ESTEEM

Evaluating the clinical and cost-effectiveneS of TEstosteronE to improve Menopause-related quality of life

Participant Information Sheet

We are inviting you to take part in a research trial run by researchers at Cardiff University and Hywel Dda University Health Board, together with Swansea University.

Please read this information sheet carefully and discuss it with family and friends if you wish. This information will help you understand why the research is being done and what it means for you if you decide to take part. A doctor or nurse will also talk to you about the trial and can answer any questions you may have.

- **Part 1**: explains why this trial is being done and what taking part involves for you.
- **Part 2**: gives you details on what happens if you choose to stop taking part and how your data will be handled if you take part, and more general information about the conduct of the trial.
- **Part 3:** gives you details about the optional components of the trial and long-term use of your health data.

Please take time to decide whether or not you wish to take part.

PART 1

WHAT IS THE PURPOSE OF THE TRIAL?

There are around 13 million people who are estimated to be peri-menopausal or menopausal in the UK. For many women, menopause is a process which can cause anxiety and distress because of a wide range of symptoms. Hormone Replacement therapy (HRT) is currently the most effective and widely used medical treatment for menopausal symptoms but for many women symptoms continue to impact their lives despite its use.

Testosterone has been shown to improve libido in post-menopausal women. However, we do not know whether other symptoms, not well managed by usual HRT, can also be improved by adding testosterone. We also need to identify any possible harms of testosterone to assess whether benefits outweigh any side effects (for example acne, hair growth) and risks (for example hypertension).

We are doing this trial to find out if adding testosterone to standard HRT can help reduce menopausal symptoms such as disturbed sleep and insomnia, cognition; 'brain fog', and difficulty in concentrating, headache, hot flushes and night sweats, lack of motivation and low energy levels.

You will be allocated at random (by computer) to testosterone cream treatment or placebo. A placebo treatment is a sham medical treatment, like a sugar pill or a saline shot, that researchers use to see how well a new medicine works by comparing the results of the real treatment to the effects of the placebo.

You will then be monitored for 12 months and asked to complete some questionnaires about your health and ongoing symptoms.

This will help us to decide whether testosterone should be given to women to improve menopause-related quality of life. We are looking to recruit 416 women remotely from across the UK and also from GP surgeries.

WHY HAVE I BEEN ASKED TO TAKE PART?

You have been invited to participate in this study because you have been receiving hormone replacement therapy for at least six months but still experience symptoms that affect your daily life despite the HRT treatment.

To take part, you must be using standard HRT at licensed doses (no higher than 100 microgram oestrogen patch, 4 pumps of oestrogen gel or equivalent). This includes oestrogen (as tablets, patches, gels, or sprays) and, if needed, a progestogen (as capsules, tablets, pessaries, patches, or a hormone-releasing intra-uterine device (IUD), eg. Mirena coil). Vaginal oestrogen pessaries or cream taken to manage vaginal dryness for example, are not classified as HRT, and taking this alone would not qualify you to participate in the trial. The research team will check your current HRT to make sure it meets the trial requirements.

You will not be able to take part if you have used testosterone, tibolone, or medicines with anti-androgen effects (such as spironolactone, finasteride, minoxidil, or cyproterone) in the past six months.

WHAT HAPPENS IF I TAKE PART?

If you decide to take part in the trial:

- We will explain the trial in more detail and answer any questions you may have.
- If you are happy to continue, we will ask you to sign a consent form to confirm your agreement to take part and will take a blood sample to confirm continued eligibility.
- Once your blood test is back and has been reviewed by doctors within the trial team, you will be informed that you can proceed with the trial.

YOU WILL THEN BEGIN YOUR INVOLVEMENT IN THE FOLLOWING PROCESSES:

Screening call/visit:

If you decide to take part in the trial, we will ask you for some basic information about you, your medical history and about your menopause symptoms. We will take your consent and ask you to arrange a blood sample collection so we can ensure you are eligible to continue the trial.

Entry into the trial:

Once we have confirmed your blood tests are normal, we will check that you are happy to continue in the trial, collect some information about your health, lifestyle

factors and menopause symptoms, and ask you to complete some questionnaires about your health. You will then be randomised (chosen by chance) to receive the active testosterone cream or a placebo (cream with no testosterone). There will be an equal chance of you receiving either one of those treatments. Neither you nor your doctor will know which treatment you are given.

Your allocated medication will be sent directly to your home address. To enable this, we will securely share your name, home address, email address, and phone number — with a company called SIMBEC, which is responsible for distributing the study medication.

You will be asked to install the ESTEEM trial app, either on your phone or your personal computer/laptop.

During the 12 month follow-up period:

ESTEEM trial app: The trial app will be your main place to record information about taking your medication and where you will complete all questionnaires. You will be given instructions on how to use the app.

Taking your medication: You will be asked to take your allocated medication at the same time, every day, for 12 months. You will be given full instructions on how to use your medication, along with information on any expected side effects. You will be asked to confirm that you have taken your medication each day as instructed on the trial app so we can monitor you properly.

Reporting side effects: All medications have some known and expected side effects. We will ask you to report this on the app but not all of these will be followed up. However, if you do experience any other side effects, you may ask to speak to a doctor or nurse within the trial team at any point during your participation.

Main 3, 6, and 12 month follow-ups: At 3 months, 6 months and 12 months after starting your medication, you will be required to repeat the same questionnaires as you did at the beginning and to provide additional blood samples so our clinical team can monitor you properly. You will have an opportunity to speak with one of our doctors/nurses and discuss any questions or concerns you might have.

Medical records: We will also look at your medical records so that we can collect information on healthcare costs such as prescriptions, visits to your GP and any other hospital visits.

Blood samples: As explained above, you will be asked to provide 4 blood samples, a maximum of 20 ml of blood (about 4 teaspoons) at each collection. These bloods will be taken for safety tests because you are participating in the study.

You will be able to choose between having your blood taken at your home or at a local clinic. We will be able to cover reasonable travel expenses. Drawing blood is generally a safe procedure. Potential risks include pain, bruising but these are usually mild and temporary.

Although very rare, your blood sample analysis could result in finding a condition of which you were unaware. If this happens, your GP will be informed so that appropriate medical treatment can be offered to you.

All blood samples will be stored and analyzed at the Nationwide Pathology laboratory. All samples will be labelled with a unique trial code. We will share your name and date of birth with the laboratory. Your blood samples **will not** be used for DNA analysis.

PREGNANCY

Taking testosterone may involve unknown risks to an unborn baby if pregnancy were to occur during the trial. Before you start taking your medication, we will ask you to take a pregnancy test, supplied with your medicine, to make sure you are not pregnant before starting your medication.

You will be asked to use highly effective contraception from the first day of the trial medication and throughout your treatment, and up to 6 months after the last dose of your trial treatment. More information about acceptable contraception methods will be provided to you by the trial team via the trial app.

It may still be possible for women of childbearing age to become pregnant. Due to these risks, you must not participate in the trial if you are pregnant or plan to become pregnant during the research trial period or are breastfeeding a child.

If you are a woman of childbearing potential, by signing the consent form you confirm to the best of your knowledge that you are not pregnant and you do not intend to become pregnant during the trial.

WHAT ARE THE POSSIBLE ADVANTAGES TO TAKING PART IN THIS TRIAL?

By taking part in this trial, regardless of which trial group you are in:

- You will be helping us to understand whether adding testosterone to standard HRT can reduce menopausal symptoms other than sexual function, such as such as disturbed sleep, 'brain fog' and difficulty in concentrating, headache, hot flushes and night sweats, lack of motivation and low energy levels.

WHAT ARE THE POSSIBLE DISADVANTAGES OF TAKING PART IN THIS TRIAL?

Taking part in the trial will mean you are agreeing to take part for 12 months. Participation will take up some of your time to arrange blood sample collection, complete the questionnaires, and record when you have taken your medication.

As with any medicines, using testosterone cream can sometimes cause side effects. If you do experience any side effects, most of these will be minor and temporary. It is important that these are recorded in the trial app. Testosterone has been approved for use in other countries for a long time for treating women with menopausal symptoms.

Less serious side effects include:

- acne and oily skin
- increased body hair particularly on the face
- loss of head hair or thinning
- voice changes

Serious side effects include:

- nausea and vomiting
- yellowing of the skin and/or eyes, also called jaundice
- swelling of the ankles
- weight gain
- persistent headaches
- deepening of the voice
- changes in tissue of the breast
- vaginal bleeding
- ovulation and menstrual periods may stop in premenopausal women
- enlargement of the clitoris
- allergic reaction-related such as shortness of breath; wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin

Detailed information on what to do when you experience any of the above side effects will be provided to you via the trial app.

WHAT SHOULD I KNOW WHILE USING TESTOSTERONE

Testosterone may be transferred to another person during close skin contact with the area where the cream has been applied. You must be particularly careful to avoid potential transfer to children and pregnant women. Detailed information about recommended precautions (such as wearing clothes that cover the cream application area) will be provided to you via the trial app.

DO I HAVE TO TAKE PART?

No. Taking part in this trial is entirely voluntary and you are under no obligation to take part. It is up to you to decide. You may refuse to take part or end your participation (withdraw) at any time without having to give a reason. If you do decide not to participate, or to withdraw from the trial, this will not affect the standard health care that you receive in any way. If you do decide to take part, we will send a letter to your GP to inform them of your participation and what is involved.

CAN I CHOOSE WHICH TREATMENT I RECEIVE?

No. To get the most reliable information about how well the medication works, we must ensure that every participant is given an equal chance (50:50) of receiving either the testosterone or the placebo, and this is chosen at random.

INVOLVEMENT OF YOUR GP

Your GP may have invited you to participate in this trial, or you might have applied to take part on your own. If it's the latter, we will ask for your consent to contact your GP to confirm your eligibility and also will send a letter to your GP to inform them about your involvement in the trial.

If you are thinking about taking part in the trial, please read more information in Part 2.

Part 2: More detailed information on the conduct of the trial

WHAT WILL HAPPEN IF I DO NOT WANT TO CARRY ON TAKING PART IN THE TRIAL?

Taking part is entirely voluntary. If you decide to take part, you can decide to stop at any time without giving a reason, but we will keep information about you that we already have. If you are finding it hard to take part, you can talk to your GP or you can let us know via the trial app.

It is helpful for us to understand the reasons why participants withdraw so we may ask you why you have decided to withdraw and what parts of the trial you want to stop. However, you do not have to give any reasons.

If you decide to withdraw completely:

We will stop collecting any further data and samples from you but will keep and use data already collected in the analysis. This is to ensure the validity of the trial, as allowed by UK and EU laws, to keep the quality of research done in the public interest. Reliable results are crucial as they may affect the treatment patients receive in the future.

Personal data (data that identifies you personally) collected for the purposes of contacting you (including your name and contact details) and for arranging blood sample collection **will not** be included in the analysis. However, you can request that we destroy this within 28 days of you telling us that you no longer want to continue in the trial however we will delete this information as standard at the end of the trial. If we have collected samples from you, we will need to ask you for your consent to keep these.

Please note there might be situations where we cannot fulfil your request immediately, for example if we need to contact you directly about your safety. We will need to keep all safety reports. If you wish to stop taking part in the trial completely, we may need to see you one last time for an assessment and tests. This will be for your own safety. If you are suffering a serious reaction to the trial treatment when you decide to stop, we will need to continue to collect information about you for as long as the reaction lasts.

We will inform you in a timely manner if information becomes available that may be relevant to your willingness to continue taking part in the trial. We foresee no reasons under which your participation in the trial may be terminated.

WHO HOLDS MY INFORMATION?

Your information will be held at Cardiff University. Cardiff University is the sponsor for this trial based in the UK and is the data controller. Cardiff University will be using information from your medical records to undertake this trial and will act as the data processor for this trial. This means they are responsible for looking after your information and for using it properly. Your rights to access change or move your information are limited, as your information needs to be managed in specific ways for the research to be reliable and accurate.

If you withdraw from the trial, we will keep the information about you that we have already obtained. Cardiff University will keep identifiable information about you for 5 years after the trial has finished. To safeguard your rights, the minimum personally identifiable information possible will be used.

How will we use information about you?

We will use information from you and your medical records. This information will include your NHS number, initials, name and contact details (including home address and postcode). We will use this information to do the research and to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will be assigned a code number instead. You will not be able to be identified by this number.

We will collect your device's (mobile phone, tablet or personal computer) IP address (your device's unique address when connected to a network) to ensure network and information security. It is standard practice to record each IP address which connects to a CTR server and this record is stored in the server log files which record all server-level activity. We do not link this address to other data which we are collecting. Nor do we analyse the data unless we have specific reason to look at an individual IP address. We collect it in the spirit of recital 49 of EU GDPR (http://www.privacy-regulation.eu/en/recital-49-GDPR.htm) which allows us to process personal data to ensure network and information security.

We will keep all information about you safe and secure.

Once we have finished the trial, we will keep some of data so we can check the results. Our reports will be written in a way that no-one can work out that you took part in the trial.

Your data will not be shared outside of the UK.

Monitors, auditors, and the regulatory authorities will be granted direct access to your original medical records for verification of the trial procedures and/or data, without violating your confidentiality, to the extent permitted by the applicable laws and regulations. By signing a written informed consent form, you are authorising such access.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?

Yes. All information which is collected about you during the trial will be kept strictly confidential. If you have self-referred to participate in the trial, we will ask for your consent to contact your GP. With your permission we will share your consent form with you GP to request your summary medical record to confirm your eligibility. Your GP will be informed about your participation in the trial and will be kept up to date with your progress to ensure your safety, but they will not see any answers to trial questionnaires.

Your medical records may be examined by the research team but will be kept confidential. Your name (or any other identifiable information) will not be given out or appear on any publications.

The only people at Cardiff University who will have access to information that identifies you will be people who need to contact you to collect more information, take part in an optional interview, send you the results of the research or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

The sponsor will keep information about you securely, for a minimum of 15 years after the trial has finished. The sponsor will keep personal data about you from this trial for 5 years after the trial has finished.

The trial team and regulatory authorities are trained in data protection and are bound by the UK General Data Protection Regulations (GDPR) and the Data Protection Act 2018.

WHAT ARE YOUR CHOICES ABOUT HOW YOUR INFORMATION IS USED?

Whilst you can stop being part of the trial at any time, we will keep information about you that we already have. If you choose to stop taking part in the trial, we would like to continue collecting information about your health from central NHS records/your hospital. If you do not want this to happen, tell us and we will stop.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. We are required to store your data for 15 years.

If you would like more information about the use of personal data for research, ask one of the research team or visit:

- https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/template-wording-for-generic-information-document/
- https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection

If you want to complain about how researchers have handled your information, you should contact the research team. If you are not happy after that, you can contact the <<Insert Data Protection Officer or equivalent>> [*Insert local name, phone, email*].

If you are not happy with their response or believe they are processing your data in a way that is not right or lawful, you can complain to the Information Commissioner's Office (ICO) (www.ico.org.uk or 0303 123 1113).

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

Sometimes, during the course of a clinical trial, new information becomes available about the treatment that is being studied. If this happens, we will tell you about it so you can consider whether you want to continue participating in the trial. You will have the option to decide whether to withdraw or remain in the trial. If you choose to continue, you will be asked to sign a new consent form.

WHAT HAPPENS TO THE RESULTS OF THIS TRIAL?

We hope that the results of this trial will improve the care of patients in the future. At the end of the trial, the results may be published in medical journals and presented

at medical conferences. This will allow us to tell other doctors and healthcare professionals about the results of the trial. Information that identifies you **will not** be presented. We can send you information on where to access the trial publications and a summary of the results can be sent to you if you would like.

IS MY DATA LIKELY TO BE USED FOR FUTURE RESEARCH?

The use of your data for future research is optional. If you wish to take part in the trial, you may do so without giving your consent for your data to be used in any future research.

FUTURE USE OF SAMPLES

With your permission, your blood samples will be passed to a biobank at the end of this trial. You can withdraw your sample from the Biobank at any point without giving a reason, if you do withdraw your consent any sample that has not already been used for research will be destroyed according to local practices.

WHO HAS REVIEWED AND FUNDED THIS RESEARCH?

All research in the NHS is assessed by an independent NHS Research Ethics Committee (REC), who make sure the trial is conducted ethically to protect your interests.

The trial has been reviewed and given a favourable opinion approved by XX REC [Ref: XXXX].

This trial has been funded by the National Institute for Health and Care Research (NIHR) through the Health Technology Assessment (HTA) programme and is being managed by Cardiff University.

WHAT IF THERE IS A PROBLEM?

If you have a concern about any aspect of this trial, you should speak with to the local research team, or the researchers at the Centre for Trials Research, Cardiff University (contact numbers below), who will do their best to answer your questions.

If you remain unhappy and wish to complain formally:

- In England you can do this through the Patient Advice and Liaison Service (PALS) who provide advice and support to patients, their families and their carers; website: http://www.nhs.uk. [Insert contact numbers for sites].
- In Wales, you can do this through the NHS Complaints Procedure via the Patient Concerns Service (Wales) [Concerns Department, Cardiff and Vale University

Health Board Headquarters, University Hospital of Wales, Heath Park, Cardiff CF14 7XB, telephone 02920742202].

- In Scotland this can be done via the Patient Advice and Support Service (PASS) telephone: 0800 917 2127 or through the web contact forum https://pass-scotland.org.uk/contact/.

We have no reason to believe that you will be placed at any greater risk to your health by taking part in this trial. If something does go wrong, and you are harmed during the research, and this is due to someone's negligence then you may have grounds for legal action for compensation. However, there are no compensation arrangements over and above the usual routes available to any patient treated within the NHS and you may have to pay your legal costs. Taking part in the trial will not affect your legal rights.

WHAT DO I NEED TO DO NOW?

If you agree to take part in the trial, you will be asked to sign a consent form to confirm you are happy to take part. The ESTEEM trial team will then advise how to arrange for a blood sample to confirm your continued eligibility. Once your eligibility has been confirmed, your medication to be sent to you.

HOW TO CONTACT US:

If you have any further questions or require more information about taking part in this trial, you can contact (during normal working hours):

Telephone: 02920 687 463 (ESTEEM Trial Manager)

Email: ESTEEM@cardiff.ac.uk

Address: Centre for Trials Research, Cardiff University, 7th Floor, Neuadd Meirionnydd, Heath Park, Cardiff, CF14 4YS

Please note that this is only for queries regarding the trial.
If you have an urgent medical problem, please contact your hospital or your GP in the normal way.

The Co-Chief Investigators for this trial are Dr C Helen Munro, Consultant in Community Sexual and Reproductive Health at Hywel Dda University Health

Board and Professor Mike Robling, Co-Director at the Centre for Trials Research at Cardiff University.

If you would like more information about clinical research, the UK Clinical Research Collaboration (a partnership of organisations in the UK) have published a booklet entitled ‘Understanding Clinical Trials’. For a copy contact UKCRC: Tel: 0207 670 5452 or visit their website www.ukcrc.org

Please let us know if you change your contact details during the trial, so we do not lose touch with you. You can also let us know if you want to change the main way we contact you.

Part 3: Optional components of the ESTEEM trial

LONG-TERM FUTURE RESEARCH STORAGE OF BLOOD SAMPLES

In order to maximise the potential of your sample, information collected through this trial might also be passed to a biobank, such as your NHS number, information about your samples and information from your medical records (both now and in the future).

- We are not able to predict all possible uses of the samples in the future and this may include DNA analysis. You will not be informed, or asked for permission, about any future tests.
- Samples will only ever be used in research that has the aim of helping patients or the general public.
- We will always store, process or destroy your samples in accordance with very strict legal and regulatory requirements.

Samples may be released for further analysis to researchers from other universities or commercial companies. This may include research undertaken outside of the United Kingdom. Your samples will always be anonymous and none of the information released would enable you to be identified. Any other laboratories that may request to use the blood samples for future research will be approved by Cardiff University, the study sponsor. Further ethical approval will be sought from the Ethics committee for any future research on these samples.

HEARTT: HORMONAL EFFECTS AND RISK TRACKING IN TESTOSTERONE THERAPY SUB-STUDY

In addition to the main trial, we will also ask for your informed consent to enable us to take small additional amounts of blood (20 ml, about 4 teaspoons) for an optional research sub-study called HEARTT. These blood samples will be taken alongside the ESTEEM trial blood samples. The decision to do this is completely up to you and it will not in any way affect participation in the trial.

The HEARTT study is looking into how testosterone affects women's heart health. While we know that low levels of estrogen can increase heart-related risks, the impact of testosterone is not fully understood yet. This study will analyze your blood samples to find out if testosterone therapy changes any heart-related markers in the blood. There's also a chance that this research could uncover new markers that are

specific to women using HRT. By exploring these differences, the HEARTT study aims to provide initial information about how testosterone therapy could affect women's heart health and help create safer and more personalized treatments for HRT.

LONGER-TERM FOLLOW-UP USING HEALTH DATA

As mentioned in Part 1 above, after the trial ends, we may like to see how you are doing in the longer term by using routinely collected health data. This is information that your GP and hospital collect about you for health. We will need to use information from you and your medical records for this.

This information will include your:

- NHS number
- Surname
- Postcode
- Date of birth
- Sex at birth

In the longer-term, we will be collecting health information from your GP and hospital records through data linkage services like NHS England (formerly NHS Digital) and Secure Anonymised Information Linkage (SAIL) in Wales (and Information Services Division (ISD) in Scotland and Northern Ireland Statistics and Research Agency (NISRA) in Northern Ireland, if applicable). This data is routinely collected as part of your healthcare.

The reason we may want to look at this information is to assess the wider effects on your well-being and health following the trial. This is an optional part of the trial. With your consent, the research team would provide your personal details to identify you to NHS England or agencies as above, for those professionals to provide relevant information about your ongoing health. NHS England would then collect information on how trial participants have used different health services (e.g., how many hospital visits) and for what reasons.

NHS England will then provide this data to Cardiff University. No identifiable data will be sent to the database. Instead, a study number will be assigned to each individual and this will be used to join pieces of information together. Data viewed by the research team will not be identifiable. In other words, when we look at your health information, all we will see is a database containing numbers – we will not see your name. A Data Manager will use the study number to identify a person and join up

the information. We will not know who you are in the database. The data will be held on a secure server and only the research team will have access to it.

OPTIONAL INTERVIEW TO SHARE YOUR EXPERIENCES

In addition to the main trial, we will be inviting women participating in the trial to take part in an optional interview about their experiences with the trial, the processes involved, how they have been finding their participation and anything they might want to share about their experiences with taking testosterone. The decision to do this is completely up to you and it will not in any way affect participation in the trial.

OPTIONAL TRANSLATIONAL RESEARCH

As part of this study, we would also like to ask for your permission to collect a small extra amount of blood (about 20 ml, which is roughly 4 teaspoons) for an optional research sub-study. These samples will be taken at the same time as your blood samples for the main ESTEEM trial, so no extra visits are needed.

This part of the research is optional. You can choose whether or not to take part in it. Saying no will not affect your participation in the main trial in any way.

The blood samples will be stored in Nationwide Pathology and may be used in future research to help us better understand menopausal symptoms and how treatments like testosterone — might work. Before doing this, we will apply for separate ethical and regulatory approvals to ensure the research is reviewed and properly overseen.

Thank you for reading this information sheet.