Informed Consent Form Cover Page

Official Title: Primary Ovarian Insufficiency: Phenotype and Optimal Treatment

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STUDY TITLE: PRIMARY OVARIAN INSUFFICIENCY: PHENOTYPE AND OPTIMAL TREATMENT

STUDY NUMBER: 2018-2375

FUNDING ORGANIZATION: Patty Brisben Foundation

Dr. Halley Wasserman
Name of Principal Investigator

513-636-1208
Telephone Number

INTRODUCTION

We are asking you to be in a research study so that we can learn new information that may help others. If you decide not to be in this study, we will still take good care of you. If you decide to be in this study, you may change your mind at any time during the study and you can stop being in the study. Take all the time you need to make your choice. Ask us any questions you have. It is also okay to ask more questions after you decide to be in the study. You can ask questions at any time.

WHY ARE WE DOING THIS RESEARCH?

In this research study, we want to learn more about Primary Ovarian Insufficiency (POI).We are interested in the effects of Hormone Replacement Therapy (HRT) by transdermal estradiol on bone density, mood changes, and memory.

We are asking you and other children with POI to be in the research study, because we want to learn how your body changes after starting transdermal estradiol.

WHO IS IN CHARGE OF THE RESEARCH?

Dr. Halley Wasserman is the researcher at Cincinnati Children's Hospital Medical Center (CCHMC) that is in charge of this study.

CCHMC is receiving funding from the Patty Brisben Foundation for Women's Sexual Health to carry out this study.

WHO SHOULD NOT BE IN THE STUDY

You can not be in this study if you have any of the following:

1) Have other chronic diseases in addition to POI known to affect bone health (e.g., cystic fibrosis, celiac disease, etc.)
2) Younger than 11 years old or older than 18 years old
3) Have an identified secondary cause of POI (eg radiation, chemotherapy, etc.)
4) Have POI in the setting of Turner syndrome, Fanconi Anemia, galactosemia, or Perrault syndrome
5) Have used medications known to affect bone health over previous 3 months (e.g. anticonvulsants, chronic use glucocorticoids, etc.)

6) Currently pregnant (confirmed with a positive pregnancy test)

WHAT WILL HAPPEN IN THE STUDY?

The research staff will explain each visit to you and may give you a handout that explains each visit in more detail. You will be able to ask questions to make sure that you understand what will happen.

If you qualify and decide you want to be in the study, you will come to CCHMC **five** times after this visit over the next 24 months. Each visit will last approximately 2 to 5 hours. Research staff will contact you to schedule your appointments ahead of time

These are the things that will happen to you while you are in the study:

1) You will be asked to use hormone replacement therapy (HRT) by transdermal estradiol (estrogen patches) during your 24 months of participation in the study. Transdermal estradiol is standard of care for patients with POI.
   - The PI and study staff will provide directions and tools to help keep track of when you are using the estrogen patches
   - You will be provided with the estrogen patches at each study visit. You will be provided with enough patches until the next study visit. At your 24 month study visit you will be given a prescription for continued use of 100 µg the estrogen patch.
   - At each visit, your estrogen patch dose will be increased until 18 months like it would be if you were being seen in in the outpatient clinics at CCHMC, which is described here:

Months:	0	3	6	12	18	24
Transdermal Estradiol dose	25 µg	37.5 µg	50 µg	75 µg	100 µg	100 µg

2) Your height, weight, blood pressure, respiratory rate, and pulse will be measured
3) A physical examination by a medical doctor
4) You will answer questions about your health history
5) You will complete questionnaires to assess anxiety, depression, quality of life, and sexual health
6) You will provide us information on your day-to-day meal intake and exercise habits
7) You will complete questionnaires to measure intelligence, how you process information, memory, and learning
8) DXA scan: There will be 5 scans total; one at your first study visit (today), one at your 6 month study visit, one at your 12 month study visit, one at your 18 month visit, and one at your 24 month visit. A measure of your bone density and body composition (the percent of the body that is fat or muscle) will be obtained. This test takes about 15-20 minutes and would require you to lay flat on an open table while the DXA (dual energy x-ray absorptiometry) scanner examines different parts of your skeleton. The DXA scanner is an open machine and therefore you will not be in a closed space at any time.
9) pQCT scan: There will be 5 scans total; one at your first study visit (today), one at your 6 month study visit, one at your 12 month study visit, one at your 18 month visit, and one at your 24 month visit. We will measure your bone mineral density of your bones using a machine called pQCT (peripheral quantitative computed tomography) scanner. We will measure the size and strength of the bones in your arms and legs. The pQCT is also an open machine and therefore you will not be in closed space at any time.
10) Bone Age Radiograph: There will be up to 3 x-rays total with the first one obtained during your

visit today. The study doctor will determine if you need the additional x-rays (at the 12 month and/or 24 month study visits) based on your growth.

11) Blood draw: There will be 5 blood draws total; one at your first study visit (today), one at your 6 month study visit, one at your 12 month study visit, one at your 18 month visit, and one at your 24 month visit. For the blood draw, if you want we will apply a special numbing spray over the part of the arm for the blood tests. You are not allowed to eat and drink before having your blood drawn.

12) Follow up call: we will give you a follow up phone call to ask you questions about your estrogen patch use between your 12 and 18 month study visits.

Pregnancy Testing Notice: Because the bone scans for this study involve exposure to a small dose of radiation, pregnancy testing will be performed before you undergo the scans. If you have a positive pregnancy test, we must withdraw you from the study for the safety of the developing baby. Please let the study team know if you think you are pregnant before you sign the consent form.

WHAT ARE THE GOOD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

We still have a lot to learn about this study treatment. We hope that it will help you feel better or help to reduce your symptoms associated with POI, but we do not yet know the effects of estrogen replacement on various tissues within the body. When we finish the research, we expect that we will know more about POI. This may help other adolescents with POI.

WHAT ARE THE BAD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

During your study visits with the research team, you may be asked questions that may make you uncomfortable or cause you to remember situations that were upsetting. Although unexpected, you may feel uncomfortable completing questionnaires about your health history, eating, and exercise habits.

Additionally, you may become frustrated if asked questions during testing that you do not know how to answer. You are going to be asked questions that you cannot answer. You do not need to answer any questions that you do not wish to answer and you can stop the testing at any time. If you become very upset during the course of answering questionnaires, we will end the testing. We will also offer to have you speak to someone about what you are feeling.

This study involves exposure to radiation from the DXA, pQCT, and radiograph scans. We are all exposed to radiation every day from natural sources. This is called natural background radiation. Natural background radiation in the US averages about 3000 microsieverts per year. Over the two years of this study, the DXA scans, pQCT scans, and radiographs of the hand and wrist used in this study will expose you to 180 microsieverts or less of radiation. This is about the amount of radiation we are all exposed to every four weeks from nature. The risk associated with this radiation dose is minimal, no greater than the activities of daily life.

During the pQCT scan, you will be required to sit with one leg/arm positioned in the scanner for 8-10 minutes; some people experience some discomfort from maintaining this positon during of the scan. Lying flat and still for the duration of the DXA scan may also be uncomfortable. For quality images, scans will be repeated one more time if the technician detect any movement you make in the scanners. To avoid a scan from being repeated, it is important that you remain still during both the pQCT and DXA scan as instructed by the technician. During the radiograph, you will be required to

have one arm positioned under the x-ray for <10 seconds, which generally is not associated with discomfort.

As mentioned earlier, if it is discovered that you are pregnant, you cannot take part in this research study. If there is a possibility that you could be pregnant, by signing this consent, you agree to tell the research staff on the date of your scans. In this case, the scan will be performed after a urine pregnancy test is done and found to be negative. We want to avoid causing harm to you and the developing baby.

With the blood draw, bruising and/or slight discomfort are the most common potential inconveniences. Although uncommon, fainting from blood draws may occur. Although rare, there is also risk of infection with a blood draw.

The treatment you will be receiving in this study is the standard treatment for POI. We will be collecting information to understand its effects on various bone and other tissues in the body.

There may be other risks that we do not know about yet.

WHAT OTHER CHOICES ARE THERE?

You can choose not to be in this study and continue your regular follow up visits with your POI doctor. In this case, you will not be monitored in any way or form by the research team.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE?

Making sure that information about you remains private is important to us. To protect your privacy in this research study we will make the effort to maintain the confidentiality of your medical and research information (Protected Health Information or PHI), consisting of your name and birthdate. PHI is defined as health information, whether verbal or recorded in any form (such as on a piece of paper or entered in a computer), that identifies you as an individual or offers a reasonable basis to believe that the information could be used to identify you.

By signing this consent form you are giving permission for a representative of CCHMC, the investigator, and CCHMC employees involved with the research study including the Institutional Review Board and the Office of Research Compliance, and any sponsoring company or their appointed agent to be allowed to inspect sections of your medical and research record related to this study.

The information from the research study may be published. However, you will not be identified. The publication will not contain information about her that will enable someone to identify her as a research participant.

CCHMC and/or investigator will take the following precautionary measures to protect your privacy and the confidentiality of your questionnaire results and any other records. Your research information will be identified only by your study visit date and an ID number. All collected information will be locked in storage, with only the ID numbers on it. Copies of questionnaires will be kept electronically when not being used and questionnaire results will only be seen by study personnel.

Privacy Notice: If you gives us a reason to believe that you are at risk of suicide or harming yourself,

the study team may notify your physician and/or your therapist. In this case, we cannot ensure privacy of your participation in this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time.

The Food and Drug Administration (FDA) may choose to inspect your records since you are a subject in this investigation of an off label use of a drug.

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?

The researcher or study doctor will tell you if they find out about new information from this study that may affect your health, safety, or willingness to stay in this study. If during the course of the study we have a reason to believe that you are at risk for suicide or otherwise harming yourself, we are required to take necessary actions. The study personnel will request that you speak with a clinician/therapist immediately, to make sure you are safe. If this were to occur, as already stated, we will not be able to assure confidentiality.

WILL IT COST YOU ANYTHING EXTRA TO BE IN THE RESEARCH STUDY?

It will not cost you anything to be in this research study. All of the research services and medication you will receive are being performed only because you are taking part in this study. These services and medication will be paid for by the study and will not be billed to you or your health insurance company.

Because the treatment is standard of care, it will be your responsibility to cover costs of treatment of any side effects associated with the estrogen patches. Additionally, you will be responsible for costs of any referrals that might result from research like additional scans, follow-up for suicidal thoughts, counseling, and physician appointments.

WILL YOU BE PAID TO BE IN THIS RESEARCH STUDY?

You will be reimbursed for her time, effort and travel while you are in this research study. You will receive payment for this study in the form of a reloadable debit card (Clincard). We will give you a handout that will explain how to use the card. Because you are being paid for your participation, CCHMC is required by the Internal Revenue Service (IRS) to collect and use your social security number (SSN) or taxpayer identification number (TIN) to track the amount of money that we pay. You will need to complete a Federal W-9 form for this income tax reporting. This form requires your Social Security number. This form will be given to the CCHMC business office. It will not be kept as part of your study chart. If you move, you will need to complete another W-9 with an updated address.

You will be paid $50 for each study visit as reimbursement for your time and effort for a potential total compensation of $300 for completing all study visits.

- $50 Baseline Visit (Today)
- $50 3-Month Visit
- $50 6-Month Visit
- $50 12-Month Visit
- $50 18-Month Visit

$50 24-Month Visit

WHAT HAPPENS IF YOU ARE INJURED FROM BEING IN THIS STUDY?

If you believe that you have been injured as a result of this research you should contact the researcher, Dr. Halley Wasserman, at 513-636-1208 as soon as possible to discuss the concerns. Treatment for injuries is available at CCHMC. If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in a research study. If possible, you should give them a copy of this consent form.

CCHMC follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about this research study you can contact the study person listed on page 1 of this document.

If you would like to talk to someone that is not part of the research staff or if you have general questions about your research study rights or questions, concerns, or complaints about the research, you can call the CCHMC Institutional Review Board at 513-636-8039.

WHAT ELSE SHOULD YOU KNOW ABOUT THE RESEARCH?

If for some reason you have an adverse effect to estrogen therapy, it can be stopped without the need to taper the dose. Most patients with POI actually feel much better after starting estrogen therapy.

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your "protected health information" (called PHI for short).

What protected health information will be used and shared during this study?
CCHMC will need to use and share your PHI as part of this study. This PHI will come from:
- Your CCHMC medical records
- Your research records

The types of information that will be used and shared from these records include:
- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- If applicable, information concerning HIV testing or the treatment of AIDS or AIDS-related conditions, drug or alcohol abuse, drug-related conditions, alcoholism, and/or psychiatric/psychological conditions (but not psychotherapy notes).

Who will share, receive and/or use your protected health information in this study?
- Staff at all the research study sites (including CCHMC)
- Personnel who provide services to you as part of this study
- Other individuals and organizations that need to use your PHI in connection with the research,

including people at the sponsor and organizations that the sponsor may use to oversee or conduct the study.
- The members of the CCHMC Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your PHI is not misused?
People that receive your PHI as part of the research are generally limited in how they can use your PHI. In addition, most people who receive your PHI are also required by federal privacy laws to protect your PHI. However, some people that may receive your PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?
You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about you will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Please note that if you do not attend the study visits and/or are deemed by the study physician to be noncompliant with the estrogen patches, you can no longer be in the study.

Will this permission expire?
Your permission will expire at the end of the study. If the study involves the creation or maintenance of a research database repository, this authorization will not expire.

Will your other medical care be impacted?
By signing this document you are agree to participate in this research study and give permission to CCHMC to use and share your PHI for the purpose of this research study. If you refuse to sign this document you will not be able to participate in the study. However, your rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

SIGNATURES

The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research you will document your consent by signature below.

You will receive a copy of this signed document for your records.

_____
Printed Name of Research Participant

_____ _____
Signature of Research Participant Indicating Consent — Date

_____ _____
Signature of Legally Authorized Representative* — Date

_____
* If signed by a legally authorized representative, a description of such representative's authority must be provided

_____ _____
Signature of Individual Obtaining Consent — Date