EFFECT OF GENDER-AFFIRMING ESTROGEN THERAPY ON DRUG METABOLISM, TRANSPORT, AND GUT MICROBIOTA

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UNIVERSITY OF WASHINGTON
CONSENT FORM
EFFECT OF GENDER-AFFIRMING ESTROGEN THERAPY ON DRUG METABOLISM, TRANSPORT, AND GUT MICROBIOTA

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HSD#: STUDY00014091

24-hour emergency telephone number: Lauren Cirrincione, PharmD, MPH, Assistant Professor, 650-353-7782

We are asking you to be in a research study. This form gives you information to help you decide whether or not to be in the study. Being in the study is voluntary. Please read this carefully. You may ask any questions about the study. Then you can decide whether or not you want to be in the study.

KEY INFORMATION ABOUT THIS STUDY

- Your participation is voluntary. The purpose of this form is to give you the information you need to help decided whether to be in the study or not.
- We are asking you to be in this study because you identify as transgender or gender-diverse and are starting hormone therapy for your medical care. Your hormone therapy contains estradiol, which is a hormone that helps align your physical characteristics with your gender expression goals. The purpose of this study is to determine how estradiol treatment affects other medications and the natural bacteria that lives in your gut.
- This study is up to 88 weeks long and starts before you take your first dose of estradiol. Being in this study involves two long study visits (25 hours each) at the University of Washington Medical Center Translational Research Unit (TRU) and 2 short study visits (30 mins each) at the School of Pharmacy Procedure Room. There is also one phone visit. You will be asked to self-collect a stool sample before both of the two long visits at the TRU. You will also be asked to self-collect urine samples during and after both of these visits.
- You will be asked to fast for 8 hours before each long study visit. Breakfasts, lunch, and dinner will be provided during the long study visits at the TRU.
- You will also receive a stool collection kit and diet diary to fill out before the long study visits. The study coordinator will instruct you on how to collect your stool and document your dietary intake before the first study visit at the TRU.
- At the TRU visits we will do measurements to make sure it is safe for you to receive the study drugs. You will receive the following approved medicines by mouth: 0.25 mg digoxin (1 tablet), 2 mg midazolam (1/2 teaspoon syrup), 500 mg acetaminophen (1 tablet). You will also receive 1/5 of a teaspoon of midazolam solution administered in a vein in your arm. Your blood will be collected during this visit using a small tube that will be placed in your arm. Your urine will be collected during this entire visit.
- Midazolam causes drowsiness. You may consider taking public transportation, a rideshare, or arrange a ride to and from each long study visit day.

- After each study drug visit, you will be given a urine collection kit so that you can collect your urine for 24 hours after you leave the unit. If possible, you will be asked to keep the home urine container refrigerated during collection or to use a portable cooler with ice as an alternative to a refrigerator.
- You will be asked to return to the UW School of Pharmacy Procedure Room the next morning and the morning after that to give the study staff your collected urine and to have blood taken.
- The same activities will occur during the 2nd long study visit at the TRU and the other visit at the School of Pharmacy procedure room.
- You are not expected to get any benefit from participating in this study.
- You will need to wait to take your first dose of estradiol until after the first long visit at the TRU.
- There may be side effects from the study tests and from the tracer-doses of medications administered at each study visit, which may be severe. The risks are explained later in this form.

PURPOSE OF THE STUDY

We are asking you to be in this study because you identify as transgender or gender-diverse and are starting hormone therapy for your medical care. Your hormone therapy contains estradiol, which is a hormone that helps align your physical characteristics with your gender identity.

Your body creates and uses estradiol naturally. Estradiol is also prepared as a liquid injection or tablet that you can take to increase your hormone levels. Changes in estradiol levels in your blood may affect how your body handles other medicines in your body.

The purpose of this study is to find out how estradiol therapy (estradiol injection or estradiol tablet) affects the amount of midazolam, digoxin, and acetaminophen in your blood, and to confirm estradiol treatment does not affect natural bacterial in your gut. We are looking to have 16 people complete all study procedures.

STUDY PROCEDURES

If you choose to take part in this study, we will ask you to sign this consent form before proceeding. You will be asked to complete a consenting/screening visit and two study visits at the UWMC Translational Research Unit, and two follow-up visits at the University of Washington School of Pharmacy Procedure Room. The screening visit will either happen during one of your regular clinic visits, or you will have your screening conducted at the University of Washington School of Pharmacy Procedure Room. In addition, you will be contacted by phone once. The total study duration is up to 88 weeks.

Consenting/Screening Visit:

- You will sign this consent form before the screening visit begins.

- The consenting/screening visit will last approximately 60 minutes and will occur at either the clinic where you receive your gender-affirming care or at the University of Washington School of Pharmacy procedure room. The study coordinator will specify if you need to travel to the University of Washington for this visit.
- Health questionnaire. The health questionnaire will ask sensitive questions about addiction to drugs/alcohol and access to addictive drugs. It will also ask about past gender-affirming medical care.
- Demographics
- Blood draw (~7 mL or 1 ½ teaspoons) to check your liver and kidney function. We will also check your blood sugar and vital signs (heart rate, pulse, blood pressure).
- You will be provided with a stool sample collection kit. The study coordinator will tell you how to use it. You will be asked to collect and bring a stool sample with you to Study Visits 1 and 2.
- You will be provided with a Diet Log. The study coordinator will tell you how to use it. This will help us characterize the natural bacteria in your gut. You will be asked to record your food intake for up to three days prior to Study Visits 1 and 2.
- You must not eat grapefruit, pomelo, or use any grapefruit- or pomelo-containing products for the duration of the study.
- You must not use any herbal supplements during the study.

Before each study visit:

- You must abstain from alcohol for 24 hours
- You must fast after midnight prior to the study visit. You may drink water.
- If you have taken any medications since your last visit, let the study staff know before the visit. They will ask you about medication use at each visit.

Study Visit 1 (no more than 365 days <u>before</u> starting estradiol therapy)

- Will last approximately 25 hours at the UWMC Translational Research Unit. You must check-in at the Research Unit by 7:00 am, and the visit is expected to end at about 8:00 am the following day.
- You will have a physical exam documented within 30 days of Drug Visit 1 or upon check-in at Drug Visit 1.
- You will have a single ECG at check-in. If your ECG is irregular, you will not be able to participate in the study and study staff member will tell you how to follow up with your regular doctor.
- You will be provided a single dose of the following medications: 0.25 mg digoxin (1 tablet), 2 mg midazolam (1/2 teaspoon syrup), 1 mg midazolam (1/5 teaspoon solution administered via an arm vein), 500 mg acetaminophen (1 tablet).

- During your visit, your blood will be drawn 20 times and your urine will be collected during the entire visit. Your blood will also be drawn to check your hormone levels, lipids, and anemia, infection or clotting risk (also called a Complete Blood Count or "CBC"). Approximately 15 tablespoons (~230 mL) of blood will be collected during this visit. Approximately ½ teaspoon (~2.5 mL) of collected blood will be used for DNA isolation. DNA will be analyzed as part of this study to understand how certain genetic factors may influence the way your body processes medicines or other naturally occurring substances in the body. Your stool sample (self-collection) and 3-day diet diary will be collected by the study coordinator at the start of the visit.
- Your vital signs (heart rate, pulse, blood pressure) will be measured.
- Breakfasts, lunch and dinner will be provided during the long visit.
- A urine collection kit will be dispensed so that you can collect your urine for the 24 hours after discharge from the Research Unit.
- You will be asked to return to the UW School of Pharmacy Procedure Room the next morning (24 hours after you were discharged from the TRU). You will collect your urine and bring it with you. You will also have ~10 ml or 2 teaspoons of blood drawn. This visit will last approximately 30 mins. If possible, you will be asked to keep the home urine container refrigerated during collection or to use a portable cooler with ice as an alternative to a refrigerator.

Phone Visit 1 (1 week before Study Visit 2)

- The study coordinator will contact you by telephone and ask questions about how you took your estradiol therapy since Study Visit 1.
- You will be reminded about your upcoming visit and the study coordinator will answer any questions you may have about the visit.

Study Visit 2 (up to 36 weeks after starting estradiol therapy)

- At this visit, you will be asked to do all of the same procedures and tests listed in Visit 1. An ECG will not be performed at this visit. Your liver and kidney function also will be checked as part of the blood work during this visit.
- You will be asked by the study coordinator about how you took estradiol therapy over the weeks before this visit and about any doses you might have missed.

RISKS, STRESS, OR DISCOMFORT

There may be side effects from the tracer-doses of medications administered at each study visit.

Midazolam may cause drowsiness, upset stomach, or dizziness. Midazolam can cause respiratory depression or difficulty breathing. You may consider taking public transportation, a rideshare, or arrange a ride to and from each long study visit day.

Digoxin may cause upset stomach, diarrhea, headache, dizziness or confusion, or heart arrhythmias (abnormal heartbeat).

Acetaminophen may cause upset stomach or headache.

Any drug may cause an allergic reaction, including rash, itching, or difficulty breathing.

Risks of blood draws: pain, bleeding, or bruising where the needle enters the skin; in rare cases, fainting or infection.

Risks of fasting: Fasting may be bothersome or make you feel anxious, irritable, or hungry.

Risks of ECG: When you have the ECG for the study, we may uncover an irregular heart rhythm and you could have psychological (mental) discomfort in learning of a potential health condition. Possible skin irritation may occur where the electrodes for the ECG machine are placed.

Other risks:

- Some items in the questionnaires may make you feel uncomfortable. You may refuse to answer any question or item in any test, inventory, questionnaire, or interview.
- You may feel uncomfortable with collecting fecal samples due to unpleasant odors and inconvenience.
- The urine collection may be inconvenient.
- You will not be able to start your estradiol therapy until after Study Visit 1.
- There is a potential risk of loss of confidentiality.
- It is possible that other rare side effects could occur which are not described in this consent form. It is also possible that you could have a side effect that has not occurred before.

BENEFITS OF THE STUDY

You are not expected to get any benefit from being in this research study. Information learned from this study may lead to future studies to help understand effects of hormone therapy on different medications in other transgender or gender-diverse adults.

SOURCE OF FUNDING

The University of Washington School of Pharmacy is providing financial support for this study.

The study team and/or the University of Washington is receiving financial support from the National Institutes of Health.

CONFIDENTIALITY OF RESEARCH INFORMATION

You will be assigned a study number linked to your name in a separate, secure electronic file. We will keep this key until the research is complete and for the retention period required by law. Use of de-identified data may continue.

All blood, urine, and stool samples for laboratory analysis outside UWMC will be labeled by a study number, not your name. All of the information you provide will be confidential. You will not be personally identified in any reports, studies, publications or presentations.

The link between your identifiers and the research data will be destroyed after the records retention period required by state and/or federal law.

All of the information you provide will be confidential. However, if we learn that you intend to harm yourself or others, we must report that to the authorities.

Your participation in this study will be noted in your UW medical record. A copy of the consent form will be placed in your medical record.

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.

We have a Certificate of Confidentiality from the federal **National Institutes of Health**. This helps us protect your privacy. The Certificate means that we do not have to give out information, documents, or samples that could identify you even if we are asked to by a court of law. We will use the Certificate to resist any demands for identifying information.

There are some limits to this protection. We will voluntarily provide the information to:

- a member of the federal government who needs it in order to audit or evaluate the research;
- individuals at the institution(s) conducting the research, the funding agency, and other groups involved in the research, if they need the information to make sure the research is being done correctly;
- the federal Food and Drug Administration (FDA), if required by the FDA;
- individuals who want to conduct secondary research if allowed by federal regulations and according to your consent for future research use as described in this form;
- authorities, if we learn of child abuse, elder abuse, or the intent to harm yourself or others.

The Certificate expires when the NIH funding for this study ends. Currently this is 7/31/26. Any data collected after expiration is not protected as described above. Data collected prior to expiration will continue to be protected.

USE OF INFORMATION AND SPECIMENS

Returning Results to You

Information obtained in the course of the study that will not be shared with you is individual midazolam, digoxin, and acetaminophen blood or urine concentration results or gut microbiota analysis. By signing this form, you are confirming that you understand you will not be able to see any results of the study tests until the research is finished.

If you request information regarding your measured estradiol or testosterone levels or other clinical blood tests (liver, kidney, lipids, or CBC) during your participation in the study, this information will be shared with you by a study staff member as well as information on how to follow up with your regular doctor. Your provider will then discuss your study hormone values, along with a management plan with you if necessary, based on these study results.

If we find an irregular ECG result, you will not be able to be in the study. If this result is found, a research staff member will talk with you about how to follow up with your regular doctor.

Using Your Data in Future Research

The information and/or specimens that we obtain from you for this study might be used for future studies to look at the effect of estradiol on compounds in the body. We may remove anything that might identify you from the information and specimens. If we do so, that information and specimens may then be used for future research studies or given to another investigator without getting additional permission from you. It is also possible that in the future we may want to use or share study information that might identify you. If we do, a review board will decide whether or not we need to get additional permission from you.

OTHER INFORMATION

You may refuse to participate and you are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. If you wish to withdraw, please contact the researcher listed on page 1 of this consent form.

The UW will reimburse participants $480 for completing each 25-hour Drug Study Visit and $30 for completing the 30-minute follow-up visit at 48 hours. Participants will receive an additional $75 for completing all study visits. Participants who travel to the UW for the consenting/screening visit will be reimbursed $20. The possible total compensation for the study if participants finish all procedures is $1115. All payments will be either: 1) Zelle, 2) pre-paid VISA cards or 3) check payments. For pre-paid VISA cards: a pre-paid card will be provided at the completion of each study visit. For checks: each check will be mailed to you. Any mailed checks will be sent to your preferred mailing address within two weeks after the associated Drug Study Visit and 48-hour follow-up is completed.

- For participants who travel to UW for the consenting/screening visit only: The first payment will be provided or mailed after completing the consenting/screening visit.
- Payments for the Drug Study Visit 1 overnight visit ($480) and the return 48-hour visit ($30) will be provided after completing each visit.
- Similar to Study Visit 1, payment will be provided to you after completing Drug Study Visit 2 and the 48-hour return visit. Additional payment for completing all study procedures ($75) will be included with the 48-hour return visit payment (for a total amount of up to $105).

To receive payment, you must provide your social security number, name and address in order to comply with Internal Revenue Service (IRS) reporting requirements. When payment is reported to the IRS, we will not say what the payment is for, only that you have been paid. If you do not wish to provide this information, you can still participate in the study; however, you will not be paid. If you earn $600 or more in subject payments from the University of Washington during this calendar year, the UW Financial Management Office will report this to the Internal Revenue Service as Miscellaneous Income.

You will be responsible for any applicable insurance deductibles and co-payments associated with your transgender care and estradiol therapy.

Study-specific drugs and tests will be provided at no cost to you.

A copy of the consent form will be emailed to you at an email address that you provide. It will be a "PDF" document. Most computers already have PDF viewer software installed, which will allow you to open, read, or print the consent form. The email we send you will include a link to PDF viewer software (such as Adobe Acrobat Reader) in case your computer doesn't already have it. If you would

prefer to receive a paper copy of the consent form at no cost to you, please contact the researcher listed on page 1 of this consent form.

RESEARCH-RELATED INJURY

For a life-threatening problem, call 911 right away or seek help immediately. If you think you have a medical problem or illness related to this research, contact Lauren Cirrincione 206-685-1864 right away. You can tell this investigator in person or call them at the number(s) listed at the top of this form. This number is monitored 24 hours a day. They will refer you to treatment.

If you are injured as a result of being in this study, necessary medical treatment will be offered at a UW Medicine facility.

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 UW's 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.

Consent Presenter Statement

I have provided this participant and/or their legally authorized representative (LAR) with information about this study. The participant/LAR has been given sufficient time to consider participation and I have answered any questions they had. The participant and/or their LAR indicated that they understand the nature of the study, including risks and benefits of participating.

Printed name of study staff obtaining consent Date

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, or if I have been harmed by participating in this study, I can contact one of the researchers listed on the first page of this consent form. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098 or call collect at (206) 221-5940. I give permission to the researchers to use my medical records as described in this consent form. I will receive a copy of this consent form.

Printed name of subject Signature of subject Date

Copies to: Researcher
Subject
Subject's Medical Record