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(This document must be scanned into the Austin Health SMR once the participant has consented)

Participant Information Sheet/Consent Form

Non-Interventional Study - *Adult providing own consent*

AUSTIN HEALTH

Title	A randomised double-blind trial comparing the effectiveness of anti-androgen medications in trans and gender diverse individuals
Short Title	Anti-androgens in trans feminine individuals
Protocol Number	1
Project Sponsor	N/A
Coordinating Principal Investigator	Dr Ada Cheung
Principal Investigators	Prof Mathis Grossmann, Prof Jeffrey Zajac
Location	Austin Health and Repatriation Campus

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you are about to start or have started feminising hormone therapy for gender transition, but you are not currently on anti-androgen (Testosterone blocker) therapy and your total testosterone levels are greater than 10nmol/L. This research project aims to compare the effectiveness of two commonly used anti-androgen medications (cyproterone acetate and spironolactone) in lowering testosterone levels and inducing feminising characteristics.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and research involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read
• Consent to take part in the research project
• Consent to the tests and research that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Anti-androgens (commonly known as testosterone (T) blockers) are commonly used with estrogen (estradiol) as feminising hormone therapy in trans and gender diverse individuals. The goal of feminising hormone therapy is typically to increase estradiol and lower testosterone to achieve hormone levels in the female reference range. Anti-androgens are commonly used together with estradiol to lower or block testosterone, which in turn leads to breast development, feminises the body shape, softens skin and reduces body and facial hair. The two most commonly used anti-androgen medications in Australia are cyproterone acetate and spironolactone, however no research exists to show which drug is more effective.

The aim of this study is to compare the effectiveness of additional anti-androgen treatment (cyproterone acetate versus spironolactone) in breast development, to lower testosterone levels and aid development of feminine body shape.

The need for specific, rigorous research to guide hormonal therapy guidelines for the trans and gender diverse community is very much needed. The results from the study will inform clinical care and treatment choice for both trans and gender diverse people undergoing feminising hormonal treatments as well as their treating clinicians.

This research has been initiated by the study doctors, Dr Ada Cheung and Professor Jeffrey Zajac. The research has been funded by the Endocrine Society of Australia, Austin Medical Research Foundation and the Royal Australasian College of Physicians Cottrell Fellowship.

3 What does participation in this research involve?

3.1 Study design

There will be approximately 64 people who will participate in the study and they will be randomly assigned (like the toss of a coin) to one of two groups: half the participants will be receiving cyproterone acetate 12.5mg daily, while the other half of participants will receive spironolactone 100mg daily. To avoid bias, neither you nor the study doctors will know which group you have been assigned to and both capsules will look the same. The research trial anti-androgen capsules will be supplied without charge. All participants will receive standard care, which will include a standard prescription (obtained from your local pharmacy) for estrogen (not supplied by the study).

3.3 How the research will be monitored

The study doctors are responsible for monitoring you and your test results and will inform you and your local doctor if any issues arise. This research will be conducted in accordance with Human Research Ethics Committee approval.

3.4 Access to personal records that may be required

Medical records may be accessed as part of this study. This may mean accessing medical records from Austin Health or other doctors with your consent. This study does not involve any audio recordings.

3.5 Results of the study

Neither you nor the study doctors will know which study group you have been assigned to. This research project has been designed this way to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

3.6 Costs and reimbursement

There are no costs associated with participating in this research project, nor will you be paid. You will still need to undertake standard medical care including obtaining estrogen medications and your regular doctor visits. The research trial anti-androgen medication, and tests required as part of the research project will be provided to you without charge.

4 What do I have to do?

Participants will be invited to attend an initial study visit to assess their eligibility to participate in the study and to gain their consent to participate. You will then be asked to attend 2 subsequent study visits over a 6-month period at 3 months and 6 months in person (plus an additional blood test at 1 month and 2 months to check your estradiol levels). You are under no obligation to participate in the study, and if you later decide you no longer wish to participate in the study, this will not affect your ongoing care.

Once we confirm that you are eligible to participate in the study, we will randomise (like the toss of a coin) to one of the two research trial anti-androgen medications (either cyproterone acetate or spironolactone) which will be supplied to you without charge by the hospital pharmacy at the first study visit. Neither you nor the study staff will know which medication you are allocated to. You will be asked to take the research trial medication daily together with your standard estradiol medication.

The first study assessment at Heidelberg Repatriation Hospital will take approximately 1 – 2 hours and will involve the following:

- Medical interview: One of our study doctors will ask about your medical history and any medications you are taking. We can get some of this information from your medical records and will confirm with you that the information is correct.

- Physical examination: Includes height, weight, blood pressure, and a tape measurement of your chest circumference to measure your breast size, hip and waist circumference.

- Chest photography: Using a special 3D camera, standardised photos will be taken of your chest (without clothing) from the front and from the side. Computer software will analyse the images to calculate your breast volume. The photos will not include your face and will be deidentified (the photographs will only be labelled with your study code and will not include your name or any other identifying information).

- Electrocardiograph (ECG): An ECG is a tracing of your heart's electrical activity. It involves placing sensors on your chest, arms and legs. Leads are then connected to the sensors and the ECG machine. This procedure takes about 5 minutes and is not painful.

- Baseline blood test: These are routine blood tests taken from your arm to check your hormone levels, blood count, kidney and liver function. Additional blood (6mL) will be collected and transferred to immunology researchers at the Murdoch Children's Research Institute to study changes in your immune function that occur before and after commencing hormone therapy.

- Baseline DXA (Dual energy X-ray Absorptiometry) scan: DXA is a safe, painless test that will be performed to measure your body composition to determine the amount of muscle and fat and the pattern in which it is distributed (i.e. masculine or feminine pattern). It is like an x-ray lying on a bed. This will be performed at Austin Health (Heidelberg Repatriation Hospital) and will take approximately 15 minutes.

- Questionnaires: The Patient Health Questionnaire 9 is a self-rated questionnaire used to measure depression and for monitoring any changes in severity and characteristics of depression during interventions. You will also complete the Gender Preoccupation and Stability Questionnaire as a measurement for assessing gender dysphoria. These questionnaires will take about 5 minutes to complete.

The 4 subsequent study visits will be shorter in duration and will involve:

- Visit 2 and 3 (at month 1 and 2 – blood test only): A blood test as described above to check your estradiol levels. You will be contacted by telephone with the results. If they are below the female reference range, then your estradiol medication will be changed at each time point until you achieve target levels as per standard care.

- Visit 4 (at 3 months – visit to Heidelberg Repatriation Hospital in person): Completing the 2 questionnaires, a physical examination, checking your blood pressure and a blood test. You will also collect ongoing research trial anti-androgen medication from the hospital pharmacy for the remaining 3 months.

- Visit 5 (at 6 months - visit to Heidelberg Repatriation Hospital in person): Completing the 2 questionnaires, a physical examination, checking your blood pressure, chest photography, ECG, blood test, and a DXA scan.

The table below outlines the assessments or tests performed at each time point.

Table: Outline of study visits

Assessment/ Procedure	Visit 1 (0 months)	Visit 2 (1 month)	Visit 3 (2 months)	Visit 4 (3 months)	Visit 5 (6 months)
Clinical assessment including breast size	x			x	x
Depression & gender dysphoria questionnaires	x			x	x
Blood Collection	x	x	x	x	x
Chest photography	x				x
DXA body composition	x				x
Blood pressure (safety measure)	x			x	x
ECG	x				x

There are no lifestyle or dietary changes involved in this study. If you are a blood donor, you will be able to continue to donate blood. You will continue to take all your regular medications as prescribed. If you commence any new medications during the course of the study, please discuss this with our study doctors as we may need to withdraw you from the study. We will not prevent you from taking any medications that you need for your medical care.

It is your responsibility to inform the study doctors immediately if you have any issues or concerns during study visits or with tests performed as we can assist you with these issues.

5 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Austin Health.

6 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; these include continuing with your standard treatment. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

7 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research. However, this research will contribute to the understanding of the most effective anti-androgen medication for feminisation and will potentially benefit the transgender community through improvements in the way we understand the use of hormone treatment.

8 What are the possible risks and disadvantages of taking part?

If your participation in this research uncovers a medical condition of which you were unaware, we will support you in accessing appropriate information and management.

Depression is a possible side-effect of cyproterone acetate, although it is unclear whether this is related to the drug itself or the testosterone-lowering effect. Participants will be asked to complete questionnaires to monitor for depression and gender dysphoria.

We will be using spironolactone which can cause high potassium levels in individuals with renal (kidney) impairment, although this is unlikely to occur in participants with healthy kidney function. Spironolactone can also increase the amount of urine that you produce and sometimes cause low blood pressure. We will monitor blood pressure and take a blood sample to monitor your renal function and potassium levels to ensure safety.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team.

Having a blood sample taken may cause some discomfort, bruising, minor infection or bleeding.

This study involves the use of a DXA scan that uses a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 1.5 millisieverts (mSv) each year. The effective dose from this research project is about 0.002 mSv. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. This risk is believed to be minimal.

9 What will happen to my test samples?

9.1 Test sample collection and analysis

A mandatory part of participation in this study is the collection of blood samples. Your blood samples will be analysed by Austin Health or an equivalent pathology service on as soon as possible after your blood is collected from you and then the samples will be discarded within 14 days. The results of these tests will go into your Austin Health medical record and also be collected separately in your study file.

9.2 Test samples and indefinite storage

With your consent, each time you have a blood test for this study, an extra 7.5ml (2 teaspoons) will be stored in a locked freezer in the Austin Health Endocrine Department Laboratory. Your blood will be stored by a coded study number. Your study will be linked to your hospital record

number on a password-protected file on a University of Melbourne, Department of Medicine-Austin Health server. This means that your study doctors will be able to re-identify you in order to gain access to your clinical information recorded in your paper or electronic medical record during this research project. All personnel reviewing your sample results and medical records will be required to keep all the information confidential in accordance with the law.

The frozen samples will be stored indefinitely in the locked freezer in the Endocrine Department Laboratory. This is in case any blood tests need to be repeated and in the event a new research question arises which we could answer by going back to these old blood samples.

9.3 Test samples and other research organisations

Samples of your blood obtained for the purpose of this research project will be transferred to Monash Pathology and to the Murdoch Children's Research Institute at the Royal Children's Hospital. Monash Pathology will perform highly sensitive measurements of your sex hormone levels (e.g. testosterone, estradiol). Your blood samples will not be sold by Austin Health. The Murdoch Children's Research Institute will analyse the blood samples looking at changes in how your immune system functions before and after hormone therapy.

9.4 What are the possible benefits of storing my blood for future research?

It is unlikely that future research done using your blood samples will provide you or your family with a direct benefit. The results generated by research are expected to be of interest only to the researchers. Because your samples will be stored indefinitely and be made available for future research, they may not be used for many years once new research approaches or techniques are developed. Therefore, any benefit might not be to you but to future generations.

9.5 What are the possible risks of storing my blood for future research?

Genetic analysis involves the study of genetic material (DNA and/or RNA), which is shared with your blood relatives. Some genetic research has the potential to identify genetic abnormalities that might have implications for family members. If a genetic abnormality (also known as a mutation) is detected that has relevance for a living participant or family member, the Austin Health Human Research Ethics Committee will be informed and guidance will be sought on how best to communicate this information to you and your family.

9.6 What if new information arises from my blood stored for future research?

Discoveries arising from research carried out using your samples are not expected to have medical importance for you and your family. However, if such a discovery is made, the researcher is required to contact the Austin Health Human Research Ethics Committee. The committee will examine the research data and decide whether or not it may be in your interests for you to be contacted.

9.7 Do I have to have my blood stored for future research and can I withdraw consent later?

Providing consent to have your blood stored for future research is voluntary. If you decided to participate and later change your mind, you are free to withdraw consent at any stage. You would need to notify a member of the research team so that any samples still remaining can be destroyed. Please contact the study team member names at the end of this document if you

would like to withdraw your consent. It would not be possible to withdraw research information that has already been published.

10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

It is possible that on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

11 Can I have other treatments during this research project?

It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project.

12 What if I withdraw from this research project?

If you decide to withdraw from this research project, please notify a member of the research team before you withdraw. A member of the research team will inform you if there are any special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the study staff up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

13 Could this research project be stopped unexpectedly?

It is unlikely that this research project would be stopped unexpectedly as both medications used in this research trial are currently part of standard care.

14 What happens when the research project ends?

At the conclusion of this study you will be asked to have ongoing monitoring and management through your usual treating doctor.

The results of this study may be published in academic journals and/or presented in medical meetings. You will not be identified in these publications or presentations. Information will be presented in such a way that you cannot be identified. The research staff can let you know the results of the study when they are available.

Part 2 How is the research project being conducted?

15 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential and securely stored. Only the researchers named above will have access to it and it will only be disclosed with your permission. Information on paper will be stored in a locked filing cabinet within a locked office located at Austin Health. Your information will be stored in a folder that will contain a study number only and not your name. The code to match names with study numbers will be kept electronically. Electronic information such as this will be stored on a password protected computer system on a server at The University of Melbourne – Austin Health. Your paper and electronic data will be stored for 15 years following completion of this study. At the end of 15 years, any information that does not also form part of your Austin Health medical record will be permanently destroyed (shredded or deleted).

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the research team accessing health records if they are relevant to your participation in this research project. Information about your participation in this research project will be recorded in your health records.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the Australian Government's Therapeutic Goods Administration (TGA), or Austin Health Human Research Ethics Committee, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant research personnel and regulatory authorities as noted above.

In accordance with relevant Australian and/or Victorian privacy laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information.

16 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital. You can also speak to a consumer liaison officer at the Centre for Patient Experience by calling (03) 9496 3566.

17 Who is organising and funding the research?

This research project is being conducted by the study doctors named at the top of the first page. These doctors work at Austin Health. This research has been funded by The University of Melbourne Early Career Research Grant, and additional funds may be provided by the Australian Government National Health and Medical Research Council.

By taking part in this research project you agree that anonymised data generated from this study may be provided to external research organisations. Neither you nor your family will benefit financially from your involvement in this research project even if your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to the study doctors, their institutions, or external research organisations using the knowledge acquired through this research.

No members of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

18 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Austin Health.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

19 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the following principal study doctors:

Clinical contact person

Name	Dr Ada Cheung
Position	Principal Investigator
Telephone	(03) 9496 2260
Email	anti-androgen@unimelb.edu.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Complaints Contact Person
Position	Office of Research
Telephone	(03) 9496 4090
Email	ethics@austin.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC and Local HREC Executive Officer Details

Reviewing HREC name	Austin Health HREC
HREC Executive Officer	Chelsea Webster
Telephone	(03) 9496 3248
Email	ethics@austin.org.au

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Consent Form - *Adult providing own consent*

Title	A randomised double-blind trial comparing the effectiveness of anti-androgen medications in trans and gender diverse individuals.
Short Title	Anti-androgens in trans feminine individuals.
Protocol Number	1
Project Sponsor	N/A
Coordinating Principal Investigator	Dr Ada Cheung
Principal Investigators	Prof Mathis Grossmann, Prof Jeffrey Zajac
Location	Austin Health and Repatriation Campus

Consent Agreement

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Austin Health concerning my condition and treatment for the purposes of this project. I understand that such information will remain confidential.

I understand that, if I decide to discontinue the research project treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

I consent to the storage and use of blood samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for (tick one option)

This specific research project only	
This research project and any future research EXCEPT genetic testing	
This research project and any future research INCLUDING genetic testing	

Declaration by Participant – for participants who have read the information

Name of Participant (please print) _____

Signature _____ Date _____

Place Patient Label Here
(This document must be scanned into the Austin Health SMR once the participant has consented)

Declaration - for participants <u>unable</u> to read the information and consent form

Witness to the informed consent process
Name (please print) _____
Signature _____ Date _____
* Witness is <u>not</u> to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may <u>not</u> act as a witness to the consent process. Witness must be 18 years or older.

<u>Declaration by Study Doctor/Senior Researcher†</u>

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.
Note: All parties signing the consent section must date their own signature

Place Patient Label Here
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Form for Withdrawal of Participation - *Adult providing own consent*

Title	A randomised double-blind trial comparing the effectiveness of anti-androgen medications in trans and gender diverse individuals.
Short Title	Anti-androgens in trans feminine individuals.
Protocol Number	1
Project Sponsor	N/A
Coordinating Principal Investigator	Dr Ada Cheung
Principal Investigators	Prof Mathis Grossmann, Prof Jeffrey Zajac
Location	Austin Health and Heidelberg Repatriation Campus

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Austin Health.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.