Informed Consent Cover page

Title: Effectiveness, safety, and tolerability of different estradiol dosing regimens in transgender females.

NCT Number: NCT05010707

Date: May 26, 2022

INFORMED CONSENT DOCUMENT

Project Title: Effectiveness, safety, and tolerability of different estradiol dosing regimens in transgender females

Principal Investigator: Ginger Nicol, MD.

Research Team Contact: Samuel Cortez, MD. Office phone number: (314) 286-2339
(314) 454-6051

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights and responsibilities as a research participant. By signing this form, you are agreeing to participate in this study.

- You should read and understand the information in this document, including the procedures, risks, and potential benefits.
- If you have questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you are a transgender woman between 18-45 years of age.

The purpose of this research study is to evaluate the effectiveness, safety, and tolerability of estrogen treatment options, specifically sublingual and transdermal estradiol. There are no previous data comparing the different presentation of estrogen options in transgender women. This study will provide useful information to close the medical knowledge gap to provide safe and competent care to transgender female patients. We will closely look for changes in the way your body processes sugars and fats. We will also obtain coagulation factors to evaluate the risk of blood clots.

17-beta estradiol is approved by the U.S. Food and Drug Administration to treat vasomotor symptoms and vaginal atrophy in post-menopausal women. However, the use of 17-beta estradiol is considered investigational in this study. Spironolactone is approved by the U.S. Food and Drug Administration to treat high blood pressure or fluid retention. However, the use of Spironolactone is considered investigational in this study.

WHAT WILL HAPPEN DURING THIS STUDY?

Participants will be recruited at the Washington University Transgender Center. After the screening visit, if you are eligible to *continue* in the study, you will be randomly assigned to receive one of the three study treatments: spironolactone with transdermal 17-beta estradiol OR spironolactone with once a day sublingual 17-betaestradiol OR spironolactone with twice a day sublingual 17-beta estradiol. Random assignment means that in the study the treatment you receive will be determined purely by chance. You will have a 1 in 3 chance of receiving any

one of the study treatments or 33.33% of getting assigned to one of the regimens. Once you are started on 17-beta estradiol, you will be asked to attend 4 more visits for the 2 years duration of the study as described in the table below. Also, once you are assigned to a study treatment, we will do monthly blood work until your hormone level are at goal, this step is required whether you are in the study or not.

Study visit	Baseline	6 months	12 months	18 months	24 months
Vital signs and body measurements	]	]	]	]	]
Metabolic factors	]	]	]	]	]
Hormone levels	]	]	]	]	]
Electrolytes	]	]	]	]	]
Liver function test	]	]	]	]	]
Coagulation factors	]	]	]	]	]
Lipid Panel	]		]		]

During the length of this study, you will be seen every 6 months for the length of the study. During each visit, we will obtain your weight, height, body mass index (relationship between your weight and height), blood pressure, and waist circumference. We will also do blood work while fasting. The blood work will look into possible side effects of the medications that you are taking, including changes in your potassium level (electrolytes), the way your body is processing sugar and fats (blood sugar and cholesterol levels). Because of concerns of possible blood clots, we will study coagulation factors in your blood.

Will you save my research information and blood to use in future research studies?

We would like to use the data and blood we are obtaining in this study for studies going on right now, as well as studies that are conducted in the future. These studies may provide additional information that will be helpful in understanding the effect of gender affirming therapy effects in the body which may lead to the development of investigational tests, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your data and blood you give up any property rights you may have in the data and blood.

Your data and blood will be stored without your name or any other kind of link that would enable us to identify which sample(s) or data are yours. Therefore, it will be available indefinitely for use in future research studies without your additional consent and cannot be removed.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 80 people will take part in this study conducted by investigators at Washington University.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for 2 years**.** You will have 5

visits that will range from 30 to 45 minutes in length.

WHAT ARE THE RISKS OF THIS STUDY?

Potential risks with this study are no different than the risks that may occur while receiving any form of gender affirming therapy. These may include, but are not limited to, changes in the way your body processes fats increasing the risk of changes in their lipid profile and triglycerides level, increased risk of blood clots, diabetes, high blood pressure, heart disease, and liver damage. Laboratory testing will be completed about every 3 months for the first year and about every 6 months the second year.

Blood draw.

Common risks include:

- The blood draw may cause bleeding, bruising, or pain.

Rare risks include:

- You could become dizzy or feel faint.
- Infection

Estradiol.

Common side effects include:

- Headache
- Breast tenderness
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Weight change
- Decrease in frequency of erections

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors ("fibroids") of the uterus
- A spotty darkening of the skin, particularly on the face
- Skin rash
- Reddening or irritation at the application site (transdermal patch)

Rare side effects include:

- Breast cancer
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease

These are some of the warning signs of the rare side effects:

- Breast lumps
- Dizziness and faintness
- Changes in speech
- Severe headaches

- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Spironolactone.
Common side effects include:

- Breast enlargement
- Headache
- Drowsiness
- Increase in urination
- Diarrhea
- Nausea and vomiting
- Skin rash

Rare side effects include:

- Hyperkalemia (elevated potassium level)
- Hypotension (low blood pressure) and worsening renal (kidney) function
- Electrolyte and metabolic abnormalities
- Impaired neurological function/coma in patients with hepatic impairment, cirrhosis, and ascites

Breach of Confidentiality
One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?
You will not benefit from being in this study.

However, We hope that, in the future, other people might benefit from this study because the information learned from this study may help us improve services and treatment options for the future.

WHAT OTHER TREATMENT OPTIONS ARE THERE?
Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could receive treatment with intramuscular estradiol or you can receive another similar treatment or therapy without being in the research study.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?
As part of this study, you will receive tests and procedures that are similar to what you would

receive during routine clinical care of your transition. Your health plan/insurance company will be billed for some or all of these costs, and you will be responsible for any co-pays and deductibles that are normally required by your health plan/insurance. Not all insurance plans cover the costs associated with being in a study. Even if they do, you may be responsible for more out-of-pocket expenses, such as co-pays and deductibles, when there are more tests and procedures or more expensive tests and procedures involved in the study than if you were to receive routine clinical care outside the study.

If you wish to know whether there are more tests and procedures or more expensive tests and procedures in the study, you should ask your study doctor.

If you wish to know whether your insurance will pay, you should contact them directly, or speak with the study team about obtaining a financial pre-certification prior to enrolling in the study.

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. You will be given a $30 through debit card for each visit. There will be 3 paid in-person visits, for a total of $90. You will be asked to provide your social security number (SSN).. We will provide you with information about any fees or restrictions on the use of the debit card.

WHO IS FUNDING THIS STUDY?

The National Institutes of Health (NIH) is funding this research study. This means that Washington University is receiving payments from the NIH to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from the NIH for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator at : (314) 286-2339 OR (314) 454-6051, and/or the Human Research Protection Office at 1-(800)-438-0445.

Decisions about whether payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

Other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you. We will keep your participation in this research study confidential to the extent permitted by law.

- Government representatives (including the Office for Human Research Protections) to complete federal or state responsibilities.
- The U.S. Food and Drug Administration
- The National Institutes of Health

- Hospital or University representatives to complete Hospital or University responsibilities.
- Information about your participation in this study may be documented in your health care records and will be available to anyone with access to your health care record, including your health insurance company. This information may also be released as part of a release of information request.
- The last four digits of your social security number may be used in hospital or University systems to track billing information for research procedures.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.
- Any report or article that we write will not include information that can directly identify you. The journals that publish these reports or articles require that we share your information that was collected for this study with others to make sure the results of this study are correct and help develop new ideas for research. Your information will be shared in a way that cannot directly identify you.

To help protect your confidentiality, we will:

- Consent will be obtained in a private setting
- Obtain only the minimum necessary private information
- Procedures (like blood draw) will be conducted in a private setting
- All information will be secured in a password-protected secured environment (REDCap database)
- Access to the information collected will be limited to the research team members only
- Each participant will be provided a unique code/number to collect their information (coded information)
- Information collected from participants will be saved under the assigned code/number
- Blood sample will be collected under the code/number assigned to each participant, this way we will assure the specimens are de-identified.

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.

To further protect your privacy, this research is covered by a Certificate of Confidentiality from the federal government. This means that the researchers can refuse to disclose information that may identify you in any legal or court proceeding or to anyone who is not connected with the research except if:

- there is a law that requires disclosure, such as to report child abuse and neglect, or harm to self or others*;*

- you give permission to disclose your information, including as described in this consent form; or

- it is used for other scientific research allowed by federal law.

This Certificate may not be effective for information held in foreign countries.

You have the right to share your information or involvement in this study with anyone at any time. You may also give the research team permission to disclose your information to a third party or any other person not connected with the research.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect:

your treatment or the care given by your health provider.
your insurance payment or enrollment in any health plans.
any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research.
- This authorization does not expire.

You may later change your mind and not let the research team use or share your information (you may revoke your authorization).

- To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ or you may request that the investigator send you a copy of the letter.
    - **If you revoke your authorization:**
        - ♣ The research team may only use and share information already collected for the study.
        - ♣ Your information may still be used and shared as necessary to

maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.

♣ You will not be allowed to continue to participate in the study.

Can we contact you by email and text message?

We would like to contact you by email and text message for the purposes listed below. Some of these messages may contain health information that identifies you.

- Educational material regarding your condition and medications that you are taking
- Remind you about future/upcoming appointment
- Coordinate future appointments
- Discuss blood work and medication updates
- Ask about prescription refills

Only the research team will have access to your email and text communications. We will only communicate in this method to send you the information listed above. If you have any questions, wish us to stop sending these messages or need to contact us for an urgent or emergent situation, please contact the research team member identified at the top of this document.

You should be aware that there are risks associated with sending your health information via email and text.

- Text messaging is not a secure communication method.
- There is always a risk that the message could be intercepted or sent to the wrong email address and/or phone number. To avoid this, we will send a test message to ensure we have the correct email address and/or phone number.
- For email, when using any computer you should be careful to protect your username and password. Make sure you log-out before getting up from the computer.
- If you share a home computer or cell phone with other family members, and do not want them to know you are participating in this study make sure you provide an email address that only you can access.
- Your employer will have access to any messages sent or received on any electronic devices used for work or through a work server.
- If you lose your phone, others may be able to access the messages that we send.

Do you agree to allow us to send your health information via email?

_____ **Yes** _____ **No**
Initials **Initials**

Do you agree to allow us to send your health information via text?

_____ **Yes** _____ **No**

Initials **Initials**

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. Any data that was collected as part of your participation in the study will remain as part of the study records and cannot be removed.

If you decide not to be in this study, or if you stop participating at any time, you will not be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?

You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ under Withdrawing from a Research Study.

Will I receive new information about the study while participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we will promptly provide you with that information.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact Ginger Nicol, MD at (314) 286-2339 OR (314) 454-6051

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office 1-(800)-438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, http://hrpo.wustl.edu. To offer input about your experiences as a research participant or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your

participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 04/12/23.

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that they understand the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

_____
(Name of Person who Obtained Consent - printed)