 mg SUBLINGUALLY after time 0 blood draw on day 2.

Benefits

We don't know if this project will help you. Your condition may get better but it could stay the same or even get worse.

My Other Options

You do not have to join this project. Your other options may include:

- Joining a different project
- Routine care for this condition
- Getting no treatment for this condition

If you have more questions about this project at any time, you can call Jenna Sarvaideo at (845) 548-4536

If you have questions about your rights as a participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

CONSENT TO PARTICIPATE IN RESEARCH

A1. INTRODUCTION – WHY ARE WE ASKING YOU TO PARTICIPATE?

You are being invited to participate in this research because you are a transgender male-to-female individual who is naïve to hormone therapy. You meet the requirements of being an English speaker, 18 years of age or older, without a severe needle phobia or history of orchiectomy. You also do not have a history of breast cancers, active or recent clotting disease or liver disease.

A total of about 10 people are expected to participate in this research the Medical College of Wisconsin/Froedtert Hospital.

The Director of the project is Jenna Sarvaideo, DO, in the Division of Endocrinology and Molecular Medicine at the Medical College of Wisconsin. A research team works with Dr. Sarvaideo. You can ask who these people are.

The Endocrine Society and the Medical College of Wisconsin are funding this study. There are no financial conflicts or conflicts of interest in this study.

A2. DO I HAVE TO PARTICIPATE?

You can decide whether to take part in this research or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this project, you do not have to stay in it. You may stop at any time.

A research project is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the research procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS PROJECT BEING DONE?

In this study, we want to find out more about the pharmacokinetics (way a drug is processed by the body) of oral and sublingual estradiol in transgender women. This pilot study will investigate the estrogen levels in the blood for both routes of administration, which will help us determine whether different doses may be necessary for the two methods in transgender women. We are looking specifically at these two ways of giving estradiol because it has been suggested that sublingual estradiol may be safer and/or more effective than oral administration.

The data from this pilot study may be used later to design larger studies on safety and efficacy, since there are no well-conducted studies that have evaluated how effective or safe sublingual estrogen therapy is in the transgender population. Estradiol has been approved by the FDA for use in biologic females, but its use in transgender women is considered “off-label.” We hope to obtain data that will increase our understanding of its use in transgender women as well.

This study will likely not help you directly. We hope the information from this study will help us develop a better understanding of the pharmacokinetics of sublingual estradiol in transgender

women. This will allow us to continue studying this potentially safer, more effective option for hormone replacement therapy.

B1. WHAT WILL HAPPEN IF I PARTICIPATE?

Screening procedures:
If you decide to join, some screening questions will be asked first to see whether you are eligible. A study team member will meet with you in person or over the phone to discuss the requirements. To participate in this study, you must:

- Be 18 years or older
- Be a male-to-female transgender individual
- Be an English-speaker
- NOT have had an orchiectomy (surgical removal of one or both testicles)
- NOT have a phobia of needles
- NOT have a serious bleeding disorder
- NOT have a history of breast cancer
- NOT have a known sensitivity or allergy to any components of the medications used
- NOT have active deep vein thrombosis, pulmonary embolism or history of these conditions
- NOT have active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction)
- NOT have liver dysfunction or disease
- Stop taking potent CYP3A4 inhibitors or inducers, as determined by team pharmacist
- NOT be taking a medication that may cause additional physical or mental harm if stopped

During this screening visit, you are welcome to ask questions about the study and voice any potential concerns. We will also ask you questions about any medications or supplements you are taking. If you are taking certain medications that may interact with estrogen, we will ask you to go through a washout period for the drug(s).
Washout: This study may involve a washout period; the length of time will depend on which medicine you are taking, since some medicines leave the body faster than others. A washout period is the time that you go without medicine in order to get all of the medicine out of your body. This is done to make sure your old medicine does not interact with the drugs (estrogen) in the study. The time without medicine may make your condition or symptoms that are treated by your medicine worse for a period of time.
If the screening information shows that you meet the requirements, then you will be able to start. The research team will schedule your participation visits based on your availability and the availability of the Adult Translational Research Unit. If the screening information shows that you cannot be in the research, the research doctor will discuss other options with you and/or refer you back to your regular doctor.

Research groups
Every participant in this study will receive the same drug, in the same dose and route of administration. There will be no placebo group, no randomization, and no blinding.

Summary of Procedures

DAY 1: After determining that you are eligible and scheduling your Day 1 visit and Day 2 visit, you will report to the Adult Translational Research Unit (A-TRU) at 7:30 AM on the pre-scheduled date. The research team and assigned nurse will check you in and escort you to the assigned suite within the unit.

1. Study team or PI will read and discuss this consent form with you. During the consenting, you are able to ask questions, voice concerns, and ask for more time to process/think about the information. You will have a minimum of 10 minutes—or longer if needed—before deciding to sign.
2. If you consent to participation, the A-TRU nurse will take your vitals. This includes collecting your height and weight, taking your pulse and respiration rate, and measuring your blood pressure.
3. The nurse will then draw the first of seven blood draws (time 0 hr).
4. You will be provided estradiol 1 mg to take ORALLY (swallow whole).
5. One hour after swallowing the estradiol, the nurse will return to draw your blood again (time 1 hr). This will be repeated at time 2,3,4,6, and 8 hr after taking the estradiol. You are required to stay within the A-TRU during this 8-hour period.
    a. During your time in the private A-TRU suite, you are free to eat food, which can be ordered from the staff present. A bed and TV are provided in the suite.
    b. One of the research team members will be present during the day for you to ask questions.
6. A research team member will meet with you at time 8 hr to discuss the visit and ensure your Day 2 visit is scheduled for one week later.
7. We ask that you refrain from smoking on the morning of your Day 2 visit, this may interfere with your tissues ability to absorb the sublingual estradiol.

DAY 2: You will report to the A-TRU at 7:30 AM on the pre-scheduled date. The research team and assigned nurse will check you in and escort you to the assigned suite within the unit.

1. The A-TRU nurse will take your vitals.
2. The nurse will draw the first of seven blood draws (time 0 hr).
3. You will be provided estradiol 1 mg to take SUBLINGUALLY.
    a. A research team member will be present to describe the precise way of taking the tablet.
    b. You will be instructed to hold the tablet under your tongue until it is entirely dissolved. DO NOT swallow the tablet.
4. One hour after taking the sublingual estradiol, the nurse will return to draw your blood (time 1 hr). This will be repeated at time 2,3,4,6, and 8 hr after taking the estradiol. You are required to stay within the A-TRU during this 8-hour period.
    a. During your time in the private A-TRU suite, you are free to eat food, which can be ordered from the staff present. A bed and TV are provided in the suite.
    b. One of the research team members will be present during the day for you to ask questions.
5. A research team member will meet with you at time 8 hr to discuss the visit. You will be provided a brief survey to complete.
6. You will be given your $100 VISA gift card at the end of your Day 2 participation.

The blood draw samples will be sent to Wisconsin Diagnostic Laboratories and provided to ARUP for analysis. ARUP stands for Associated Regional and University Pathologists. ARUP is a national reference laboratory based in Salt Lake City, UT that provides laboratory testing services for Wisconsin Diagnostic Laboratories. Serum levels of estradiol and estrone will be measured by LC-MS (liquid chromatography mass spectrometry). Liquid chromatography-mass spectrometry is a lab technique used to make measurements in many types of samples, including blood and urine. Liquid chromatography is used to separate different components of the sample. Then, mass spectrometry is used to measure a chemical "signature" unique to individual compounds and determine their concentration. In this study, liquid chromatography-mass spectrometry will be used to measure the concentration of estrogen in the blood.

B2. HOW LONG WILL I BE IN THE PROJECT?

⇒ You will be in this research project for about two weeks, with two days of study procedures in the A-TRU.
⇒ You will take the estradiol a total of two times: Day 1, and about one week later on Day 2

B3. CAN I STOP BEING IN THE PROJECT?

You are free to withdraw from the project at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the research doctor.
The research doctor may take you out of this project at any time. This would happen if:

- They think it is in your best interest.
- You do not follow the project rules.
- The whole project is stopped.

If this happens, the research doctor will tell you.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE PROJECT?

There are risks to taking part in any research project. There is a risk that you may experience unexpected effects during the blood draws that will not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from estradiol itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the project for problems (side effects). **You need to tell the research doctor or a member of the research team immediately if you experience any problems, side effects, or changes in your health.**

C2. RISKS OF ESTRADIOL

The research drug, estradiol, may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away.

Systemic estradiol is associated with many adverse effects including, but not limited to swelling, hypertension, blood clots, headache, mood changes, skin rash, weight gain and GI disturbance. These effects may occur by many routes of estradiol administration, including oral and sublingual. Many go away soon after you stop taking the estradiol, and it is important to note that drugs can affect individuals in many different ways.

The side effects that other people have experienced so far with the sublingual estradiol are minimal. In the Price et al study from 1997, one of the only studies to examine sublingual estradiol dosing, subjects tolerated sublingual administration well. Subjects reported no taste or other sensation, and the tablet dissolved quickly, within approximately 1-2 minutes.

Washout Period: This study will involve a washout period of 7 days between the first dose of estradiol (oral) and the second dose of estradiol (sublingual). A washout period is the time that you go without medicine in order to get all of the medicine out of your body. This is done to make sure the previous dose of estradiol does not impact the results of the second dose.

C3. OTHER RISKS OF THIS RESEARCH PROJECT

The frequency of blood draws during this project may pose some risk to you. If you are anxious around needles, this may cause you emotional or psychological distress. You may experience some pain in the region of the venipuncture during or after the blood draw, as well as bruising or hematoma. Despite proper sterilization and precautionary measures, it is also possible to acquire an infection as a result of peripheral intravenous catheters.

Additional risks include loss of confidentiality.

C4. REPRODUCTIVE RISKS

We do not anticipate any reproductive risks from participating in this study.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE PROJECT?

This study is not likely to help you, but we hope the information from this study will help us develop a better understanding of how sublingual estradiol is metabolized in transgender individuals. The data that we collect on the pharmacokinetics of estradiol from your participation may contribute to the limited body of research in transgender medicine. Furthermore, from the data we collect in this study, we will be better able to design future studies on sublingual estradiol and investigate whether it is an effective alternative to oral estradiol. This may lead to better safety and efficacy information about estrogen replacement therapy in the transgender population.

D1. ARE THERE ANY COSTS TO BEING IN THE PROJECT?

⇒ There are no direct costs to you for any of the services you receive in this project, which includes time spent in the A-TRU, blood draw expenses, lab expenses, and estradiol tablets. If you have questions regarding costs, please contact Dr. Sarvaideo.

⇒ Potential outside costs to you from being in this project are related to the time requirement (two 8-hour days spent in the Translational Research Unit). This may require missing work, school, or additional obligations on these dates. The research team will work with you to schedule your involvement on days that work well for you, but preferred dates are not guaranteed. If you have questions regarding costs, please contact Dr. Sarvaideo.

If you participate in this research, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance.

D2. WILL I BE PAID FOR PARTICIPATING IN THE PROJECT?

⇒ You will receive $50.00 in the form of a VISA gift card for the Day1 visit and the Day 2 visit, for a total of $100.00. The study team will give the gift card to you at the end of the Day 2 visit.

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this project. You are free to say yes or no. If you do not join this project, your research doctor can discuss other healthcare choices with you.
Your other choices may include:

- Beginning hormone replacement therapy sooner, rather than delaying until after participating in the study
- Joining a different research project

The research doctor can explain both the possible benefits and the risks of other options that are available to you.

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE PROJECT?

If we learn any important new information estradiol that might change your mind about being in the project, we will tell you about it right away. You can then decide if you want to stay in the project.

When research biospecimens such as blood are collected and analyzed , there is the chance of finding something clinically relevant. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as feeling worried about a finding for which no treatment is required or appropriate).

In this study, you will be informed of any findings of possible clinical significance that may be discovered during review of results from your research blood samples. The results of your research estradiol and estrone levels will not be placed in your medical record.

The results from the estradiol and estrone levels we collect in this research study are the same quality as what you would receive as part of your health care. The estradiol and estrone levels will be reviewed by a physician who normally reads such results. We will provide you with this information so that you may discuss it with your primary care physician. This information will be provided only if a participant asks for their lab results, in which case both estradiol and estrone levels will be shared.

D5. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE PROJECT?

Emergency medical treatment for injuries directly related to your participation in this research project will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this project, contact the research doctors right away. Contact information: Jenna Sarvaideo, (845) 548-4536, jsarvaideo@mcw.edu

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE PROJECT?

If you have more questions about this project at any time, you can call Jenna Sarvaideo at jsarvaideo@mcw.edu, (845) 548-4536.

- If you have questions about your rights as a research participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this project?

To be in this research project, the research team needs your permission to access, collect and use some of your health information. If you say no, you cannot be in the project. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the project.

The protected health information (PHI) originates from services you will or have received at one or more of the following locations: the Medical College of Wisconsin (MCW); BloodCenter of Wisconsin (BCW); Children's Hospital of Wisconsin (CHW); any Froedtert Health Affiliate-Froedtert Memorial Lutheran Hospital (FMLH), Inc.; Community Memorial Hospital (CMH) Menomonee Falls, Inc.; St. Joseph's Community Hospital (SJH) West Bend, Inc.; Froedtert & The Medical College of Wisconsin Community Physicians Clinics, Inc. (FMCWCP); the West Bend Surgery Center, LLC; and the Froedtert Surgery Center, LLC.

The health information to be collected and used for this project is:

- ⇨ Medical records of the care you receive for this project
- ⇨ Lab values (estradiol, estrogen serum levels) from your blood samples

E2. Who will see the health information collected for this project?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the research team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

Because this project involves the use of drugs and/or devices, the FDA also has the right to inspect all project records.

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different project without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed from your health information and biospecimens, the information and/or biospecimens may be used for future research or distributed to another investigator for future research without additional informed consent from you or your legally authorized representative. The information might also be used or released for other purposes without asking you. Results of the project may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research project is that more people will handle your personal health information collected for this project. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the research doctor about whether this could apply to you.

E4. How long will you keep the health information for this project?

If you sign this form, we plan to keep your information for 10 years, as required by MCW policy, in case we need to check it again for this project.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to Jenna Sarvaideo at:

Medical College of Wisconsin
Division of Endocrinology
8701 Watertown Plank Road
Milwaukee WI 53226

You can also email Dr. Sarvaideo at *jsarvaideo@mcw.edu*. The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the project. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE PROJECT

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.

You can look up this project by referring to the ClinicalTrials.gov number (NCT04036500) or by asking the research team for a printed copy.

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CONSENT TO PARTICIPATE

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The project's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the research team use and share the health information and other information gathered for this project.
- I voluntarily agree to participate in this research project. I agree to follow the procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**

Name of person discussing/ obtaining consent *please print*	**Signature of person discussing/obtaining consent**	**Date**

Name of Principal Investigator __ I participated in consent process __ I acknowledge enrollment of this subject into the project	**Signature of Principal Investigator**	**Date**