Title: Protocol for Clinical Trials in Humans 2020

Section 2

Informed Consent Form for Participation in Medical Research

[Ministry of Health logo and Clinical Trials Department information]

The form is written in masculine form for convenience but is intended for all genders.

You have been offered to participate in  a medical research. Medical research is a process that is essential for the development of new treatments or procedures that are not yet accepted or proven to be effective in Israel or worldwide. This form explains the research and your rights regarding participation. We ask you to read the information carefully and discuss it with whomever you wish: family, friends, primary care physician, or medical staff who are not involved in the research. You can also get additional information about the research or the treatment from the research team.

Before deciding on participation in the research, it is very important to know the risks and rights involved. This process is called "informed consent."

Your participation in the research is voluntary (of your own free will). You can choose not to participate in it and not sign the consent form. You can withdraw from the research at any time without giving a reason. Your decision to refuse or withdraw will not have a negative impact on the medical treatment you are entitled to, and treatment options will remain at your disposal.

If you are interested in participating in the research, you will be asked to sign this form. You will receive a signed copy for safekeeping and follow-up at the medical institution.

[Fields for Name, Family Name, ID Number, and Address]

1) Information about the research [to be filled in]:

Research topic: Use of estradiol only for women in combination with spironolactone / compared to estradiol treatment combined with cyproterone acetate for feminization hormone therapy in transgender women at the Institute of Endocrinology, Metabolism and Hypertension at Tel Aviv Sourasky Medical Center.

1.1) Prof. Karen Tordjman received approval to conduct the clinical research from the institutional Helsinki Committee of the Tel Aviv Sourasky Medical Center, in accordance with the Public Health Regulations (Clinical Trials in Humans) 1980.

1.2) Research objective: To compare the efficacy and safety, over 6 months, of two different hormone therapy regimens for feminization in transgender women. The conventional treatment includes estradiol (estrogen) and cyproterone acetate. The research treatment includes estradiol with spironolactone. Both treatments are given in a dose of 2 mg twice a day, with spironolactone 50 mg twice daily or cyproterone acetate 10 mg once daily.

1.3) Research treatment: The treatment given to you, according to your choice, is estradiol taken sublingually twice daily, 4 times a day for 6 months. The aim of the treatment is to induce feminine changes. The expected changes are breast development and fat redistribution.

1.4) Research method: Estradiol is the main female hormone. It is responsible for the development of female secondary sex characteristics: breast enlargement, skin softening, hair reduction, and more. The research compares two treatments (estrogen), which are standard in the feminization treatment of transgender women. If you choose to participate, you will be given, together, in a dose of 2 mg 4 times a day, 0.5 mg tablets, and you will be asked to take them under the tongue. Before starting treatment and during follow-up visits, blood tests will be performed to monitor hormone levels (as detailed in the research protocol). In addition, your doctor will assess your body composition, and the function of 10 ml of adipose tissue taken in accepted methods, not invasive and painless at all. These tests are not performed as part of the standard treatment, but are additional tests required for research purposes. You will be asked to report any side effects that you experience, and so your medical follow-up will be closer. You will be asked to come for a follow-up visit after about 3 months, and you will need to undergo blood tests again, and measurement of body composition and fat function. At the end of 6 months, you will be asked to undergo blood tests again, body composition measurement, and fat function. A questionnaire/form will be filled out about your feelings, mood changes, and sexual function that will include 11-13 questions, and will end after 6 months. At the end of the research, you can continue with the standard treatment at the clinic.

1.5) Your responsibilities as a participant in the research: In accordance with the research requirements, you should not participate in other studies where use is made of research drugs, in any period of the study. If you feel any side effects (including mild and transient ones), you should consult with the responsible doctor or the research team. You are free to decide to stop your participation in the research at any time before the end of the study, and you can continue to receive the standard treatment at the clinic.

1.6) What are the expected risks and/or discomforts as a result of participating in this research? Among other things, in order to examine the effects of the treatment given, estradiol will be given to transgender women in a way that is not yet proven in research. Due to the known effects of estradiol given in the conventional way, the main risk, which is very rare, is the formation of blood clots. In addition, there may be side effects that this treatment does not normally cause. The treatment does not particularly increase the risk of breast cancer or other cancers that you should continue to monitor.

Nausea, vomiting, and headaches may occur. In addition, there may be changes in your weight and mood, including symptoms that are not known/cannot be predicted in advance.

1.7) What are the benefits expected for you as a participant or for others as a result of the research? By participating in this study, you will be able to learn about the effect of feminization treatment on your body composition and on the function of adipose tissue cells, tests that are not usually performed as part of gender-affirming treatment.

1.8) Are there alternative treatments? As recommended to you, you could choose standard treatment in the research framework or not in the framework. There are several protocols for hormonal treatment for gender affirmation. It is generally accepted that a combination of estradiol with anti-androgens is more effective, but there is a hormonal treatment that suggests that the effect of estradiol alone is sufficient. The research team will explain to you about the risks and benefits of other treatment options for you.

1.9) What are the circumstances under which your participation in the medical research may be terminated or the research may be stopped? In the event that side effects that endanger your health appear, or if it becomes clear that there are other treatment options that are safer at the time of the research period, as detailed in writing to the family doctor.

1.10) Participation in the research is free of charge. You will not receive any financial compensation.

2) Information on Samples and/or Genetic Tests

Use of samples and/or genetic tests will be for this research only.

This research will not include any genetic studies.

2.1) Samples that will be taken during the research: Blood samples that will be taken during the research, including blood samples that will be taken during the research as detailed. These tests do not involve any risk and are performed only to monitor hormone levels and for blood count.





2.2) The purpose of taking the samples, and the tests that will be used in the research:

Blood samples will be taken to perform tests that will help determine the effect of treatment on the body. These are routine tests performed after initiation of hormonal treatment for gender affirmation. These tests are intended to show the effectiveness of the treatment (hormone levels) and safety (liver function, kidney function, etc.).

2.3) To whom will the samples be transferred, location, and manner of storage: As stated, these samples will not be transferred at all to the laboratory as part of the usual patient care.

2.4) Duration of sample storage, what will be done with the samples when the research ends or if you stop participating: As mentioned, the samples will not be stored beyond the time required for routine testing (to determine hormone levels and treatment safety).

3) General Information

3.1) For any problem related to the medical research, you can contact the researcher at any time of the day by phone: 052-7360181. In any case of a medical problem, event, or other health incident during the research period, you should report immediately to receive appropriate medical treatment and additional details about rights in this context. In case of emergency requiring immediate medical attention, go to the nearest emergency room and report that you are participating in medical research.

3.2) The Ethics Committee (Helsinki Committee) has approved participation in the research (including performing genetic testing). However, the committee's approval does not constitute an instruction to participate in the research.

The medical findings (including genetic findings) may be published in medical journals without revealing your identity. Positive results regarding diseases that are reportable by law will be reported to the Ministry of Health (such as: tuberculosis, syphilis, hepatitis, HIV, etc.).



3.3) Any new information that could influence your decision to participate or continue in the research will be brought to your attention promptly.

3.4) You are entitled and will be asked to answer questions. You may choose not to answer all the questions or part of them.

3.5) The research team pays the medical institution for the expenses involved in conducting the research. This research is not funded by any external body, and it is not financially supported by any commercial company.

3.6) The research team does not receive payment for conducting the research throughout the research period, not even retroactively.

3.7) The research team and the medical institution have insurance coverage in case of injury resulting from the research.

You will be able to continue receiving treatment even after the end of the research, and during the research, it will be possible to be monitored by the treating clinic team.

3.10) The results of the research may have commercial value and may be used as part of a patent, drug development, medical devices, etc. Research participants have no rights regarding patents, drugs, or devices that will be developed as a result of the research in which they participated.

3.11) A description of this medical trial appears on the Ministry of Health's clinical trials website: MyTrials. The site will not include information that could identify you. You can search this site at any time.

4) Maintaining Privacy and Confidentiality of Information



[Informed Consent Form for Participation in Medical Research]

[Estradiol treatment protocol only)

4.1) In the research you are asked to participate in, medical and personal information will be collected as part of the research. This information is kept in the medical record and it is the responsibility of the treating team to maintain medical confidentiality. Your right to receive information from the medical record in accordance with the law and privacy protection remains.

4.2) The medical record will store information such as: results of medical tests, drug doses, biological or synthetic materials, biopsies or procedure details, and the like.

4.3) Your consent to participate in the research also includes consent that medical and personal information collected during the research will be transferred to the research sponsor, who will use it for research purposes. The information transferred to the external entity will not include: your name, ID number, address, telephone numbers, or any other identifying information provided to you by the state authorities.

4.4) In general, coded information is given to the external entity. The connection between the code and your identifying details will be kept separately by the principal investigator in a secure manner. In some cases, the connection between the code and your identifying details will be kept by the researcher.

4.5) The coded research data will be kept for the period specified by law (at least 15 years from the end of the research).

4.6) Additional information may be collected about you during the research such as: test results for biomarkers, clinical data, etc.

4.7) For the purposes of verifying the medical research and data, authorized entities only will be given access to your medical record (for example: representatives of the Ministry of Health, the Helsinki Committee, and this medical institution's audit committee). This access to your medical information will be carried out in accordance with the provisions of the law and while maintaining confidentiality.

4.8) Your identifying details will not appear in any scientific publication or other publication.

5) Withdrawal from the Medical Research

At any stage of the research, you can withdraw from it by notifying the principal investigator or his representative. You are not obligated to explain your decision. The principal researcher may use the samples and data collected up to the point of withdrawal.

From the moment you notify about withdrawal from the research, no additional information will be collected about you. However, if information with medical significance for you is received, it will be brought to your attention and you will be able to receive the information.



6) [Information on Privacy (including any privacy waiver / authorization / agreement):]

6.4) If information about a future pregnancy exists - you will receive an explanation about pregnancy preservation. Hormonal treatment may affect the ability to become pregnant in the future and therefore, before starting treatment, it is recommended to perform fertility preservation for anyone who wishes to do so. This option is presented to you as part of your entry into the research.

7) Consent Statement:

Participant: By my signature, I declare that I have read the contents of this document, it has been explained to me about the research, and I agree to participate in it.

Name (First and Last): _____ Signature: _____ Date: _____

Principal Investigator: By my signature, I declare that I have explained verbally to the participant about the research in accordance with what is written in this form. I am convinced that the participant understood the explanation and had sufficient time to read the content and express their desire to participate in the research.

Name (First and Last): _____ Signature: _____ Date: _____

(Including professional title)

Impartial Witness: I, the undersigned below, was present during the explanation about the medical research, as the content of this document was explained verbally to the participant, and I witnessed that the participant expressed their consent to participate in the research.

Name (First and Last): _____ Signature: _____ Date: _____

* To be used only in cases where the participant is unable to read the informed consent form (illiterate or visually impaired) or is unable to sign (due to physical limitations). The impartial witness must be present during the explanation about the medical research.

[Additional consent that is not mandatory:]



[Informed Consent Form for Participation in Medical Research]

[Estradiol treatment protocol only]

The research team requests to make additional use of the data and/or samples that will be collected in the framework of this research for additional studies. The additional use is not part of the current research plan. Non-consent to this part does not prevent your participation in the research.

There is no obligation to allow the use of information collected in this research for future studies.

8) [Samples and/or genetic tests that are not mandatory in this research]

8.1) Additional samples that will be requested to be collected during the research, the information that will be collected, and how it will be stored: [Optional information, these are the relevant sections from the research protocol]

8.2) Purpose of taking the samples, and the tests that will be used in them:

8.3) To whom will the samples be transferred, location and manner of storage:

8.4) Duration of sample storage, what will be done with the information at the end of the period:

9) [Use of information for future studies]

9.1) The information that will be collected and how it will be stored:

9.2) To whom will the coded information be transferred:

9.3) Duration of information storage:

By your signature, you agree that these data and/or samples will be used for future studies that will be approved as stated. You have the right to cancel this consent at any time, by notifying the principal investigator or his representative, without giving an explanation.

Participant:

Name (First and Last): _____ Signature: _____ Date: _____

Principal Investigator: By my signature, I declare that I have verbally explained to the participant about the implications of transferring the samples and/or information in accordance with what is written in this form. I am convinced that the participant understood the explanation, had sufficient time to read the form, and expressed their consent.

Name (First and Last): _____ Signature: _____ Date: _____

(Including professional title)