ESTEEM: EVALUATING THE CLINICAL AND COST-EFFECTIVENESS OF TESTOSTERONE TO IMPROVE MENOPAUSE-RELATED QUALITY OF LIFE

Protocol version 2.0 1/12/2025

Sponsor:	Research and Innovation Services Cardiff University Research Integrity, Governance & Ethics Team Research and Innovation Services Cardiff University Cardiff Joint Research Office 2nd Floor, Lakeside Building University Hospital of Wales Cardiff CF14 4XW
Sponsor ref:	SPON 2006-24
Funder:	NIHR Health Technology Assessment
Funder ref:	NIHR159538
REC ref:	TBC
IRAS number:	1008601
ISRCTN/ ClinicalTrials.gov ref:	ISRCTN number TBC
Q-Pulse Document Template Number:	TPL/003/001 v5.0

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Trial Sponsor:	**Signature**	**Date**
Helen Falconer Research Governance Officer, Research Integrity, Governance and Ethics		
Director, Co-Chief Investigator:	**Signature**	**Date**
Prof Michael Robling		
Co-Chief Investigator:	**Signature**	**Date**
Dr Helen Munro		

General Information This protocol describes the ESTEEM clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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Trial Co-ordination:

The ESTEEM trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University (CU), a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the ESTEEM Trial Management Group (TMG).

For **all queries,** please contact the ESTEEM team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigator.

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Randomisation
Online randomisation is through the Trial Database: <link>
(See section 9.5 for more details).

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All clinical queries will be directed to the most appropriate clinical person.

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to CTR Safety Team within 24 hours of becoming aware of the event (See section 14 for more details).
Contact details: CTR-safety@cardiff.ac.uk

Table of Contents

Glossary of abbreviations

ABPI	The Association of the British Pharmaceutical Industry
AE	Adverse Event
API	Application Programming Interface
AR	Adverse Reaction
BNF	British National Formulary
BMI	Body Mass Index
BP	Blood Pressure
CACE	Complier Average Causal Effects
CBT	Cognitive Behavioural Therapy
CCRT	Central Clinical Review Team
CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTCAE	Common Toxicity Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
CTR	Centre for Trials Research
CU	Cardiff University
DSUR	Development Safety Update Report
EMQ-R	Everyday Memory Questionnaire- Revised
EU	European Union
FBC	Full Blood Count
GAD-7	Generalised Anxiety Disorder Assessment
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GMP	Good Manufacturing Practice
GP	General Practitioner
HbA1c	Haemoglobin A1c Test
HE	Health Economics
HER	Electronic Health Record
HITS	Hurt, Insult, Threaten, and Scream
HPQ	Health and Work Performance Questionnaire
HRT	Hormonal Replacement Therapy

IB	Investigator Brochure
IC	Informed consent
ID	Identification
ICECAP-A	ICEpop CAPability measure for Adults
ICH	International Conference on Harmonization
ICTRP	International Clinical Trials Registry Platform
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRB	Institutional Review Board
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
LAM	Lactational Amenorrhoea Method
LBT	Liver blood test
LC-MS	Liquid chromatography-tandem mass spectrometry
LT	Life threatening
MA	Marketing autorisation
MENQOL-I	Menopause-Specific Quality of Life – Intervention
MHRA	Medicine and Healthcare products Regulatory Agency
MI	Multiple Imputation Framework
MRC	Medical Research Council
MS	Mass spectrometry
MS QoL	Migraine-Specific Quality of Life Questionnaire
MS-TSQ	Satisfaction with treatment measure: Menopause Symptoms Treatment Satisfaction Questionnaire
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NMB	Net Monetary Benefit
ONS	Office for National Statistics
PCT	Primary Care Trust
PE	Process Evaluation
PHQ-9	Patient health questionnaire

PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PSQI	Pittsburgh Sleep Quality Index
QA	Quality Assurance
QALY	Quality-adjusted Life Years
QC	Quality control
QL (QoL)	Quality of Life
QP	Qualified Person
QRI	Quintet Recruitment Intervention
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RUM	Resource Use Measure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SDM	Shared Decision Making
SHBG	Sex Hormone Binding Globulin
SmPC	Summary Product Characteristics
SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFT	Thyroid Function Test
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
U+E	Urea and Electrolytes
UK	United Kingdom
URL	Uniform Resource Locator
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
N/A			

2 Synopsis

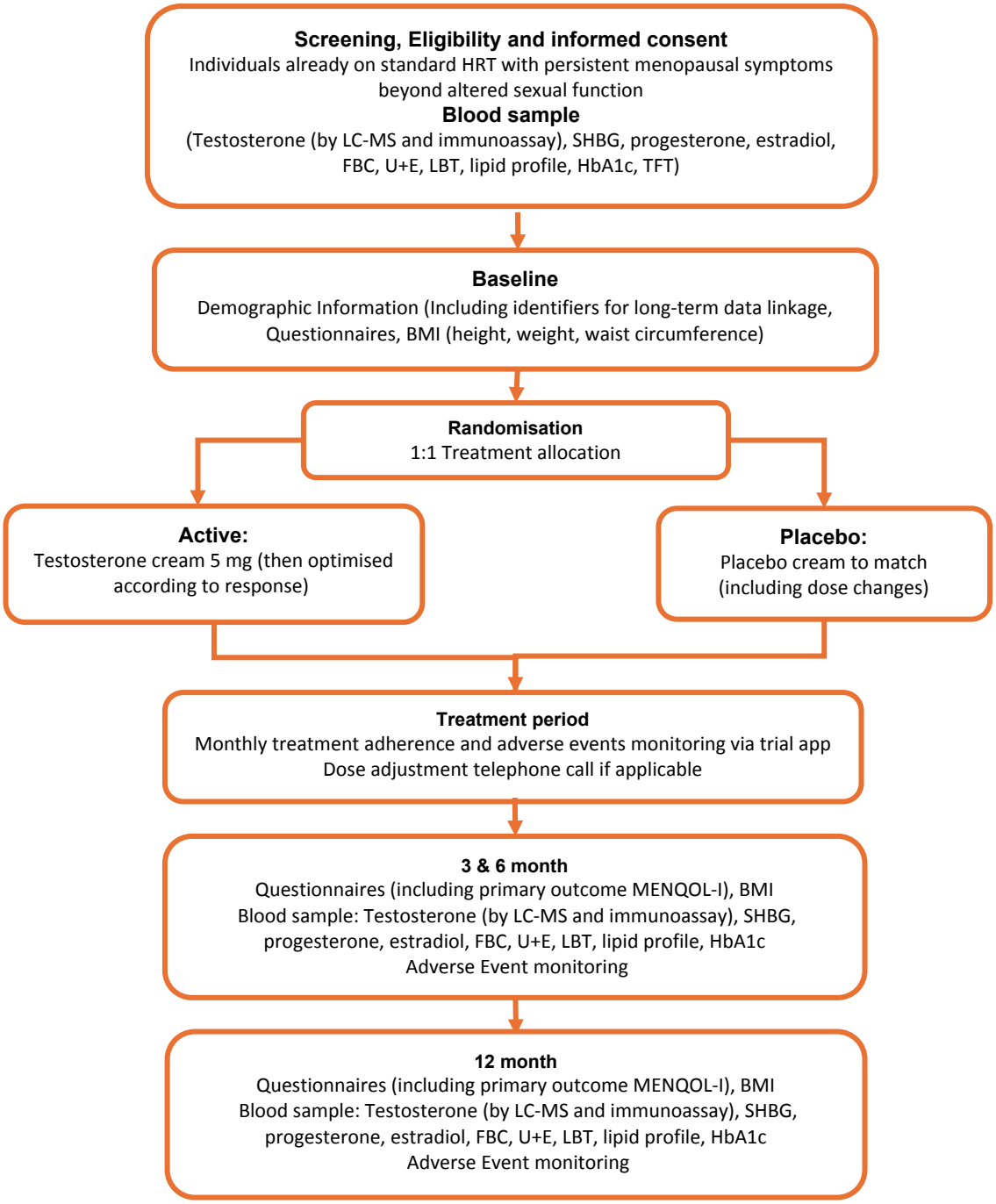
Short title	ESTEEM - Evaluating the clinical and cost-effectivenesS of TEstosteronE to improve Menopause-related quality of life
Acronym	ESTEEM
Internal ref. no.	1558
Clinical phase	Phase III
Funder and ref.	NIHR 159538
Trial design	Double-blind, placebo-controlled, individually randomised, parallel, superiority trial with internal pilot, process evaluation and economic evaluation
Trial participants	women aged >45 years with symptoms attributed to the menopause despite standard HRT
Planned sample size	416
Planned number of sites	15-20
Inclusion criteria	1. Women receiving standard HRT for at least 6 months who remain symptomatic 2. Willing to stay on current standard HRT for duration of trial 3. Able/willing to provide informed consent, including proof of ID 4. At any stage in perimenopause or menopause, including those with Premature Ovarian Insufficiency and medical/surgical menopause already taking standard HRT 5. Able to receive transdermal testosterone 6. Able/willing to adhere to a 12-month follow-up (including regular use of app throughout the trial participation) 7. Able/willing to have blood tests at baseline, 3, 6 and 12 months and as necessary 8. Individuals assigned female sex at birth who are aged > 45 years at the time of consent
Exclusion criteria	1. Women with altered sexual function as their only symptom attributed to the menopause. 2. High baseline testosterone level outside the pre-menopausal physiological range (above 0.591 ng/mL by Liquid Chromatography Mass Spectrometry) Allergy to almonds 3. Pregnant, breastfeeding, or planning a pregnancy during the study period or within six months after the final dose, or participant of childbearing potential who is unwilling or unable to use a highly effective protocol-approved method of contraception. 4. Active malignancy or treatment for malignancy (<6/12); known or suspected carcinoma of the breast; known or suspected androgen-dependent neoplasia 5. Women with nephrotic syndrome 6. History of hypercalcaemia 7. Involvement in another clinical trial for investigational medicinal product (CTIMP) at the time of consent 8. Androgen treatment (testosterone or tibolone) or antiandrogen therapy within the past 6 months (eg. Spironolactone, finasteride, minoxidil, cyproterone)

	9. Women who are also using; oral anticoagulants, corticosteroids or adrenocorticotropic hormone (ACTH), oxyphenbutazone, bupropion, ciclosporin, conjugated equine estrogens and any oral contraception containing an estrogenic steroid hormone 10. Less than 1 month use of complementary and/or prescribable non-hormonal alternatives to HRT, which have been shown in trial to be of benefit, such as Fezolinetant, Oxybutinin, Selective Serotonin Reuptake Inhibitor (SSRI), or SNRI/SSRI, Gabapentin, Pregabalin, Clonidine, St Johns Wort, Isoflavones and Black Cohosh.
Treatment duration	12 months
Follow-up duration	12 months
Planned trial period	51 months Month 1-12: Study set-up, contracts, regulatory approvals, Investigational Medicinal Product manufacture and import Month 10-15: Internal pilot, site set-up and recruitment Month 16-17: Review of internal pilot Month 18 – 29: Main recruitment Month 30-41: Participant Follow-up Month 42- 51: Analysis and report
Primary objective	To establish the effectiveness of testosterone in reducing symptoms attributed to the menopause, beyond altered sexual function, in women already receiving standard HRT as measured by a validated tool of menopause-specific quality of life
Secondary objectives	1. Confirm feasibility of adequate and equitable trial recruitment, retention and data quality in an internal pilot 2. Establish the cost-effectiveness of testosterone based on a primary outcome of Quality Adjusted Life Years 3. Assess safety profile and potential harms of testosterone treatment 4. Gain patient consent and link data to allow long-term monitoring of health outcomes using routinely collected data 5. Explore barriers/facilitators amongst service providers and women to future prescribing and uptake of testosterone 6. Work with lay research partners to design, deliver and report a trial that meets the needs of all women who may experience symptoms attributed to the menopause.
Primary outcome	The primary analysis of the primary outcome of Menopause-Specific Quality of Life-Intervention (MENQOL-I) will assess summary scores over time, incorporating 3-, 6- and 12-month response.
Secondary outcomes	• Questionnaires: ○ Individual domains (vasomotor, psychosocial, physical functioning, sexual) and summary MENQOL-I score ○ Sleep quality (PSQI) ○ Everyday Memory Questionnaire - Revised (EMQ-R) ○ Patient health questionnaire (PHQ-9) ○ Generalised anxiety disorder assessment (GAD7)

	○ Migraine-Specific Quality of Life Questionnaire (MS QoL) ○ Satisfaction with treatment measure: Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ) ○ Health-related quality of life (EQ-5D 5L) ○ Capability (ICECAP-A) ○ Resource use measure (RUM) • Self-reported BMI (height, weight), waist circumference • Adverse events • Adherence to treatment groups
Investigational Medicinal Products	Transdermal testosterone cream 10 mg/mL (AndroFeme®)
Form	Cream in 50 mL airless pump-pack delivering 2.5mg testosterone per pump
Dose	5mg /day (2 pumps) (subject to dose adjustment, see section 11.5)
Route	Applied to clean dry skin (upper outer thigh or buttock)

3 Trial summary & schema

3.1 Trial schema



3.2 Participant recruitment flow diagram

3.3 Trial lay summary

The ESTEEM trial aims to find out if adding testosterone to standard Hormone Replacement Therapy (HRT) can reduce symptoms attributed to the menopause beyond its effect on sexual function (libido). The ESTEEM trial will establish for the first time the impact of testosterone on symptoms related to the menopause, other than sexual function, 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. Further benefits for women may include improved mood and increased focus in the workplace.

The study is a randomised controlled trial (RCT) funded by the National Institute for Health and Care Research (NIHR). Over 400 peri-menopausal and menopausal women will be able to self-refer to the study or enrol through their GP practice.

There are around 13 million people who are estimated to be peri-menopausal or menopausal in the UK. The average age of menopause in the UK is 51 years and is defined when no periods have occurred for at least 12 consecutive months. The time prior to this, where fluctuations in estrogen levels occur and where women can start experiencing symptoms attributed to the menopause and changes in the menstrual cycle, is called the peri-menopausal period. Symptoms can last on average 7 years, effecting 80-90% of women, with 25% describing them as severe and debilitating. HRT is currently the most effective and widely used medical treatment for symptoms associated with the menopause 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 standard 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 and risks (for example weight gain, acne, hair growth).

The ESTEEM trial participants will be patients whose sex assigned at birth was female. We will invite women on HRT but still experiencing symptoms attributed to the menopause to register an interest in taking part. Women will report their current symptoms when they join the study, and then at 3, 6, and 12 months. We will measure whether symptoms improve or get worse using a questionnaire. These symptoms will include vasomotor symptoms (e.g. hot flushes, night sweats), psychosocial symptoms (e.g. mood, cognition), and physical symptoms (e.g. muscle aches, headache, mood, and energy levels). We will measure costs to women due to their symptoms such as time taken off work and costs to health and social services.

We will advertise the trial widely through GP practices, pharmacists and social media. A healthcare professional will contact women registering their interest to see if they are suitable for the trial. A computer programme will put women into one of two groups at random (like tossing a coin). One group will be given testosterone cream. The other group will be given a cream which looks the same as the testosterone one but has no active medication in it. Both groups will use their creams for 12 months and continue their usual HRT treatment.

We will ask women's permission to access their medical records in the future to explore longer-term health outcomes. We will interview some women who decided to take part in the study, some who did not, and

some health professionals to find ways to make it easier for women to join the study, stay involved and gain access to testosterone in the future.

4 Background

The menopause affects 51% of the population and usually occurs between the ages of 45 and 55 years when the ovaries stop producing estrogen. The process can take several years, and as a result of fluctuating hormone levels, multiple symptoms can occur. Women experience symptoms to varying degrees during the perimenopause and menopausal period. Many women manage symptoms in non-pharmacological ways, but where quality of life is significantly impacted, hormone replacement therapy (HRT) can be used where there are no contraindications (Menopause: identification and management).

Standard HRT includes all current licensed preparations of systemic oestrogen, with or without a progestogen (synthetic or micronised), which can be used as treatment for the Menopause, as listed within the British National Formulary (BNF) and which do not exceed the recommended licensed doses. This can include transdermal and oral preparations of oestrogen, together with oral, transdermal or intra-uterine (in the case of the 52mg-LNG IUD) progestogen in women with a uterus or requiring it for management of endometriosis. The oestrogen and progestogen components may be in a fixed combined dose or separate prescriptions, as per current guidance.

Recently, the menopause and its management has gained mainstream media attention led by personal accounts from high profile celebrities encouraging wider discussion amongst the public. As a result, more women are requesting HRT from their GPs including testosterone (Hormone Replacement Therapy – England – April 2015 to June 2024) and there has been an increase in the number of women receiving prescription for HRT (1, 2). At the same time, there is considerable disparity in HRT access by deprivation and barriers for women from ethnic minority communities in seeking and receiving care (3, 4). Under-representation of women with various protected characteristics in underpinning research is also recognised by policy (Inquiry to assess the impacts of menopause and the case for policy reform).

Testosterone use in women is not supported in the UK for any indication other than low sexual desire and even in such circumstances only administered on expert advice (BNF Testosterone monograph). NICE recognise the lack of evidence supporting testosterone use beyond altered sexual function and the profound impact for women of the menopause (NHS Menopause Treatment). Currently, testosterone cream for reduced sex drive remains unlicensed and access to care is often via specialist doctors/clinics (Testosterone Replacement in Menopause). More broadly, hormone treatment patterns in UK primary care indicate variability in menopause care suggesting educational needs and support for patients and clinicians (5). The ESTEEM trial will provide clear evidence for the use of testosterone when added to standard HRT for quality of life and a broad range of symptoms beyond sexual function.

Observational evidence includes women reporting improved self-confidence, self-worth, mental acuity, greater efficiency and communication within their work and less depression when testosterone is used (6). There is also some evidence suggesting that testosterone may improve headache and migraine (7-9). However, Islam and colleagues 2019 systematic review of testosterone for women found insufficient

evidence of benefit for indications beyond altered sexual function (10). Despite searching for trials including effects on sexual function, cardiometabolic variables, cognitive measures and musculoskeletal health, twenty of the 36 trials in the review had sexual function as the primary outcome. The number of women included in studies examining different primary outcomes was often small (e.g. only 3 studies had a primary outcome of cognition and included a total of 165 patients, followed up for 26 weeks or less). Some trials reported positive outcomes for cognition and mood with testosterone therapy but often involved methodological limitations. For example, Davison and colleagues reported improvements in verbal learning and memory for 9 patients receiving testosterone in an open label pilot study at 26 weeks (11). Davis's larger (n=89 postmenopausal women) single centre trial reported moderate improvements at 26 weeks on measures of verbal learning and memory (12). Considering mood and wellbeing, an RCT involving 34 women found transdermal testosterone therapy improved well-being and mood in premenopausal women with low libido (13). Finally, Islam's review highlighted some adverse effects of testosterone (e.g. acne, hair growth, weight gain) but speculated that these may be of less concern to women than the symptoms associated with the menopause. Methodologically, attrition was found to be an important source of bias, particularly in control groups and in trials with follow-up of several months. In practice, women increasingly seek access to testosterone (10).

Beyond Islam's review, we searched the literature using the search terms 'testosterone' and 'menopause*' using Medline (1946-2023) and Embase (1947 – 2023). We also searched the Cochrane Central Register of Controlled Trials and the International Clinical Trials Registry Platform (ICTRP) to look for any registered trials related to testosterone and the menopause. We found no further published papers of randomised controlled trials of testosterone in menopausal or peri-menopausal women. A small proof of concept study (n=24) of women with surgical menopause found that testosterone increased trunk muscle mass (14). We also found a further systematic review, published in December 2022, but for women who had undergone surgical menopause, and all included studies of testosterone were before 2006 and so would have been eligible for Islam's review (15).

Most trials of testosterone, registered with the Cochrane Central Register of Controlled Trials or the ICTRP, related to women with premature ovarian failure, surgical menopause or focussed on low libido. One study proposed to examine the effects of testosterone on pelvic floor muscles (TPELVIC trial). This was registered in 2019 but has been withdrawn. A pilot study of testosterone in postmenopausal women already on HRT was registered in 2009, but the target sample size was only 20 and the outcomes were limited to arterial compliance, insulin resistance and sexual desire (Testosterone Patch's Effects on the Cardiovascular System and Libido).

We found one RCT of testosterone in menopausal women, registered on 17/2/2023: Evaluating Prevention of Muscle Loss After Menopause Using Testosterone: The PAMELA study. This study has recruited 156 menopausal women aged 55-70 who are not taking any other HRT. The primary outcome is change in body-weight corrected power with other key secondary outcomes related to body composition and bone density. Our proposed trial is different, and complementary to this trial, as we will recruit women who have already been using standard HRT for at least six months (to allow optimisation and side-effect resolution including unscheduled bleeding) and our primary outcome measure is broader incorporating the wide range of symptoms experienced by women in the menopause.

Testosterone implants have been used safely in women since 1938 and many of the side effects and safety concerns attributed to testosterone are associated with oral use or secondary to increased aromatase activity which can occur for a variety of reasons. Glaser found no conclusive evidence that testosterone therapy causes voice changes in women, reduced scalp hair growth, adverse effects to the liver or clotting factors, anxiety, irritability, aggression or an increased risk of breast cancer, despite high (supraphysiological) testosterone blood levels (8).

In a systematic review of the efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder, it was concluded that the use of transdermal testosterone is associated with increase in androgenic adverse events such as acne but is not associated with any serious adverse events (16). Islam and colleagues' 2019 systematic review found that administration of testosterone via non-oral routes (transdermal) and using dosages that pertain to pre-menopausal physiological levels, in the short-term did not adversely affect lipid profile or cardiometabolic safety concerns, and had a neutral overall effect on blood pressure (10). Long-term safety via this route remains unknown.

Although no published economic evaluations of testosterone use in the menopause were identified, economic evaluations of HRT have been identified. A systematic review of cost-effectiveness evaluations of HRT reported that no evaluation provided complete information on how data sources for costing were selected, provided unit costs or resource quantities (17). The limited evidence of the cost implications surrounding symptoms is a considerable limitation for economic evaluation of potential treatments.

4.1 Rationale for current trial/Justification of Treatment Options

It is well established that testosterone plays a critical role in the reproductive function and hormonal balance in women physiologically. However, the role of androgens supporting general health and well-being beyond sexual function is not clearly understood and poorly evidenced to date. Due to the recent focus in the media and wider social attention to the menopause and the use of HRT, both women and healthcare professionals are asking for greater 'evidence-based' guidance on the role of testosterone, indications for its use, the risks, benefits and best practice prescribing advice needed to support women holistically. There is a clear need for a large, blinded, multi-site trial of sufficient duration, with challenges to retention addressed in an internal pilot phase. This would provide high-quality evidence to inform policy, practice and patients about the benefits, potential harms and costs of testosterone treatment in women experiencing symptoms attributed to the menopause, despite standard HRT. This research will answer these key questions and provide health care professionals with the evidence required to have informed discussions with their patients, enabling effective clinical practice. Equally, the outcomes of this research will help to shape and inform better services for women, supporting delivery where it is most effective and in the most appropriate way. Finally, this research will provide greater clarity about the role of testosterone in women across their life course. It will help to shape the educational discourse and ensure that understanding, knowledge, attitudes and behaviours towards the subject is built on evidence.

To summarise, the ESTEEM study will address ongoing research needs to assess whether testosterone is an effective and safe treatment for symptoms attributed to the menopause beyond sexual function when added to standard HRT.

5 Trial objectives/endpoints and outcome measures

The primary aim is to investigate, in menopausal women already receiving standard HRT treatment, whether testosterone is effective in reducing symptoms attributed to the menopause beyond altered sexual function. The word 'woman' is used to describe individuals whose sex assigned at birth was female, whether they identify as female, male or non-binary.

5.1 Primary objective

- To establish the effectiveness of testosterone in reducing symptoms attributed to the menopause, beyond altered sexual function, in women already receiving standard HRT as measured by a validated tool of menopause-specific quality of life.

5.2 Secondary objectives

1. Confirm feasibility of adequate and equitable trial recruitment, retention and data quality in an internal pilot
2. Establish the cost-effectiveness of testosterone based on a primary outcome of Quality Adjusted Life Years
3. Assess safety profile and potential harms of testosterone treatment
4. Gain patient consent and link data to allow long-term monitoring of health outcomes using routinely collected data
5. Explore barriers/facilitators amongst service providers and women to future prescribing and uptake of testosterone
6. Work with lay research partners to design, deliver and report a trial that meets the needs of all women who may experience symptoms attributable to the menopause

5.3 Primary outcomes measure(s)

Mean summary score from validated Menopause-Specific Quality of Life-Intervention (MENQOL-I) questionnaire, self-reported over time, at 3-, 6- and 12-months.

5.4 Secondary outcomes measure(s)

Secondary outcomes measured at baseline, 3-, 6- and 12-months:

- Questionnaires:
  - Individual domains (vasomotor, psychosocial, physical functioning, sexual) and summary MENQOL-I score
  - Sleep quality (PSQI)
  - Everyday Memory Questionnaire- Revised (EMQ-R)
  - Patient health questionnaire (PHQ-9)
  - Generalised anxiety disorder assessment (GAD7)
  - Migraine-Specific Quality of Life Questionnaire (MS QoL)
  - Satisfaction with treatment measure: Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ)
  - Health-related quality of life (EQ-5D 5L)
  - Capability (ICECAP-A)
  - Resource use measure (RUM)
- Self-reported BMI (weight, height), waist circumference
- Adverse events
- Adherence to treatment groups

Additional outcomes:

- *Blood samples (Measured at baseline, 3, 6 and 12 months):*
  Outcomes are: Testosterone (by LC-MS and immunoassay), sex hormone binding globulin (SHBG), progesterone, estradiol, full blood count (FBC), kidney function test (urea and electrolytes - U+E), liver blood test (LBT), lipid profile, haemoglobin A1C test (HbA1c). Thyroid Function Test (TFT) measured at baseline only.
- *Resource use and costs:*
  Health and social care resource use, personal costs and lost productivity will be collected using a bespoke participant-reported resource use measure (RUM). We will develop the RUM following good-practice guidance and adapt items from existing measures (e.g. work productivity and absenteeism from WHO Health and Work Performance Questionnaire (HPQ)). The RUM will be co-developed with the research team and initial items tested in a modified Delphi study to assess content validity (18-20). The final version will be used in the internal pilot to assess acceptability and completion rate.
- *Individual patient-level linkage to routine health care data:*
  We will seek consent to access electronic health records from primary and secondary care from NHS England and SAIL Databank (Wales) and link to trial data. Outcomes to include cancer, cardiovascular disease, stroke, cognitive impairment (e.g. dementia), mental health diagnosis, bone fractures/osteoporosis, type 2 diabetes, deep vein thrombosis/pulmonary embolisms, and mortality. Funding will be sought separately to undertake linkage/analysis.

6 Trial design and setting

ESTEEM is a multi-centre, double-blind, placebo-controlled, individually randomised, parallel, superiority trial with internal pilot, process evaluation and economic evaluation. The trial will compare testosterone to a placebo control in women with symptoms attributable to the menopause, despite standard HRT, and assess for superiority over placebo. We will adapt a model of blended recruitment successfully used in the PANORAMIC trial (21) to enrol 416 women aged over 45 years over a 12 month recruitment period. We will utilise both remote patient self-referral methods and recruitment in NHS primary care organisations in England supported by Research Delivery Networks (RDN) and in Wales supported by Health and Care Research Wales (HCRW) infrastructure, selected to promote ethnic diversity/inclusion by deprivation indices (22, 23). The dual recruitment model is detailed below and summarised in Section 3.2 (Participant Recruitment Flow Diagram).

Our recruitment method facilitates an opt-in approach where individuals can volunteer for trial participation. This removes the need for a gatekeeper for access to the trial. The recruitment strategy utilises a multi-dimensional approach, including social media and community groups, to ensure that equitable and person-centred access to the trial is facilitated. All patient-facing documents (including recruitment adverts) will be translated into common languages to facilitate engagement with individuals from ethnic minority backgrounds, who are often under-represented in research. Participants will also be supported to take part within the trial if they have visual or learning difficulties by the option of telephone completion for outcome measures (instead of using the Trial App).

Recruitment via NHS Primary Care Hubs

We will utilise the primary care teams within local RDNs in England and HCRW infrastructure in Wales who will provide local intelligence (e.g. identification of "Deep End" practices) on the suitability of GP sites to act as primary care hubs/sites based on local assessment of capacity and capability. Participant Identification Centres will be established to feed into ESTEEM hubs.

ESTEEM Hubs across England and Wales will include GP sites (either single practices or a federation of practices that are able to operate under a single site agreement and PI to undertake trial procedures as detailed in the protocol). Either face-to-face or by telephone, a clinically qualified professional at the participating GP site will explain the trial to the potentially eligible participant; collect screening and contact information; take informed consent; and confirm eligibility (see section 13 for each trial procedure).

Central Recruitment (self-referral)

Potential participants can present directly to the central trial team via the trial website, in addition to via an ESTEEM Hub/GP site. Screening, contact information can be self-completed by the potential participant on the trial website, or completed during a telephone call with a member of the central trial team. A clinically qualified professional delegated to this task will access potential participant's summary care records to confirm eligibility.

Following informed consent and a blood sample confirming eligibility, all participants will be randomised using online randomisation to receive testosterone or matched placebo (using a 1:1 treatment allocation

ratio) for a period of 12 months. Following randomisation, participants will be provided with a participant pack (see section 11.3 Treatment prescribing). For self-referring participants, a copy of a GP letter will be sent to participant's GP informing them that a patient under their care is participating in the ESTEEM trial and providing essential details about the patient to ensure proper management during the study.

Follow-up data collection will take place at 3, 6 and 12 months using electronic case report forms (eCRFs) and blood sample assessments.

The end of the trial will be defined as the date of final data capture to meet the trial endpoints.

6.1 Central Clinical Review Team

The Central Clinical Review Team (CCRT) will be responsible for screening and consenting participants recruited via the self-referral route and for reviewing all patient data (to include SAEs) collected during the trial following randomization, thus ensuring consistency and standardized oversight for all participants recruited. The team will comprise general practitioners, central trial team research nurses and the CI - Dr Helen Munro. All participating clinicians will be adequately trained on trial protocols and data collection procedures.

6.2 Safeguarding considerations

Data from the ONS for England and Wales, show that a higher proportion of women than men are victims of domestic abuse with four in ten women killed by men in the UK in the 36-55 age group. Evidence suggests intersection between menopause and domestic abuse (Domestic Abuse and Menopause: Stuck in the Middle with You – Literature Review). As part of the recruitment to ESTEEM women will be asked the HITS (Hurt, Insult, Threaten, and Scream) questions, which is a widely used screening tool for intimate partner violence. Outcome of scores will be managed as per the ESTEEM Safeguarding SOP.

6.3 Internal Pilot

An internal pilot will examine recruitment, retention and adherence and assess against stop-go criteria using descriptive statistics (Table 1). Descriptive/qualitative progression criteria regarding the establishment of approaches to promote inclusive recruitment are also provided (Table 2).

Internal pilot outcomes: After 6 months of the study opening for recruitment, an internal pilot will examine recruitment rate, retention (at 3 months) and adherence (all assessed against stop-go criteria).

Table 1: Internal Pilot stop-go statistical criteria

Criterion	**Red**	**Amber**	**Green**
	% Threshold	% Threshold	% Threshold
Trial **Recruitment** rate at 6 months	<25% of overall sample size (<60% of target sample size project month 15)	25-33% of overall sample size (60-99% of target sample size at project month 15)	>33% of target sample size (100% of target sample size at project month 15)
Total **number recruited** after 6 months	<104 participants	104-136 participants	≥137 participants
Retention (loss to follow up at 3 months)	> 20% of participants lost to follow up	5-20% of participants lost to follow up	<5% of participants recruited lost to follow up
Non-adherence after 6 months (using Trial App)	>30% of participants recruited lost due to treatment non-adherence	15-30% of participants recruited lost due to treatment non-adherence	<15% of participants recruited lost due to treatment non-adherence

Table 2: Descriptive/qualitative progression criteria

Criterion	Red	Amber	Green
Establish pathways for both remote recruitment and via primary care hubs addressing inclusivity	Pathways with explicit plan for inclusivity not implementable during pilot.	Pathways with explicit plan for inclusivity implemented during pilot. Selection of primary care hub sites in areas reflecting diversity (supported by evidence of demographic diversity). This may include geographical targeting for remote recruitment reflecting diversity. Narrative evidence from process evaluation indicating changes required to address feasibility and / or effectiveness.	Pathways with explicit plan for inclusivity implemented during pilot. Selection of primary care hub sites in areas reflecting diversity (supported by evidence of demographic diversity). Geographical targeting for remote recruitment reflecting diversity. Narrative evidence from process evaluation indicating operation as expected and is both feasible and effective.

Implement a communication strategy, including social media to address inclusivity	Social media strategy not implementable during pilot.	Social media strategy implemented in pilot covering both remote and in person recruitment pathways. Narrative evidence from process evaluation indicating changes required to address feasibility and / or effectiveness.	Social media strategy implemented in pilot covering both remote and in person recruitment pathways. Narrative evidence from process evaluation indicating operation as expected and is both feasible and effective.
Establish training and guidance (e.g. 'top tips' document) for recruiters addressing inclusivity	Process evaluation informed training guidance (e.g. 'top tips') not achievable by end of pilot phase or unlikely to delivered in main phase.	Process evaluation informed training guidance (e.g. 'top tips') available by end of pilot phase. Variable evidence from process evaluation (e.g. via recruiter workshops and adapted QRI methods) supporting the feasibility and effectiveness of training materials. Further changes to training materials indicated. Plans to rapidly review training in main phase, in addition to ongoing monitoring of training delivery, uptake and amendment.	Process evaluation informed training guidance (e.g. 'top tips') available by end of pilot phase. Evidence from process evaluation (e.g. via recruiter workshops and adapted QRI methods) supporting the feasibility and effectiveness of training materials. Plan in place for ongoing monitoring of training delivery, uptake and amendment.

6.4 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as a TYPE B where the level of risk is somewhat higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 25.1) and will be reviewed at least annually.

7 Site and Investigator selection

This trial will be carried out at participating general practice (GP) sites within England and Wales. All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial. Where electronic health records are being used, site teams must be willing and able to take steps to avoid unintentional unblinding through EHR system. Cardiff University Central Trial team will be set up as a non-NHS site and will be responsible for recruitment of self-referring participants.

Before any NHS Site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the ESTEEM Trial email account (esteem@cardiff.ac.uk):

- ☐ Confirmation of Capacity and Capability (C&C) from R&D department following sharing of local information pack.
- ☐ Favourable opinion of host care organisation/PI from Main Ethics committee
- ☐ MHRA approval
- ☐ A signed Trial Agreement
- ☐ Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- ☐ Completed Site Delegation Log and Roles and Responsibilities document
- ☐ Full contact details for all host care organisation personnel involved, indicating preferred contact
- ☐ A copy of the most recent approved version of the Participant Information Sheet and Consent Form on host care organisation headed paper

- A copy of the most recent Pregnancy Information Sheet and Consent Form on host care organisation headed paper
- Attendance of key study personal at site initiation visit (at minimum: PI, nominated study nurse, pharmacy representative)

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the general practice is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive a trial pack holding all the documents required to recruit into the trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be facilitated by the central trial team.

8 Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All women will have a discussion (in person or by telephone/video) with a clinical professional to confirm eligibility prior to randomisation. All queries about participant eligibility should be directed to the Trial Manager before randomisation/registration.

8.1 Inclusion criteria

1. Women receiving standard HRT for at least 6 months who remain symptomatic
2. Willing to stay on current standard HRT for duration of trial
3. Able/willing to provide informed consent, including proof of ID
4. At any stage in perimenopause or menopause, including those with Premature Ovarian Insufficiency and medical/surgical menopause already taking standard HRT
5. Able to receive transdermal testosterone
6. Able/willing to adhere to a 12-month follow-up (including a regular use of app throughout the trial participation)
7. Able/willing to have blood tests at baseline, 3, 6 and 12 months and as necessary
8. Individuals assigned female sex at birth who are aged > 45 years at the time of consent

8.2 Exclusion criteria

1. Women with altered sexual function as their only symptom attributed to the menopause
2. High baseline testosterone level outside the pre-menopausal physiological range (above 0.591 ng/mL by Liquid Chromatography Mass Spectrometry)
3. Allergy to almonds
4. Pregnant, breastfeeding, or planning a pregnancy during the study period or within six months after the final dose, or participant of childbearing potential who is unwilling or unable to use a highly effective protocol-approved method of contraception.

5. Active malignancy or treatment for malignancy (<6/12); known or suspected carcinoma of the breast; known or suspected androgen-dependent neoplasia
6. Women with nephrotic syndrome
7. History of hypercalcaemia
8. Involvement in another clinical trial for investigational medicinal product (CTIMP) at the time of consent
9. Androgen treatment (testosterone or tibolone) or antiandrogen therapy within the past 6 months (eg. Spironolactone, finasteride, minoxidil, cyproterone)
10. Women who are also using; oral anticoagulants, corticosteroids or adrenocorticotropic hormone (ACTH), oxyphenbutazone, bupropion, ciclosporin, conjugated equine estrogens and any oral contraception containing an estrogenic steroid hormone
11. Less than 1 month use of complementary and/or prescribable non-hormonal alternatives to HRT, which have been shown in trial to be of benefit, such as Fezolinetant, Oxybutinin, Selective Serotonin Reuptake Inhibitor (SSRI), or SNRI/SSRI, Gabapentin, Pregabalin, Clonidine, St Johns Wort, Isoflavones and Black Cohosh.

9 Recruitment, Screening and registration

9.1 Participant identification

ESTEEM trial will be advertised via both physical and virtual points, physical being healthcare and community-based organisations including but not limited to primary care/health centres, pharmacists, community centres, places of worship and other social hubs; virtual being targeted social media advertising and research websites.

Potential participants will be invited to complete an expression of interest form via the trial website. Eligibility screening will be completed by a clinically qualified professional at participating sites in-person or remotely by a clinical member of the central trial team delegated to this task. This will capture potential participants' eligibility to enter the trial and an opportunity to ask any trial related questions prior to giving informed consent.

A blood sample will be taken from all participants to establish continued eligibility to participate in the trial. All eligible participants will then be entered into the trial and randomised. All ineligible participants will be withdrawn from the trial.

Thereafter, baseline, demographic and contact information can be entered directly onto the ESTEEM Trial App. All documentation will be collected using an eCRF (built into the ESTEEM Trial App) in a decentralised trial model which will include electronic consent, baseline and follow-up data collection.

Details of protected characteristics such as ethnicity, age and gender will be captured at screening along with other data required to establish eligibility, to better understand the trial sample diversity and to ensure that our trial population reflects the key characteristics of women who may eventually benefit

from addition of testosterone in practice, following the trial. Where feasible adjustments will be made to the trial recruitment strategy to increase diversity and enable broader generalisability.

9.2 Screening logs

An electronic screening log of all ineligible, and eligible but not consented, potential participants will be maintained at each recruitment site, and centrally for self-referrals, so that bias from differential recruitment can be detected. When at site, logs may contain identifiable information, but this must be redacted prior to being sent to the CTR. The monthly screening log should be sent to the esteem@cardiff.ac.uk (see section 25 for further detail on data monitoring/quality assurance).

9.3 Recruitment rates

A total of 416 participants will be recruited at an expected average rate of 18 participants per month. This rate will be monitored during the internal pilot phase.

9.4 Informed consent

A medically qualified professional or appropriately trained research nurse with delegated responsibility will discuss each section of the PIS with the potential participant to ensure understanding, allow opportunity to ask questions and remind them that they may withdraw consent at any time without reason. Once satisfied that the potential participant understands the trial, the participant's informed consent must be obtained using the electronic trial consent form. The potential participant will be given adequate time to consider their participation in the trial before being asked to sign the consent form. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial.

Please note, only when informed consent has been obtained from the participant and they have been randomised can they be considered a trial participant.

Electronic informed consent will be obtained via a secure electronic platform, in line with current MHRA/HRA guidance for electronic consent in CTIMPs.

The electronic informed consent processes will include:

- A real-time consent discussion with a medically qualified professional or appropriately trained research nurse with delegated responsibility either in person or via secure video call;
- Identity verification of the participant prior to consent using one of the following accepted forms of identification:
    - Passport
    - Driver's License
    - Utility Bill

- Use of a validated electronic signature method, which ensures secure, attributable, time-stamped consent documentation;
- Secure transmission and storage of signed consent forms, with copies provided to the participant and retained in the Investigator Site File (ISF). The consent form will be provided to the participant electronically and will be saved in the central database. Another digital copy will be saved in the investigator site file, and a further digital copy should be kept with participant's electronic medical notes.

If a participant initiates electronic consent but does not complete the process within 30 days, their personal data will be securely deleted in accordance with the trial Data Management Plan. A record of attempted enrolment will be retained for the purposes of the CONSORT diagram.

All CCRT members and relevant participating site staff (delegated to the informed consent responsibility) will receive specific training in the electronic informed consent platform and processes. The risk assessment of the electronic informed consent process, including data protection and audit trail requirements, will be included in the overall ESTEEM trial Risk Assessment document.

The electronic informed consent process will include a discussion of planned linkage to health systems data sources: NHS Digital, Digital Health and Care Wales, GP data for the purposes of longer-term follow-up, and consequently participant consent will be requested to collect their NHS Number.

The right of the participant to refuse to participate in the trial without giving reasons must be respected. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing their further treatment.

9.5 Registration and Randomisation

9.5.1 Registration

Potential participants may express interest either directly through the trial website or via an ESTEEM participating site. Screening, contact information, and informed consent will be completed during a telephone or video call with a medically qualified professional or a trained research nurse. Eligibility will be confirmed by a medically qualified professional, and informed consent will be obtained by either a medically qualified professional or a trained research nurse. NHS Summary Care Records will be accessed to rule out any other potential health concerns that could prevent potential participants from safely participating in the trial.

9.5.2 Randomisation

Participants will be individually randomised on a 1:1 allocation ratio to testosterone or placebo, using a secure, fully validated and compliant web-based randomisation system developed and maintained by the CTR. To reduce the risk of imbalance of key covariates, the method of minimisation with an 80% random element will be used. Treatment will be assigned using stratification for the following factors:

- Recruitment path (NHS Primary Care Hubs or self-referral)
- Mode of oestrogen at baseline (oral or transdermal)
- Progestogen taken at baseline (yes or no)
- Baseline MENQoL-I score

The randomisation program will be developed by the CTR and will be embedded within the trial database with controlled access maintaining blinding. All assessments for enrolment (baseline, demographic, contact details, and blood sample) must be performed before randomisation and administration of trial treatment. The participant may only be randomised once full eligibility has been confirmed by a clinically qualified professional or appropriately trained research nurse with delegated responsibility and electronic informed consent has been obtained.

A list of trial medication pack numbers (Trial Pack IDs) will be generated by an independent CTR statistician, each allocated to either the IMP or matched placebo. This list will be shared with SIMBEC for labelling of the IMP pack. At randomisation, an authorised member of the site research team or by a central team member for remotely recruited patients, will access the web randomisation system. After confirming that the participant qualifies for randomisation, the randomisation system will assign both a study ID and a Trial Pack ID number. The Trial Pack ID links the participant to a unique trial medication pack. SIMBEC will prepare and dispatch the participant's trial medication pack containing IMP or placebo, directly to the participant at home.

If necessary, the code may be unblinded for a participant at the request of the clinician. See Section 16.2 for the procedure for unblinding treatment allocation.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in different aspects of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial.

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal of trial treatment but participant continues all follow up assessments
2. Withdrawal of trial treatment and follow up assessments (participant stops trial treatment and follow up)
3. Withdrawal from collection of translational blood samples (this may include withdrawal of consent for samples already collected and being stored for future research)
4. Withdrawal from the Migraine and Testosterone sub-study
5. Withdrawal from long-term follow-up (using routine data)
6. Withdrawal of Consent to all of the above

The withdrawal of participant consent shall not affect the use of data/samples collected prior to participant withdrawal. The use of the data/samples collected prior to withdrawal of consent is based on informed consent before its withdrawal.

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the Participant Information Sheet but briefly:

If a participant wishes to stop taking part in the trial completely, they will need to have one last clinical review assessment. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, and dependent on participant's cooperation, the trial team will endeavour to continue collecting information about them for as long as the reaction lasts, although this is dependent on participant's cooperation.

Individual qualitative interviews as part of the process evaluation will have a separate informed consent and withdrawal process described in section 17.2.

A participant may withdraw or be withdrawn from trial treatment for the following reasons:

- Intolerance to trial medication
- Participant confirmed as ineligible to participate in the trial following the review of the initial screening blood sample results
- Withdrawal of consent for treatment and follow-up assessments by the participant
- Any alteration in the participants condition which justifies the discontinuation of the treatment in the central clinical review team's or participant's GP's opinion
- Non-adherence

In all instances participants who consent and subsequently withdraw should complete a withdrawal form (via a Withdrawal Form in Trial App) or the withdrawal form should be completed on the participant's behalf by the researcher, based on information provided by the participant. This withdrawal form should be completed via the Trial App or sent to esteem@cardiff.ac.uk. The central trial team will inform participant's GP.

Any queries relating to potential withdrawal of a participant should be forwarded to esteem@cardiff.ac.uk.

In the event a withdrawal form is not completed, it must be assumed that the participant withdraws from all aspects of the trial, and any unprocessed samples retained at the central laboratory must be disposed. However, retained samples can be processed for use in the trial if the participant has signed the optional statement in the consent form that allows the samples to be retained in the event the participant does not complete the withdrawal form.

NB: If a participant is withdrawn for medical reasons by a clinician, the withdrawal form need not be completed. However, confirmation would be needed that the participant agrees to their samples being retained and used as per original consent.

10.2 Lost to follow up

A patient will be considered lost to follow-up if they repeatedly fail to comply with scheduled assessments and are unable to be contacted by the central trial team.

The following actions will be taken if a participant fails to engage with a scheduled trial assessment:

- The central team will attempt to contact the participant and reschedule the missed trial assessment as soon as possible. Participants will be counselled on the importance of maintaining the assigned assessment schedule and data collection and ascertainment of whether or not the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow up, the central team must make every effort to regain contact with the participant. This will include reminders and text messages via the trial App. Where possible, this will require at least 2 telephone calls or local equivalent methods of contact. These contact attempts will be documented in the participant's trial App record.
- If a recruited participant moves to a different country, as confirmed by GP records, without advising the central team/recruiting site, this is an instance where the participant has not explicitly removed their consent, and their data can still be used.

The central team will make every effort to reduce loss to follow-up by:

- Emphasising the importance of obtaining follow-up data to all participants at baseline and during their trial assessments, irrespective of treatment adherence
- Arranging mutually acceptable dates for the baseline visit and trial assessments; where possible, the next trial visit will be scheduled and agreed with the participant at the previous visit.
- Participants will be able to choose their own appointment slots, location and date i.e. for blood draws or trial assessments via the Trial App/Nationwide.

For avoidance of doubt, in respect to all sample collection, if the participant is lost to follow up, then they are not subject to the withdrawal processes, and the original consent stands.

11 Trial Intervention

ESTEEM is a placebo-controlled, double-blind trial. Participants will be randomised to receive either the active Investigational Medicinal Product (IMP) or placebo. The active IMP and the placebo are visually identical airless metered-dose pump pack.

11.1 Treatment(s)

Active IMP: ANDROFEME® 1 (Testosterone) 1% w/v Cream (manufactured by Lawley Pharmaceuticals Pty Ltd., Australia).

The IMP is produced is a white, opaque, oil-in-water cream, containing 1% w/v testosterone (10 mg testosterone per 1 mL). It is packaged in the form a 50 mL airless metered-dose pump pack. Please refer to IMPD, Section 2.1.P.2 1 for full list of excipients and Section 2.1.P.3.2 for drug product batch formula.

Placebo: The placebo cream is visually identical to the IMP but contains no active ingredient (testosterone). Please refer to the IMPD, Section 2.1.P.1 for list of excipients.

Dosage: The suggested dose is 5 mg testosterone (0.5 mL) applied once daily, approximately the same time each day, to either the upper outer thigh or buttock.

AndroFeme is licensed by the UK's MHRA (as of August 2025) for use in postmenopausal women. It remains the case that the product is not yet widely available on the NHS, and the approved UK version is expected to be commercially launched in 2026. Therefore, in the ESTEEM trial, the IMP may only be used by the named investigators, for the participants specified in this protocol, using the pump packs as described in the protocol.

Investigators Brochure AndroFeme® 1 Lawley pharmaceuticals Pty ltd will be used as the Reference Safety Information (RSI) and circulated to sites as required by the central trial team.

11.2 Treatment supply and storage

The IMP used in this trial will be sourced, and a matching placebo manufactured, by Lawley Pharmaceuticals Pty Ltd. who are in receipt of a declaration by a qualified person confirming that standards equivalent to EU Good Manufacturing Practice (GMP) manufacture were employed. The IMP and matched placebo will be imported from Lawley Pharmaceuticals' contracted manufacturer Orion Corporation, Finland to SIMBEC, UK, for packaging, labelling and QP release.

The IMP management will be managed as per established CTR SOPs.

- **Packaging**

Each IMP pack-pack provides a sufficient supply for 100 days of treatment, containing either the IMP or matching placebo for a 3-month period. Participants will receive 4 packs of cream following randomisation.

- **Labelling**

Labelling will comply with Annex 13 of GMP (including provision for labelling of small packaging units). Each sealed tube with a dose applicator and each pack will be labelled with a pack ID and space to add a participant ID.

- **Distribution & Supply**

SIMBEC will prepare and dispatch the IMP directly to the participant at home, in accordance with their SOPs. The IMP will be distributed via specialised courier from SIMBEC to the address provided by the participant. Participants will be provided with 2 packs of IMP or placebo.

- **Storage**

The IMP is stored below 25°C in accordance with the manufacturer's stability data.. Participants will be given clear instructions on storage.

- **Expiry date and resupply management**

The randomisation system will not permit expired IMP to be assigned to participants. Shelf-life extensions will only be implemented following submission of supporting stability data and approval via a substantial amendment by the MHRA.

11.3 Treatment dispensing

The prescription process will be managed via an integrated online prescribing module within the trial database, ensuring secure generation, tracking, and documentation of all IMP prescriptions. Full details of the prescription process will be described in the trial-specific IMP dispensing SOP.

In accordance with current UK medicines legislation, and where delegated by the Chief or Principal Investigator, appropriately qualified nurse prescribers may be responsible for prescribing the IMP (testosterone or placebo) in line with the study protocol.

Once prescribed, the randomisation system will assign both a study ID and a Trial Pack ID number. The Trial Pack ID links the participant to a unique trial medication pack. SIMBEC will prepare and dispatch the assigned trial medication pack, containing either IMP or placebo, directly to the participant at their home address.

11.3.1 Management of Delayed IMP Initiation Due to Safety Concerns

In some cases, participants may be randomised and complete baseline assessments but experience a delay in receiving or initiating trial treatment if safety concerns are flagged at baseline (e.g. elevated PHQ-9 scores indicating suicidal ideation).

If such concerns arise, the participant will be reviewed by a member of the CCRT. This may result in referral to their GP and/or temporary deferral of treatment initiation while appropriate support is provided. Participants in this situation will remain enrolled in the study.

Before IMP can be prescribed, the participant's continued eligibility must be confirmed. This will involve a documented follow-up consultation by the CCRT, including clinical judgement that it is safe to proceed. This may include repeat assessment of the PHQ-9 and/or communication from the participant's GP confirming safety to continue. The outcome of this review and rationale for proceeding will be recorded in the trial database.

Formal follow-up, including outcome assessments, will continue to be scheduled based on the date of the participant's randomisation, unless the participant is withdrawn. Participants unable to proceed with trial treatment after clinical review may be withdrawn on the basis of a continuation or alteration in the participant's condition which, in the opinion of the CCRT and/or the participant's GP, justifies discontinuation of treatment (as per protocol section 10.1).

11.4 Dosing schedule

The recommended starting dose is 5 mg testosterone (2 pumps, 0.5 mL) applied once daily, at approximately the same time each day, to either the upper outer thigh or buttock.

A **maximum daily dose of 10 mg (4 pumps)** may be used where clinically appropriate. Dose escalation may occur in **increments of 2.5 mg (1 pump)** at a time, guided by symptomatic response, blood results and the Shared Decision-Making (SDM) tool.

11.5 Dose modification

This protocol allows for drug dosing to increase or decrease depending on symptomatic response and/or blood results. It is recommended that testosterone should remain within the pre-menopausal physiological reference range and 1.5x, to reduce potential negative side effects. Blinding will be retained by using 'sham' results generated by the CTR for patients in the placebo arm and presented to the clinician at the time of review. All outcomes will be assessed by the CCRT who are blind to allocation.

All participants will commence the trial using the suggested 5mg/day (2 pumps) of testosterone. If no improvement in symptoms, and the testosterone concentration remains within the agreed reference range (premenopausal range and 1.5x), the CCRT will utilise the SDM tool to justify dose escalation. The dose can be increased to a maximum of 10mg/day (4 pumps) of testosterone, this will be done in two increments of 2.5g/0.25ml or 1 pump at a time. Blood tests will be repeated at 4 weeks after any dose adjustment.

A member of the CCRT will review the blood results at 3 and 6 months to ensure testosterone levels are not elevated and anyone with a testosterone level 1.5 times the upper limit of the pre-menopausal physiological range, will be requested to decrease the amount of testosterone cream, from 5mg (2 pumps) to 2.5mg (0.25 mL/1 pump). Blood tests will be repeated in 4 weeks and reviewed to ensure that the testosterone level has reduced to within the acceptable range. Participants randomised to receive placebo will go through the same procedure described above, for a randomly generated 'sham' testosterone level, to ensure that blinding is maintained.

11.6 Management of toxicity and hypersensitivity reactions

The below algorithmic approach (tables 4-7) shows how data will be used to ensure patients remain within an acceptable blood range and how the dose can be optimised. The algorithm accounts for patient-reported adverse effects, patient reported symptom improvement and blood levels. The Shared Decision-making (SDM) steps for progressing through a review consultation are defined, as is texted script for use in discussion with patients (to reduce risk of un-blinding, provide transparency and ensure patient preferences inform choice).

1. All participants will be asked via the trial App about both perceived benefit (improvement) and adverse effects at 3-, 6-months. This will be standardised regardless of blood levels data (real or sham).

2. All participants will be asked via the trial App at 3- and 6-months whether based on self-reported response to the drug and any perceived unwanted side effects or benefits, their preference would be to maintain or make changes to their dose (i.e. solely based on self-assessed harm, benefit).

3. Once 3- or 6-month blood results have been received, participants will receive one of the following messages via the trial App. An option to receive a telephone call will be offered to all participants.:

Where participant has chosen no change to IMP dose, with no self-reported unwanted side effects and symptoms have improved or somewhat improved:	
blood results in acceptable range	"Your blood results are within the pre-menopausal and trial range no change in current dosage is required"
blood results higher than acceptable range	“Your blood results are higher than the pre-menopausal range, and higher than the trial range, we need to reduce the dose by one pump and recheck your bloods in one month”
Where participant has asked for an increase in IMP dose, no reported side effects but no improvement in symptoms.	
blood results in acceptable range	"Your blood results are within the pre-menopausal range, as you are still having symptoms we suggest increasing your dose by one pump each day, we will review this again in three months' time"
blood results higher than physiological range, but within accepted trial range	'"Your blood results are higher than the pre-menopausal range, but within the trial range, we would not want you to increase any further at this time. Please continue with your current dose, and we will review again in three months' time”
blood result higher than acceptable trial range	“Your blood results are higher than the pre-menopausalrange, and higher than the trial range, we need you to reduce the dose by one pump and we will recheck your bloods in one month”.
Where participant has asked for a reduction in IMP dose and has reported mild to severe self-reported side effects.	
blood results in acceptable range	"Your blood result is within the acceptable range, but if you are having unwanted side-effects, you can reduce your dose by one pump each day. We will follow up in one month to review unwanted side effects"
blood results are higher than physiological range, and within the trial range	'Your blood results are higher than the pre-menopausal range, but within the trial range. If you are having unwanted side effects you could reduce your current dose by one pump each day. We will review again in one months' time to review unwanted side effects"
blood results higher than acceptable trial range (>2.7nmol/l)	"Your results are higher than the pre-menopausalrange, and higher than the trial range, we need to reduce the dose by one pump and recheck your bloods in one month”.

4. Next steps will be clarified:

Either follow up in one month with repeat blood tests and SDM algorithm options as above, where dose has been reduced due to high blood levels, or at one month with SDM questions if unwanted side effects only.

Or review at scheduled appointment (3-month time) as per protocol.

Shared Decision-making algorithm

Table 3. No self-reported unwanted side-effects

Testosterone attributable symptoms	Testosterone Levels			
No Side effects	Above 0.887 ng/mL	0.592-0.887 ng/mL	0.095-0.591 ng/mL	Below 0.095 ng/mL
Symptoms improved	Reduce dose as per protocol and repeat bloods in 4 weeks' time with follow up	Keep dose as is follow up as per schedule	Keep dose as is follow up as per schedule	Use SDM to discuss whether to increase dose, review at scheduled three-month interval.
Symptoms somewhat improved	Reduce dose as per protocol and repeat bloods in 4 weeks' time with follow up	Keep dose as is follow up as per schedule	Use SDM to discuss whether to increase dose, review at scheduled three-month interval	Use SDM to discuss whether to increase dose, review at scheduled three-month interval.
No improvement in symptoms	Reduce dose as per protocol and repeat bloods in 4 weeks' time with follow up	Keep dose as is follow up as per schedule	Use SDM to discuss whether to increase dose, review at scheduled three-month interval.	Use SDM to discuss whether to increase dose as per protocol, review at scheduled 3-month interval

Table 4. Mild self-reported unwanted side effects

Testosterone attributable symptoms	Testosterone Levels			
Mild Side Effects	Above 0.887 ng/mL	0.592-0.887 ng/mL	0.095-0.591 ng/mL	Below 0.095ng/mL

Symptoms improved	Reduce dose as per protocol and repeat bloods in 4 weeks' time with follow up	Use SDM to discuss whether to maintain or reduce dose	Use SDM to discuss whether to maintain or reduce dose	Use SDM to discuss whether to maintain or increase dose
Symptoms somewhat improved	Reduce dose as per protocol and repeat bloods in 4 weeks' time with follow up	Use SDM to discuss whether to maintain or reduce dose	Use SDM to discuss whether to maintain or increase dose	Use SDM to discuss whether to maintain or increase dose
No improvement in symptoms	Reduce dose as per protocol and repeat bloods in 4 weeks' time with follow up	Use SDM to discuss whether to maintain or reduce dose	Use SDM to discuss whether to maintain or increase dose	Use SDM to discuss whether to maintain or increase dose

Table 5. Significant self-reported unwanted side-effects

Testosterone attributable symptoms	Testosterone Levels			
Significant Side Effects	Above 0.887 ng/mL	0.592-0.887 ng/mL	0.095-0.591 ng/mL	Below 0.095 ng/mL
Symptoms improved	Reduce dose as per protocol and repeat bloods in 4 weeks' time with follow up	Use SDM to discuss whether to maintain or reduce dose	Use SDM to discuss whether to maintain or reduce dose	Use SDM to discuss whether to maintain or reduce dose
Symptoms somewhat improved	Reduce dose as per protocol and repeat bloods in 4 weeks' time with follow up	Use SDM to discuss whether to maintain or reduce dose	Use SDM to discuss whether to maintain or reduce dose	Use SDM to discuss whether to maintain or reduce dose

No improvement in symptoms	Reduce dose as per protocol and repeat bloods in 4 weeks' time with follow up	Use SDM to discuss whether to maintain or reduce dose	Use SDM to discuss whether to maintain or reduce dose	Use SDM to discuss whether to maintain or reduce dose

Table 6. Supporting explanation of colour coding

Reduce dose as per protocol and repeat bloods in 4 weeks' time with follow up	(Any red). Serum blood result is higher than agreed trial range, ie. greater than 1.5x pre-menopausal physiological levels. Dose needs to be reduced irrespective of testosterone attributed response or participant perceived benefit. Any unwanted side-effects will be documented as per protocol within the trial App. Following dose reduction, blood test should be repeated after 4 weeks and a consultation offered to discuss with participant. If blood testosterone remains elevated (>2.7nmol/l) on repeat testing at 4 weeks, and despite reduction in IMP/Placebo as per protocol, drug to be stopped, and blood test repeated after 4 weeks. The participant will continue to stay in the trial. Should testosterone serum levels drop to acceptable range, they will be invited to restart IMP and continue to be monitored as per protocol. Should testosterone serum level remain elevated participant to be referred to independent medical reviewer. Options once case reviewed by the IMR 1) Participant remains in the trial and will continue to collect outcome data. 2) Participant may be withdrawn from the trial.
Use SDM to discuss whether to increase dose, review at scheduled three-month interval.	(Any Purple). If participant decides to increase dose, review as per schedule, no need for sooner blood tests. Dose can be increased more than once if needed and fits within protocol.
Use SDM to discuss whether to maintain or reduce dose, clinical review only in 4 weeks to ensure side effects have improved	(Any Blue). Blood testosterone result is within acceptable trial range; however, the participant has unwanted side effects. Key follow-up is clinical only to ensure side-effect profile has improved after 4 weeks, whether dose maintained or reduced. This can be via the trial App. If unwanted side effects have not improved after 4-weeks, consider reducing dose and follow-up after 4 weeks. Follow up can either be a telephone call or through completion of questionnaire on the App (patient choice).

Table 7. Colour Range to support Shared Decision-Making Consultation.

Most likely to support reducing dose.		Least likely to support reducing dose.
most likely to support increase dose		least likely to support increase dose.

Adverse testosterone attributable symptoms, as determined by the participant and reported through the App and will be discussed as part of the SDM tool;

"Considering possible unwanted side-effects which could be related to the trial drug, would you say you have no unwanted side effects, mild, or significant"

Mild: acne and oily skin, increased body hair particularly on the face, loss of head hair (male pattern baldness) or thinning, headache, weight gain, abdominal bloating, constipation.

Significant: nausea and vomiting, yellowing of the skin and/or eyes, also called jaundice, swelling of the ankles, persistent headaches, deepening of the voice, changes in tissue of the breast, vaginal bleeding, (NB. ovulation, and menstrual periods may stop in pre-menopausal women not using contraception), enlargement of the clitoris.

Assessing symptomatic improvement, as determined by the participant and reported through the App and discussed as part of the SDM tool;

"Considering what is important to you now, would you say that your symptoms have improved, somewhat improved, or there has been no improvement?"

11.7 Management of overdose

No cases of overdose with ANDROFEME 1 have been reported in clinical trials.

Treatment of overdose would consist of discontinuation of ANDROFEME 1 together with appropriate symptomatic and supportive care. Wash the skin with soap and water.

In the event a dosing error is identified by a participant or any member of the site or central team, this should be reported to the CTR as per SOPs. Sites and the CCRT team will receive training on management of dosing errors.

11.8 Prohibited medications and interaction with other drugs

Contraindications:

- During pregnancy and breastfeeding
- Hypersensitivity to the active substance(s) or to any of the excipients listed in the product
- Known or suspected carcinoma of the breast or androgen – dependent neoplasia
- Use of contraception containing ethinyl or estradiol

11.9 Permitted concomitant medications

Use of complimentary and prescribable non-hormonal alternatives to HRT, which have been shown in trial to be of benefit, such as Fezolinetant, Oxybutinin, Selective Serotonin Reuptake Inhibitor (SSRI), or SNRI/SSRI, Gabapentin, Pregabalin, Clonidine, St Johns Wort, Isoflavones and Black Cohosh containing products is permitted. However, participants should be established on these prior to the trial (use for four weeks or greater) and aim to remain on the same dose throughout the trial. Participants will be asked to report if they are using any of the above for management of symptoms attributable to the menopause, duration, and for which symptoms, and to report any changes in dose of these medications through the research app.

All oral estrogens (oral contraceptives and oral HRT) will result in an increase in SHBG which will bind testosterone and reduce bioavailability. Participants will be stratified depending on whether they are using oral or transdermal estrogen as part of their standard HRT to account for this (see section 9.5.2) Changes in insulin sensitivity, glucose tolerance, glycaemic control, blood glucose and glycosylated haemoglobin have been reported with androgens. In diabetic patients, medication requirements may change, and this possibility will be communicated to the participant and their primary care practitioner.

11.9.1 Trial restrictions

It has been reported that high dose transdermal testosterone preparations used in men can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels and, with repeated contact, possibly adverse effects. While the recommended dose of testosterone in AndroFeme 1 is low by comparison to male doses, close skin contact with the area of application by a partner or child should be avoided.

Participants will be made aware of the consequences of making sustained long-term close physical contact with young children.

Long-term continual exposure may result in passive absorption and may have adverse effects, including virilisation, in young children.

The risk of transfer is substantially reduced by wearing clothes covering the application area. The majority of residual testosterone is removed from the skin surface by washing with soap and water prior to contact.

As a result, the following precautions will be recommended to participants:

• Wash hands thoroughly with soap and water after applying the cream.

• Cover the application area with clothing once the cream has dried.

• Wash before any situation in which skin-to-skin contact is foreseen.

Participants will be advised to be particularly careful to avoid potential transfer to pregnant women.

11.10 Accountability procedures

Accountability procedures will be as per the trial IMP Management plan, which will be signed off prior to commencement of the trial.

11.11 Compliance

Adherence will be closely monitored during the treatment period, utilising a patient-reported question collected via the Trial App. The Trial App will provide reminders to administer the IMP as well as a question as to whether the participant is well or not for purposes of adverse event monitoring (see section 14.5.1). Participants will be asked to complete a weekly dosing summary to monitor adherence to the IMP.

The central trial team will provide written and verbal information on use of the Trial App regarding recording of medication doses as part of recruitment. Using the Trial App dashboard, the central study team will be notified of any drop in adherence and will be able to monitor participant-reported treatment adherence as well as any potential adverse reactions identified. The central trial team can discuss any issues with the participants on a timely basis including using a secure chat link via the App. The CTR data manager will have oversight of the dashboard and administer user accounts as appropriate.

The central trial team will utilise the trial App dashboard to monthly assess adherence and discuss with participants when gaps in questionnaire completion are identified via a telephone call.

In addition, the participants will be asked to report disposal of trial treatment packs via the trial app (including any unused pump-packs).

Data return, SAE reporting rates and other measures may be used by the CTR and Sponsor to assess the compliance of participants to the procedures described in this trial protocol. In addition, to determine if the placebo is credible, at the 12 months visit participants will be asked which treatment they thought they had received, the IMP or placebo.

12 Sample Management

Participants will provide informed consent to blood samples taken at baseline, 3, 6 and 12 months which will include; testosterone (via LC-MS and immunoassay), SHBG, progesterone, estradiol, FBC, U+E, LBT, Lipid Profile, HbA1c.

Additionally, there will be a single TFT at baseline, to exclude differential diagnosis.

Additional blood tests to ensure testosterone levels are not elevated may be taken if dosing has been altered as part of the trial (see Section 11.5 Dose modification).

Table 8: Sample timepoints

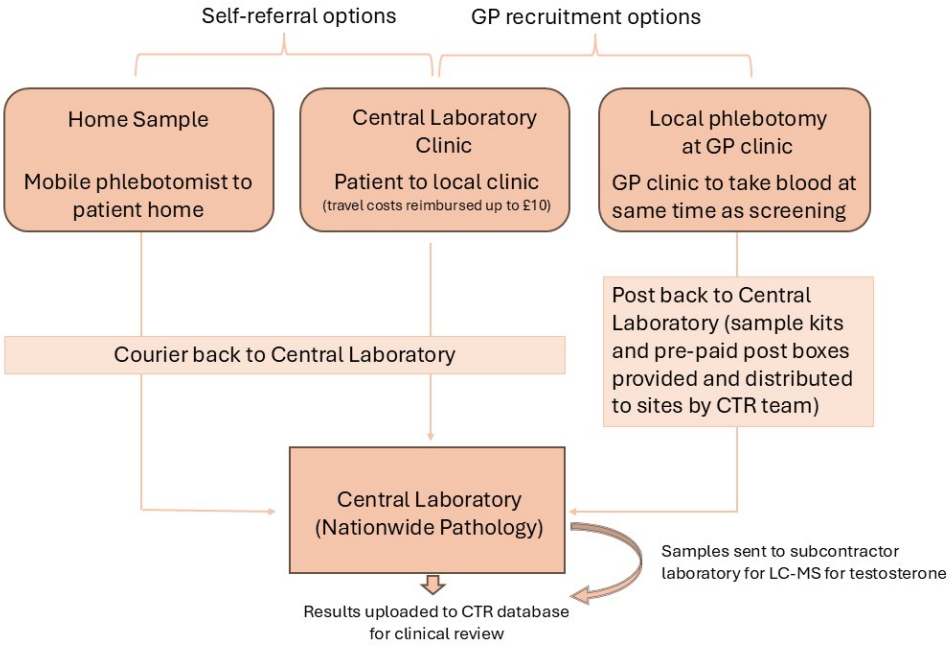
Timepoint	*Eligibility screening*	*3 months*	*6 months*	*12 months*
Blood Sample	*X*	*X*	*X*	*X*

Sample management flow is detailed in Figure 1. Detailed information on the collection, storage, and shipment of blood samples by the Nationwide Pathology central laboratory will be provided in the trial laboratory manual. All trial samples will be transported via an approved courier service.

If a participant withdraws, their samples that have not already been used for research will be destroyed according to local practices.

After the trial has finished, samples will be transferred to a human tissue bank that is licensed by the Human Tissue Authority and has appropriate REC approval will be sought, where required. The specific tissue bank is yet to be confirmed.

Figure 1: Sample management flow



13 Trial procedures

We will utilise a bespoke trial eCRF for collection of standard clinical data at each visit which will be built by the CTR database programmer. The programmer will also lead on integrating with the Trial App via Application Programming Interface (API) – available for use on mobile phones/tablets or desktop computers. The App will be the primary route for collection of patient-reported outcome measures and will facilitate remote follow-up of participants including visit scheduling and adverse event reporting, monitoring and self-reported medication use.

According to current HRT guidelines, blood pressure should be checked regularly, at least once a year, as part of routine monitoring, particularly for women with pre-existing hypertension. For women with uncontrolled high blood pressure, it is recommended to manage their BP before starting HRT. Blood pressure will therefore not be monitored as part of the trial assessments. Each participant's GP will be notified to this effect via a trial specific GP letter to confirm that the patient has been recruited to the trial.

Table 9 (see below) details trial timelines for participants.

Assessments

13.1 Screening and Eligibility

- Screening to assess eligibility of a potential participant for entry into the trial according to inclusion/exclusion criteria
- Confirmation of eligibility (by clinically medically person delegated to this responsibility)
- Invitation and PIS provision
- Informed consent
- NHS Summary Care Records will be accessed to rule out any other potential health concerns that could prevent potential participants from safely participating in the trial
- Blood sample: Testosterone (via LC-MS and immunoassay, SHBG, progesterone, estradiol, FBC, KFT (U+E), LBT, lipid profile, HbA1c. TFT measured at baseline only; will be taken from all participants to establish continued eligibility to participate in the trial. All eligible participants will then be randomised. All ineligible participants will be withdrawn from the trial.
- All women of of child-bearing potential will complete a pregnancy test at screening. Self-referring participants will be sent a CE-marked home pregnancy test kit in advance of their scheduled video screening call. They will be asked to perform the test before the call. During the screening video appointment, the CCRT clinician will verify the participant's identity (using two identifiers), confirm that the test was carried out, and visually check the result shown on the screen to confirm a negative result.
  For participants referred through GP practices, the test may be completed during the practice appointment.
- Following screening, participants will be provided with a supply of home pregnancy tests to support monthly safety checks during treatment.

13.2 Baseline and Randomisation

- Randomisation
- IMP dispensing
- Collect baseline demographic details, lifestyle factors (e.g. smoking, alcohol, exercise), current HRT regime and other current medication used (prescribed, and over the counter), medical history (e.g. diabetes, asthma, cardiovascular disease), participation in therapies (e.g. counselling, cognitive behavioural therapy (CBT), paced breathing) employment status (data collection as per e-CRF)
- Questionnaires (via trial app)

- MENQOL-I
- Sleep quality (PSQI)
- Everyday Memory Questionnaire- Revised (EMQ-R)
- Patient health questionnaire (PHQ-9)
- Generalised anxiety disorder assessment (GAD7)
- Migraine-Specific Quality of Life Questionnaire (MS QoL)
- Satisfaction with treatment measure: Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ)
- Health-related quality of life (EQ-5D 5L)
- Capability (ICECAP-A)
- Resource use measure (RUM)

- Self-reported BMI (height, weight) waist circumference (via trial app)
- Adverse Events monitoring (via trial app)
- Hurt, Insult, Threaten and Scream (HITS) Score (data collection as per CRF)

13.3 Months 1,2,4,5,7,8, 9, 10 and 11

- Treatment adherence monitoring (via trial app)
- Adverse Events monitoring (via trial app)
- Telephone call if requested by a participant or triggered by the CCRT's review of assessment (i.e. blood tests)/trial app reminder/follow up telephone call to non-responders
- Monthly pregnancy checks will be conducted via a confirmation prompt in the ESTEEM app. Participants will choose one of:
  - I've done a test this month – negative'
  - 'I haven't done a test this month but, to the best of my knowledge, I am not pregnant';
  - 'I think I am pregnant'.

  A report of suspected pregnancy will trigger immediate suspension of IMP and a CCRT safety review.

13.4 Months 3, 6 and 12

- Telephone call if requested by a participant or triggered by the CCRT's clinical review of assessment (i.e. blood tests)/trial app reminder/telephone call to non-responders
- Questionnaires (via trial app):
  - MENQOL-I
  - Sleep quality (PSQI)
  - Everyday Memory Questionnaire- Revised (EMQ-R)
  - Patient health questionnaire (PHQ-9)
  - Generalised anxiety disorder assessment (GAD7)
  - Migraine-Specific Quality of Life Questionnaire (MS QoL)
  - Satisfaction with treatment measure: Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ)
  - Health-related quality of life (EQ-5D 5L)
  - Capability (ICECAP-A)

    - Resource use measure (RUM)
- Self-reported BMI (height, weight) waist circumference (via trial app)
- Adherence to treatment groups (via trial app)
- Change in current HRT regime (via trial app)
- Change in medications including over the counter and participation in therapies e.g. Counselling, CBT, paced breathing (via trial app)
- Adverse Events monitoring (via trial app)
- Blood sample: Testosterone (via LC-MS and immunoassay, SHBG, progesterone, estradiol, FBC, KFT (U+E), LBT, lipid profile, HbA1c. (additional blood test will be completed 4 weeks after any dose modification or where clinical concern arises).
- Monthly pregnancy checks will be conducted via a confirmation prompt in the ESTEEM app. Participants will choose one of:
  -I've done a test this month – negative'
  -'I haven't done a test this month but, to the best of my knowledge, I am not pregnant';
  -'I think I am pregnant'.
  A report of suspected pregnancy will trigger immediate suspension of IMP and a CCRT safety review.
- A urine pregnancy test will be required at the end of treatment (12 months assessment).

Table 9. Schedule of enrolment, interventions and assessments

Assessment	Screening and Eligibility	Baseline and Randomization	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Assessment of eligibility	X													
Confirmation of eligibility	X													
Invitation and PIS provision	X													
Informed consent	X													
Randomisation		X												
IMP dispensing		X												
Baseline data (as per e-CRF)		X												
Treatment adherence Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X
Questionnaires		X			X			X						X
Blood Samples (please see Footnote 1)	X				X			X						X
Pregnancy test in those of reproductive age not using contraception effectively (please see Footnote 1)	B	A	A	A	A	A	A	A	A	A	A	A	A	B
Telephone call	On a participant's request or triggered by the CCRT's clinical review of assessment (i.e. blood tests)/trial app reminder/telephone call to non-responders													

Footnote 1: A blood test will be completed 4 weeks after any dose increase or where clinical concern arises.

Footnote 2: Pregnancy test: **B** = mandatory baseline and end of treatment pregnancy test; **A** = monthly pregnancy test *advised but not mandatory*. Monthly pregnancy status is confirmed in the app; participants may respond "I have not done a test this month, but to the best of my knowledge I am not pregnant."

13.5 Laboratory Assessments

Details regarding specific laboratory assessments to be performed in this trial are specified in Table 10. Laboratory assessment for eligibility screening and trial entry should be performed within 7 days prior to the randomisation. Further blood sample assessments will be carried out at 3, 6 and 12 months. Blood results must be reviewed by a delegated member of the CCRT and against the acceptable physiological range (please refer to section 11.5 for dose modification).

Table 10. Laboratory Assessments

Haematology	**Other**
Testosterone (via Liquid chromatography mass spectrometry and immunoassay)	Thyroid Function Test (required at baseline only)
Sex hormone binding globulin	
Progesterone	
Oestradiol	
Full blood count	
Kidney Function Test (Urea + Electrolytes)	
Liver blood test	
Lipid profile	
Heamoglobin HbA1c test	

13.6 Follow-up

End of follow-up is defined as completion of last visit of last participant.

The final analysis of the 5-year follow-up, outside the scope of the ESTEEM trial, will be done by working through the estimand framework where additional testosterone (participants that continue to use (intervention group) or start using (placebo group)) will be viewed as intercurrent events. We will use approaches to analysis that preserve the randomisation allocation for as long as possible (use of Inverse probability weighting or complier average causal effects analysis), enabling an estimate of the longer-term magnitude of the effects of testosterone.

14 Pharmacovigilance

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section. This also includes the named PI at the CCRT team based at Cardiff University for centrally recruited participants.

All SAEs must be reported within 24 hours of knowledge of the event by a member of the CCRT delegated to this task to the CTR PV & Safety Specialist (CTR-Safety@cardiff.ac.uk) unless the SAE is specified as not requiring immediate reporting (see section 14.2). This includes SAEs related to IMPs.

14.1 Definitions

Table 11: Pharmacovigilance Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that use or continued use of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

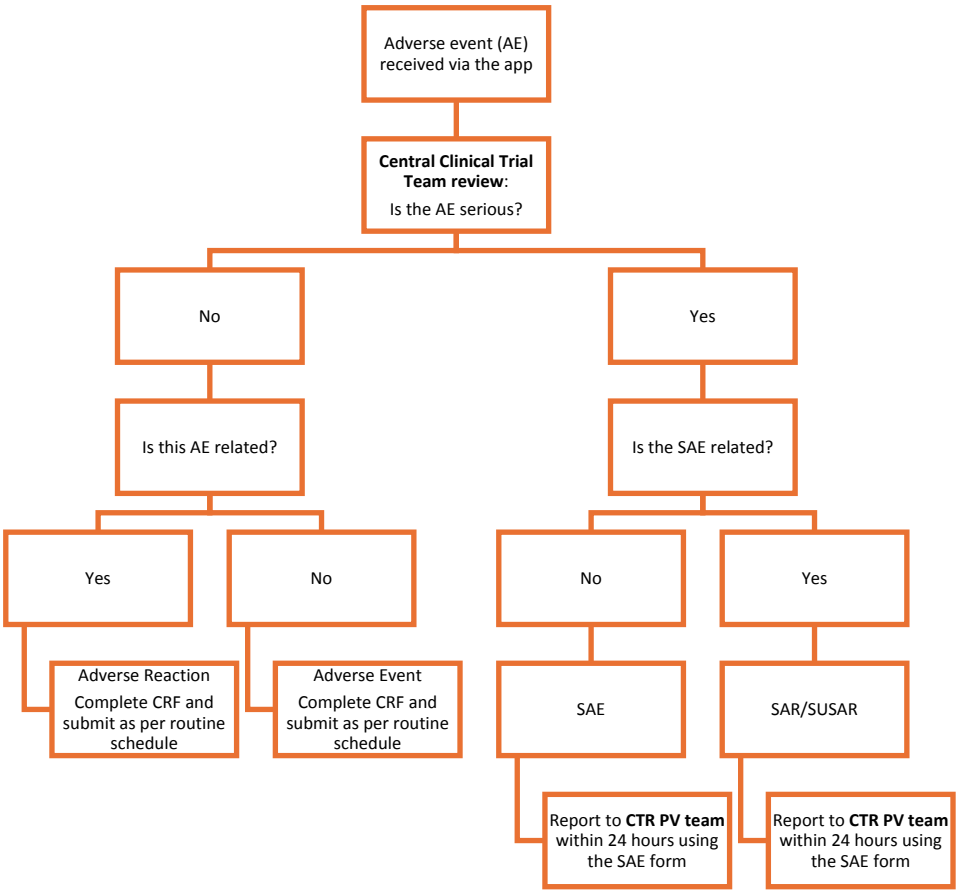
**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

*** **Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

14.2 Trial Specific SAE Reporting requirement

Figure 2 below demonstrates the pharmacovigilance reporting process for the ESTEEM trial. The CIs and PI are responsible for ensuring that all members of the CCRT and all site staff involved in this trial respectively are familiar with the content of this section.

Figure 2: PV reporting process for the ESTEEM trial



For the purposes of this trial the following events are considered foreseeable and will not require reporting as SAEs:

- Mild acne and oily skin (grade 1-3)
- Increased body hair particularly on the face (grade 1-3)
- Loss of head hair (male pattern baldness) or thinning (grade 1-3)
- Headache (grade 1-3)
- Abdominal bloating (grade 1-3)

- Constipation (grade 1-3)
- Weight gain (grade 1-3)
- Electrolyte disturbances (grade 1-3)
- Polycythemia (grade 1-3)

Reporting of pre-existing conditions will meet the definitions for an SAE if the condition worsens by at least one CTCAE grade.

14.3 Causality

Causal relationship will be assessed for IMP:

Table 12: Trial IMP

IMP: ANDROFEME® 1 (Testosterone) 1% w/v Cream **IMP:** Placebo cream visually identical to the IMP but containing no active ingredient (testosterone)

A member of the CCRT delegated to this task and Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship:

Table 13: Causality assessment

Relationship	Description	Reasonable possibility that the SAE may have been caused by the IMP?
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the	Yes

	participant's clinical condition, other concomitant treatments).	
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by a member of the CCRT cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

14.4 Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current Reference Safety Information (RSI) for the IMP. Expectedness decisions must be based purely on whether the event is listed in the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. Fatal and life-threatening (LT) SARs should not be considered expected (unless explicitly stated in the RSI and approved by the MHRA). For example, an event more specific or more severe than that described in the RSI is considered unexpected.

Table 14 below lists the RSIs that should be referenced:

Table 14: RSI Information

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
ANDROFEME® 1 (Testosterone) 1% w/v Cream	Investigators Brochure AndroFeme® 1 Lawley pharmaceuticals Pty ltd	Section 6.2.2

Reference Safety Information (RSI) for ESTEEM will be reviewed regularly according to CTR procedures.

14.5 Reporting procedures

14.5.1 Method of Detecting AEs and SAEs

The trial app will include a symptom report with lay summary information about potential side effects. The symptom report items will be devised by converting the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 into a patient-friendly format with response aligned to the standard severity grading. A free text option will be included to capture any additional symptoms not included in the symptom report. The symptom report will cover a period of 4 weeks to accommodate patients reporting

symptoms that may have already been resolved and will include additional branching question to confirm the current status.

Participants will be asked to complete and review the symptom report as part of the monthly assessments and during any additional consultations related to dose adjustments. Participants will also be able to complete the report ad hoc, anytime outside these timepoints. The trial team will address any ad hoc reports within the CTR core office hours Monday-Friday 9:00 – 17:00.

Each trial participant will be monitored regularly by the CCRT for adverse events occurring throughout the trial. They will enquire about AEs by asking the following non-leading questions during the assessment triggered by the CCRT's review of the monthly symptom report:

At the AE enquiry, trial participants will be asked:

"How are you feeling?"

At subsequent assessment trial participants will be asked:

"Since you were last asked, have you felt unwell or different from usual?"

14.5.2 Risk-Proportionate Safety Monitoring and Participant Support

Participants will be provided with clear written guidance on how to access urgent clinical care through established NHS pathways (e.g., their GP, GP Out-of-Hours services, NHS 111 and emergency services). These services should be used in the event of any acute or urgent health concerns.

The Central Clinical Review Team (CCRT) will provide enhanced daytime safety oversight during core working hours (9:00 am – 5:00 pm Monday–Friday), reviewing app-reported symptoms and laboratory results and initiating safety follow-up where required. This safety oversight complements, but does not replace, the established NHS urgent care pathways.

This risk-proportionate approach is consistent with routine clinical use of testosterone within the NHS and aligns with MHRA guidance on proportionate safety monitoring for a risk category B CTIMPs.

14.5.3 Participating Site Responsibilities

If a participant reports an adverse event as part of their GP appointment in a participating site, the PI or a suitably qualified staff delegated to this task will report the event via the trial app.

14.5.4 Central Clinical Review team (CCRT) responsibilities

The CCRT members will be trained by the CTR PV teams in all aspects of the trial pharmacovigilance requirements.

Central Clinical Review Team email address to direct safety related queries:

ESTEEM-clinical@cardiff.ac.uk

A clinical member of the CCRT delegated to this task should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. A completed SAE form for all events requiring immediate reporting should be submitted via email to the CTR Safety team within 24

hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, date of birth or year of birth and initials. The participant's name (or any other personal identifiers) should not be used on any correspondence.

It is also required that members of the CCRT respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/pharmaceutical companies may request additional information relating to any SAEs/SARs and the CCRT should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

Serious adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 7 days after the participant receives their last dose of the IMP. Serious adverse reactions (such as long-term side effects of trial treatment under investigation) should continue to be reported until the end of follow up as defined in the protocol.

An SAE form should contain at least the minimum information:

- Full participant trial number
- An Adverse Event / Adverse Reaction
- IMP or trial intervention
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log)

If any of these details are missing, the CCRT will be contacted by CTR Safety team and the information must be provided by the team to the CTR within 24 hours.

All other AEs should be reported on the CRF following the CRF procedure described in Section 15.3.

14.5.5 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a same SAE form.

The CTR should continue reporting SAEs until 7 days after the participant receives their last dose of the investigational medicinal product. Serious adverse reactions should continue to be reported until the end of follow up.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA, Main Ethics Committee and Lawley Pharmaceuticals.

14.6 SUSAR reporting

Cardiff University is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (NCAs and relevant ethics committees) and to Lawley Pharmaceuticals as follows:

SUSARs which are fatal or life-threatening must be reported to the MHRA within 7 calendar days of receipt at the CTR.

SUSARs that are not fatal or life-threatening must be reported to the MHRA within 15 days of receipt at the CTR.

If report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report, for all fatal and non-fatal, life-threatening and non-life-threatening.

Any additional, relevant information must be reported within a further 15 days.

14.7 Unblinding for the purposes of SUSAR reporting

To enable processing of a SAR in this blinded trial, expectedness should be assessed initially using the assumption that the IMP has been given to the trial participant.

If it is assessed as unexpected as per the RSI of the IMP the SUSAR will be unblinded by the CTR safety group prior to any onward reporting.

If after unblinding it is evident that the trial participant received the placebo, this event will not require expedited reporting to the NCAs and REC, unless in the opinion of the Principal Investigator or Chief Investigator the event was related to the placebo (for example an allergic reaction to an excipient).

14.8 Safety Reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA, REC, trial sponsor and Lawley Pharmaceuticals in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA CTA approval date.

The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs (to include the named PI of the CCRT based at Cardiff University for centrally recruited participants) annually throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

14.9 Contraception and pregnancy

14.9.1 Contraception

Women of Child-Bearing Potential (WOCBP) entering into this trial must agree to use a highly effective method of contraception preferably with low user dependency for at least six months after the end of the intervention. A highly effective method of contraception is considered as having a failure rate of less than 1% per. Some acceptable contraception methods are listed below;

- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable*
- Intrauterine device (IUD)*
- Intrauterine hormone-releasing system (IUS)*
- Bilateral tubal occlusion*
- Vasectomised partner*
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments.

N.B. condoms (with or without spermicides), periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

**These contraception methods are considered to be low user dependency.*

Given the reproductive toxicity profile described in the Investigators' Brochure, maintaining monthly oversight of pregnancy status is recommended. However, to maximise feasibility and participant acceptability, particularly following PPI feedback, pregnancy testing during months 2–11 is advisable but not mandatory. Monthly confirmation will be captured through the ESTEEM app using a structured prompt, and participants will be provided with a supply of home pregnancy tests.

The CCRT will review monthly pregnancy-status confirmations submitted via the trial app and will follow up any reports suggesting possible pregnancy.

14.9.2 Pregnancy reporting whilst participating in the trial

Pregnancy is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form within the trial App.

Central trial team should report pregnancy occurring within SAE reporting periods stipulated in the trial protocol. Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP Reference Safety Information (RSI) must be submitted by the CTR within expedited SUSAR time frames (7 or 15 days) to the MHRA, relevant REC and the drug manufacturer of the IMP (to comply with any contractual agreement).

14.10 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or a member of the CCRT may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the MHRA and Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

15 Statistical considerations

15.1 Randomisation

Participants will be individually randomised on a 1:1 allocation ratio to testosterone or placebo, using a secure, fully validated and compliant web-based randomisation system developed and maintained by the CTR, using a minimisation process. See section 9.5.2 for detail on process. A randomisation protocol will be written by the trial statistician and signed by the CI.

15.2 Blinding

The trial medication will be masked with allocation known only to the independent statistician who generated the initial randomisation lists and the labelling company (SIMBEC). Trial participants, researchers, and the central trial team, including the trial statistician will be unaware of the allocation. There will be no planned unblinding while the trial is ongoing.

Blinding information (i.e. codes corresponding to IMP/placebo allocations) will be held by:

- SIMBEC (IMP/Placebo distributor)
- The Pharmacovigilance team at the Centre for Trials Research, Cardiff University
- A study-independent statistician at the Centre for Trials Research, Cardiff University

Final unblinding prior to statistical analysis

The statistician responsible for conducting the final statistical analysis will be unblinded following database lock, data cleaning, and derivation of variables required to perform analysis has taken place.

Unblinding for analysis to be reported at IDMC meetings

Statistical analyses for IDMCs which require reporting of data by trial arm or for one arm only (e.g. as proposed for the internal pilot) will be prepared by a study-independent statistician.

Emergency unblinding

Unblinding will only occur in situations in which it is critical for the clinical management of the patient. In the cases of an SAE, the reporting clinician should treat the participant as if they had received the IMP. In the event of a SUSAR, the CTR safety team will be able to break the blind. The CCRT or appropriately delegated individual (listed in delegation log) is responsible for making decisions regarding emergency unblinding.

If emergency unblinding is required, sites and participants should contact the ESTEEM trial team via the main trial telephone number or ESTEEM@cardiff.ac.uk, who will coordinate immediate access to the authorised unblinding team.

The following procedure should be followed in all instances of unblinding:

1. A web-based unblinding system will be made available to the CCRT and the CTR Pharmacovigilance (PV) team. Access will be controlled using a unique username and password and will provide immediate and unrestricted access to treatment allocation for authorised users.
2. Where possible, the need to unmask the participant will be discussed with the CTR Trial Manager and CIs.
3. An authorised member of the CCRT or CTR PV team (where required for urgent safety evaluation or regulatory reporting) will log on to the unblinding system. On entering the required information, including the Pack ID of the participant, the treatment allocation will be revealed. The allocation will be transmitted to the person primarily responsible for their care.
4. A delegated member of CCRT will complete the ESTEEM Unblinding CRF, to be returned to the CTR within 24 hours of the event.

The trial treatment allocation should not be included on the CRF and the allocation should not routinely be revealed to CTR staff.

In the event the CCRT members are not able to access the unblinding system, they can contact the CTR safety team (during office hours), who will arrange for unblinding to be performed by accessing the online system or using the hardcopy master randomisation list.

In the event the online unmasking system is not available, during office hours the site may contact the CTR safety team, who will arrange for unmasking to be performed by a member of staff who is independent from the project team.

Full operational details of the emergency unblinding procedure are provided in the separate ESTEEM Emergency Unblinding SOP.

Unblinding at the 12 months assessment (if requested by the participant)

Participants will have the choice to learn the blinded treatment to which they were randomised at the end of the 12 months assessment data collection point. Unblinding will be important so that participants can make decision regarding their onwards use of testosterone. Unblinding after the outcome data is collected (post 12 months) will not negatively affect the trial study.

15.3 Sample size

Even though the primary analysis will use a repeated measures approach, the trial is powered to detect a clinically meaningful benefit of at least one point difference on the summary MENQOL-I questionnaire score at the six months follow up point. Using a repeated measures approach for analysis will result in a trial with increased power.

Using a summary mean MENQOL-I score of 4.5, a standard deviation (SD) of 1.25 (comparable with other studies) in the placebo group, and a reduction of at least one point in the testosterone group, is equivalent to a standardised effect size of 0.8, considered to represent a large effect size (24). To account for uncertainty in outcome variation in our intended population, a more conservative effect size of 0.4 was considered (equivalent to an SD of 2.5, a reduction of 0.5). To detect a difference of this size, based on 90% power and a 5% significance level, would require 266 women in total (133 women per group). Allowing for an anticipated 5% loss to follow-up and 15% treatment discontinuation (non-adherence), 416 women (208 per group) will be recruited (25).

15.4 Missing, unused & spurious data

Detail will be provided in the Statistical Analysis Plan (SAP).

15.5 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

15.6 Termination of the trial

In the event that the trial is discontinued for any reason, participants will revert to their normal clinical care. The trial as a whole will only be discontinued prior to the collection of all data if there is a clinically important difference in SAE event rate between arms and a decision is made by the Trial Steering Committee, on advice from the Data Monitoring Committee, to stop the trial. We will be monitoring SAEs closely throughout the trial.

The number of SAEs in each arm will be monitored and tabulated during intervention implementation and throughout follow-up. At regular intervals, to be decided at the first TSC and IDMC meetings, tabulated SAE data will be provided to the TSC and IDMC via an encrypted email, along with an 80% CI of the difference in rates. Any differences which indicate a significantly higher odds of an SAE in one arm compared to the other will be highlighted and discussed with the IDMC. Any decision to stop the trial early will be a joint decision based on these discussions.

15.7 Inclusion in analysis

All randomised participants will be included in the main analysis described below.

16 Analysis

16.1 Main analysis

Analysis and reporting of the main trial will accord with CONSORT guidelines. A Statistical Analysis Plan (SAP) will be developed for both internal pilot and full trial and agreed prior to database lock for the analysis.

Internal pilot
Descriptive statistics (frequency, percentage, mean, standard deviation, median, 25th to 75th centiles) will be used to describe recruitment, retention and adherence and assess against stop-go criteria.

Full trial – baseline
Descriptive statistics (frequency, percentage, mean, standard deviation, median, 25th to 75th centiles) will be used to summarise baseline characteristics (demographic and clinical measures) by randomisation arms; no formal statistical comparisons will be performed. Baseline characteristics will also be examined between those randomised and those included in the final analysis, to check for imbalances through loss to follow-up. Similarly, consent for linkage to routine health care data will be reported alongside a summary of the quality/completeness of linkage fields and participants' baseline characteristics.

Primary analysis
The analysis of the primary outcome will follow the Addendum on estimands and sensitivity analysis. We will describe the mean MENQOL-I score by trial group and at each time point (3-, 6- and 12-months). The primary analysis of the primary outcome will examine MENQOL-I scores over time incorporating 3-, 6- and 12-month response, analysed using a repeated measures linear regression model (with an interaction term for time and trial group), to investigate any divergent/convergent pattern in scores. We will adjust for baseline and randomisation strata entered as fixed effects. All analyses will be conducted on an intention-to-treat (ITT) basis, within a multiple imputation framework (MI) assuming data are missing at random. Sensitivity analyses for the primary outcome will be carried out to examine the efficacy of adherence to medication on primary outcomes. Medication adherence will be described using the ABC taxonomy of Initiation, Implementation and Persistence (26). Analyses of the primary outcome will assess influence of adherence on treatment effect estimates in a way that preserves randomisation using complier average causal effects (CACE) modelling using instrumental variables regression (27, 28). Similarly, changes to testosterone dosage will be adjusted for in the analysis.

Secondary outcomes measures will be analysed similarly to the primary outcome using repeated measures linear or logistic regression models (dependent on outcome) with time point nested within participant, and an interaction term for time and trial group. Adverse events (AEs) will be described by arm and sub-classified as individuals who have AEs within a short time period of starting medication (e.g., 3 months) and those experiencing longer terms effects (6-12 months) and analysed using logistic

regression models. Changes in current HRT regime over time will be described in both arms as well as any adjustments to testosterone dose.

The psychometric properties of the DanishMeno score will be assessed via: 1) internal consistency reliability with Cronbach's α, and 2) test-retest reliability at multiple follow-up points with intra-class correlation coefficients (ICCs) and r. Rasch analysis will be performed to determine construct validity.

The main trial results will incorporate responses over the 12-month period from randomisation to testosterone (IMP) or placebo. Longer term use and dosage of testosterone (after 12 months follow-up) will be monitored via annual participant assessments. This will be achieved by extending the established study data collection system specifically for capturing medication use. We will describe IMP uptake in both arms after the short-term study is completed as the extent of cross-over will inform the direction of the final analysis.

16.1.1 Sub-group & interim analysis

Descriptive statistics will be used to describe recruitment, retention and adherence and assess against stop-go criteria.

Subgroup analyses are pre-defined as follows: HRT type (mode +/- progesterone), premature ovarian insufficiency status and baseline MENQOL-I score, but will be fully defined in advance of any analysis being started with input from the trial team and summaries of current evidence from the literature. Appropriate interaction terms will be entered into the primary regression analysis to conduct pre-specified exploratory subgroup analyses.

16.2 Process Evaluation (Qualitative analysis)

We will undertake a process evaluation to focus on optimising methods of inclusive recruitment and retention, with an emphasis on the internal pilot phase. Additionally, we will address broader considerations and preferences for the implementation of evidence-based testosterone treatment in healthcare.

There is significant intersectionality, encompassing gender, race and socioeconomic disadvantage, which impacts access to HRT. Challenges exist in accessing general healthcare for women from ethnic minority communities (Cancer research UK 2019). In the UK, Black, Asian and ethnic minority groups are over-represented in the 20% most deprived areas (Ali 2021) and it is also in these areas with the highest index of multiple deprivation that the rate of HRT prescription is at its lowest (The Commission on Race and Ethnic Disparities Report). In the Health of the Nation report 2024, analysing data from 1.85 million female patients aged 45-55 , nearly twice as many women from the least deprived areas of England (decile 5-10) are on HRT compared to those from the most deprived areas (decile 1-2) (23% vs 12 %) and that there are approximately five times fewer black women (5.2%), and four times fewer Asian women (6.2%) on HRT compared to white women (23.3%). These differences cannot be accounted for by risk factors: A cross-sectional study of HRT prescribing in general practice during 2018 revealed that even after adjusting for risk factors, practices in the most deprived quintile had an 18% lower HRT

prescription rate compared with the most affluent (29). Additionally, the types of product prescribed varied, with a greater use of oral HRT rather than transdermal products in practices in areas of higher deprivation. There has been a notable rise in HRT prescribing in recent years, but this pattern of inverse association between deprivation and HRT prescribing has persisted (Hormonal Replacement Therapy).

Research in the United States demonstrates diverse experiences of menopausal transition across different ethnic groups (30) (31). Disparities in discussing and managing symptoms attributed to the menopause have also been identified (32). For instance, despite higher symptom burden in black women, they are less commonly prescribed HRT. In a qualitative study with UK primary care practitioners, the key professional group in providing HRT to the community, the findings suggested that the women from ethnic minority communities might be less likely to seek help for the menopause and practitioners were less likely to recognise and address menopause issues in these communities (3).

Methods: Given the HRT prescribing trends (which will affect the demographic profile of those eligible for the study) and potential practitioner biases, challenges are anticipated in recruiting a diverse population, particularly women from ethnic minority and disadvantaged communities. The trial design incorporates NIHR guidance on inclusion and patient and public involvement and engagement to build equitable recruitment and retention strategies. In an effort to mitigate these recruitment challenges we will use an adapted Quintet recruitment intervention (QRI) methodology (33). This will be designed to be flexible, guided by emerging findings while adhering to the following core components:

1. Development of materials and communication plan: We will collaborate with community groups to optimize study materials and communication strategies to ensure diverse communities are well-informed. Incorporating some decentralised methods of recruitment, including self-referral, will mean that getting the message and mode of communication right could be key to recruitment (for example in a partially decentralised trial of an acne treatment in primary care, 48% of patients recruited heard about the trial through social media) (34).
2. Recruiter Engagement: We will use a range of strategies to explore optimal ways of engaging recruiters, this will include conducting up to four recruiter workshops. Our work will be guided by the QRI model, to share knowledge, explore potential areas of challenge including potential bias and personal beliefs around testosterone and offer a “top tips” document (33) (35).
3. Interviews: We will conduct up to 60 purposively sampled qualitative interviews (guided by the concept of ‘information power’ during different trial stages, but with an emphasis on the pilot phase to facilitate optimum methods of equitable recruitment (36). We will interview up to 15 research delivery staff (e.g. GPs, research nurses, members of the CCRT) at baseline to understand their perspectives on recruitment and retention barriers and facilitators. There will be up to 45 interviews with women, including those recruited, those who were interested but not recruited, and if possible, those who withdrew or were lost to follow-up. For some of those recruited we aim to interview them up to three times during their time in the trial to capture issues relating to retention. These interviews will also explore intervention experiences, beliefs about testosterone, adherence barriers/facilitators, demographic differences, and suggestions for study dissemination. By combining interview data with quantitative recruitment data, we can comprehend recruitment from participants' perspectives, identify best practices, obstacles,

and contextualize progression criteria achievement discussions. These insights will inform strategies to optimize equitable recruitment and retention for the main trial. By focusing on early trial participants, we can conduct repeat interviews to understand retention challenges and adapt strategies as needed. Participants will be interviewed to gauge changes in recruitment approaches over time.

Analysis: Data will be thematically analysed to interpret patterns in recruitment, retention and adherence and triangulated with quantitative data (36, 37). Using a socioecological theoretical approach we will examine personal and contextual factors affecting recruitment and retention, as well as expectations about treatment and adherence. To maximise rigour and reflexivity, regular team meetings will be used to discuss development of the coding framework and data analysis.

Audio-recorded interviews will be transcribed verbatim by a member of the research team or a professional transcription service approved by Cardiff University and bound by a confidentiality agreement. Transcripts will be anonymised prior to analysis.

16.3 Cost effectiveness analysis

A health economic evaluation will provide evidence of the relative costs and consequences of adding testosterone to standard HRT to reduce symptoms beyond altered sexual function and improve quality of life, compared to standard HRT alone. The evaluation will be designed, conducted and reported following best practice, conforming to the Consolidated Health Economic Evaluation Reporting Standards (38).

(38)We will collect prospective information from trial records and a bespoke, participant-reported, resource use measure (RUM) as part of the data collection schedule, as described earlier. The RUM will adapt items from existing measures (e.g. Work productivity and absenteeism from WHO HPQ (Kessler et al. 2003)), and will be developed following good-practice guidance (18, 19, 39, 40). During trial set-up, we will work with the PPI groups and the research team to produce a RUM which captures the relevant, key drivers of health and social care resource use, personal costs and lost productivity associated with managing symptoms of menopause and associated treatments (including AEs). This will be balanced with the need for a proportionate measure to minimise participant and researcher burden, with initial tests in a modified Delphi study to assess content validity (41).

We will use the internal pilot phase to assess the use of economic measures in ESTEEM to inform the first iteration of the Health Economic Analysis Plan. Any changes required to the wording of the RUM will be made after assessment of the internal pilot phase. Resource use will be valued in £ sterling using published unit costs (e.g. Unit costs of health and social care, NHS reference costs, British National Formulary) to the most relevant price year available at time of final analysis (Unit Costs of Health and Social Care 2022 Manual; National Cost Collection for the NHS; British National Formulary (BNF). The total costs and per participant costs per intervention (including prescription costs, monitoring and AEs) and comparator group will be presented at baseline, 3, 6 and 12 months and cumulative cost presented per group over the trial follow up period.

The EQ-5D 5L will be used to generate utilities and Quality Adjusted Life Year (QALYs), chosen as it is NICE preferred measure of capturing health-related quality of life in adults (NICE 2019). We will use the most appropriate method at the time of analysis to derive utilities for a UK population (e.g. pending completion of the on-going UK EQ-5D 5L valuation exercise (Euroqol) in 2024, or using the recognised cross-walk function to the 3L version)(42). If feasible, as a sensitivity analysis, the MENQOL-I will be mapped to the EQ-5D 5L (43).

With the impact of menopause affecting beyond health-related quality of life, we will use the ICECAP-A as part of a secondary analysis to generate an incremental cost related to capability as part of a complementary assessment of non-health benefits.

Health Economic Analysis:

We will use the ESTEEM ITT population for our base-case, with appropriate adjustment (e.g. adjusting for baseline health outcomes, missing data) in line with the statistical analyses. For the within-trial analysis, discounting of costs and outcomes will not be undertaken as the time horizon is less than 12 months. Suitable regression methods will be used to derive incremental costs and effects. Our primary incremental analysis will be QALYs gained in the intervention vs. comparator group at 12 months, with presentation of net monetary benefit (NMB). A UK NHS/Personal Social services perspective will be taken for the base case. With the wider economic impact of menopause and its treatment established, a restricted societal perspective will report the additional personal costs to participants (e.g. over the counter treatments, private therapies). A further analysis will be used to derive the incremental cost per years of full capability/years of sufficient capability at 12 months if the ICECAP-A is considered acceptable for the trial (44).

Deterministic sensitivity analyses and bootstrapping will be conducted to explore the uncertainty in our findings from our analyses, including the addition of limited societal costs on our base-case findings. Cost-effectiveness acceptability curves will be presented, based on a threshold of £20,000-£30,000 per quality-adjusted life year (QALY) gain (NICE 2013) and £33,500 threshold per year of sufficient capability to estimate the probability of testosterone being cost-effective (45, 46).

17 Data Management

Table 15: Source data for the trial

Trial data	*Source Data*								
	CRF (CTR database)	*Participant medical notes*	*Participant Diary (Trial App)*	*Pharmacy File*	*Questionnaire*	*SAE form*	*PIS and consent form*	*Laboratory report*	*NHS Digital Data/SAIL database*
Eligibility Assessment		*X*							

Informed Consent							*X*		
Randomisation	*X*								
Demographics and baseline characteristics		*X*							
Medical History		*X*							
Concurrent Medications		*X*							
Dispensing of IMP				*X*					
Withdrawal criteria	*X*								
Adverse events	*X*					*X*			

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

17.1 Data collection

It is intended to develop data collection for this trial as a web-based system and self-contained software in the form of a trial app. These will be secure encrypted system accessed by unique usernames and passwords, and comply with the General Data Protection Regulation 2016 standards.

We will also utilise a bespoke-built trial database for clinical data collection and participant data management. This database will be built by the Centre for Trials Research (CTR) database programmer. The trial app and the bespoke-built trial database will function independently of each other. Data collected in the trial app and the necessary data from the trial database will be exported for analysis. The App will be the primary route for collection of patient-reported outcome measures and will facilitate remote follow-up of participants including visit scheduling and adverse event reporting.

Full details of data management are available in the Data Management Plan.

18 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

19 Translational Sub-Study: HEARTT – Hormonal effects and Risk Tracking in Testosterone Therapy

HEARTT is an optional translational sub-study embedded within the ESTEEM trial. Funding to support the additional blood collection (£20,000) has been secured.

Background and Rationale

While a lack of oestrogen is linked with increased cardiovascular risk factors, the role of testosterone in women remains unclear. The sub-study, HEARTT, will analyse blood samples collected during the ESTEEM study to explore metabolomic markers associated with cardiovascular risk. The primary aim is to determine whether testosterone therapy influences the presence or levels of established cardiovascular biomarkers identified by metabolomic analysis. Additionally, given the limited research in this area, there is potential for the HEARTT study to identify novel metabolomic markers unique to women on HRT.

By exploring these metabolomic differences, HEARTT will seek to generate preliminary data on the biochemical effects of testosterone therapy and its potential implications for cardiovascular health. This foundational research aims to pave the way for more personalised and safer HRT prescribing practices for women.

As this is an exploratory translational sub-study using a convenience sample, no power calculation is required. The sample size will therefore be determined by ESTEEM recruitment and uptake of HEARTT, and analyses will focus on estimation and exploration of metabolomic patterns rather than definitive hypothesis testing.

Primary Aim:

- To explore metabolomic differences between women taking HRT with testosterone and those taking HRT alone, focusing on biomarkers associated with cardiovascular risk.

Objectives:

1 Analyse metabolomic profiles in blood samples from both groups.
2 Assess the prevalence or concentration of known metabolomic cardiovascular biomarkers in women on testosterone therapy.
3 Investigate the potential for testosterone therapy to introduce novel biomarkers or amplify known cardiovascular risk markers.
4 Use findings to inform future studies on personalised cardiovascular risk stratification for women on testosterone therapy.

Methodology

1. **Sub-study design**

HEARTT is a case-control sub-study nested within the ESTEEM trial. Participants will be stratified into two groups:

- Women taking HRT alone (control group).
- Women taking HRT with testosterone (test group).

Participation in HEARTT will be covered by the optional HEARTT sections within the main ESTEEM Participant Information Sheet, together with a separate optional consent section in the main ESTEEM Informed Consent Form. Participation in ESTEEM is unaffected by the decision to take part in HEARTT.

2. Sample Collection and Analysis

Blood Samples: Blood samples will be collected at the same time intervals as required in the ESTEEM protocol. An additional 20 ml blood sample will be collected from each participant who consents to HEARTT.

Metabolomic Profiling: Samples will undergo mass spectrometry to identify and quantify metabolites associated with cardiovascular risk. Established biomarkers (e.g., lipids, amino acids, inflammatory markers) will be prioritised, while exploratory analyses will search for novel markers.

Comparative Analysis: Metabolomic profiles of the two groups will be compared to identify differences attributable to testosterone use.

3. Data Handling and Data transfer

Selected pseudonymised ESTEEM trial data - including treatment allocation, adherence data, and cardiovascular measures - will be transferred by CTR to Aberystwyth University using a HEARTT-specific linking ID. No identifiable data will be shared. Participants will be informed of this data flow and asked to consent to it separately.

4. Integration with Cardiovascular Data

Cardiovascular health measures from the ESTEEM study (e.g., height/waist ratio, lipid profiles, HbA1c) will be incorporated to evaluate correlations with metabolomic findings. HEARTT analyses are exploratory and will not influence clinical care or ESTEEM treatment decisions.

Expected outcomes

1. Identification of metabolomic markers previously associated with cardiovascular risk, in women taking HRT with testosterone compared to those on HRT alone.
2. Exploration of whether testosterone therapy amplifies existing cardiovascular biomarkers or introduces novel ones.
3. Insights into potential metabolomic differences between the two groups, providing a basis for future research on the long-term cardiovascular effects of testosterone therapy.

4. Generation of preliminary data to support more targeted investigations into cardiovascular risk stratification for women undergoing testosterone therapy.

Significance and Impact

Although HRT has been extensively studied in areas like cancer risk and symptom management, the molecular and biochemical effects of HRT, particularly with testosterone, remain underexplored. Testosterone use in women is growing, yet its long-term cardiovascular impact is poorly understood.

HEARTT will seek to address this gap by investigating whether testosterone therapy alters metabolomic profiles in ways that signal cardiovascular risk. By identifying specific biomarkers, this sub-study has the potential to improve safety and personalisation in HRT prescribing. Findings could inform future research, influence national HRT prescribing policies, and contribute to better health outcomes for women.

Results from HEARTT will be used for research purposes only and will not be returned to participants or used to guide clinical management.

20 Migraine and testosterone sub-study

Background and rationale

Migraine is a common condition, affecting nearly a quarter of women in the UK, and affecting two to three times more women than men (Women's experience of migraine) (47, 48). It is the second leading cause of years lived with disability worldwide and the leading cause of years lived with disability for women aged 15-49 (49). Migraine frequency and severity increase with perimenopause, causing considerable disability (50). It is estimated that 8-13% women develop migraine for the first time during peri-menopause (51). A meta-analysis of symptoms attributed to the menopause found that 44% women undergoing menopause have headaches (52). Many non-headache symptoms also occur with migraine including sensory disturbances, gastrointestinal symptoms, fatigue, dizziness, mood changes, and cognitive changes such as brain fog and poor concentration (53, 54) (Signs of a Migraine That Aren't Headache)**.**

In addition to changes in oestrogen and progesterone levels, testosterone levels also reduce in women during perimenopause, and peri-menopausal women are increasingly being prescribed testosterone. It is not clear what the effect of testosterone is on migraine and headache. There is some weak evidence suggesting that testosterone treatment may improve migraine. A pilot study published in 2012 gave testosterone implants to 27 pre- and post-menopausal women and found that 92% had improvement in headache severity (8). However, there have been no RCTs of testosterone for migraine and it is not clear whether testosterone improves migraine in women taking standard HRT or whether it is effective when administered trans-dermally (as is now standard in peri-menopausal women). It is also not known if testosterone could make migraine or headaches worse. This sub-study aims to answer the research question: Does transdermal testosterone improve headache and migraine in women already taking standard HRT?

Primary Aim

Determine if transdermal testosterone (in women already taking standard HRT) improves migraine and headache symptoms in women with migraine or headache at baseline.

Secondary aims

- Determine if transdermal testosterone (in women already taking standard HRT) improves other symptoms attributable to the menopause and quality of life in women with migraine and headache at baseline.
- Determine if transdermal testosterone (in women already taking standard HRT) increases or causes headache in women with and without migraine and headache at baseline.

Method

1. **Sub-study design**

This is a sub-study within the randomised controlled ESTEEM trial, focusing on women with migraine or headache at baseline. Outcomes in those randomised to testosterone will be compared to those randomised to placebo.

Outcomes
Measured at 3-, 6-, and 12-months:

Primary outcome

- Headache frequency (mean change from baseline in the number of monthly headache days (MHDs))

Secondary outcomes

- At least 50% reduction in monthly headache days
- MS QoL score
- MENOQOL-I Q15
- All ESTEEM outcome measures

2. **Analysis**

Power calculation

The recruitment target for the ESTEEM trial is 208 per arm (total N=416). For the migraine sub-study, we expect approximately 44% women with symptoms attributable to the menopause to have a history of headache/migraine (reported at baseline) and therefore included in the sub-group analysis (52). This would equate to 183 of the 416 women which, if those with migraine/headache are randomised equally to intervention and placebo, would be 91 women in each group.

There is no clear consensus on what a clinically important reduction in monthly headache days (MHDs) should be. The population in this sub-study will include a mixture of women with chronic migraine, episodic migraine and (unclassified) headaches. We do not know what the baseline or standard deviation for MHDs will be in this population. We have based our power calculation on previous trials for episodic and chronic migraine, and tension-type headache (55-57). For the primary outcome of headache frequency (MHDs), based on 144 women (72 per arm) allowing for a 20% dropout, we would have 97% power to detect a mean difference of 3 days, given a standard deviation of 5 days and alpha of 0.05.

Main analysis

We will identify and characterise the cohort of women who report having a headache or migraine at baseline and also women who do not. We will describe their outcomes at baseline, 3-, 6- and 12-months. Additionally, and for both groups, we will describe any headache side-effects reported over time, so that cases of new headaches developed during the trial in women with no history of migraine and headache at baseline can be understood.

The analysis of the primary outcome, in women with migraine/headache at baseline, will examine headache frequency (MHDs) over time incorporating 3-, 6- and 12-month response, analysed using a repeated measures linear regression model (with an interaction term for time and trial group), to investigate any divergent/convergent pattern in scores. We will adjust for baseline and randomisation strata entered as fixed effects. All analyses will be conducted on an intention-to-treat (ITT) basis, within a multiple imputation framework (MI) assuming data are missing at random. Changes to testosterone dosage will be adjusted for in the analysis.

Secondary outcomes measures will be analysed similarly to the primary outcome using repeated measures linear or logistic regression models (dependent on outcome) with time point nested within participant, and an interaction term for time and trial group

Sub-group & exploratory analyses

If numbers allow, a sub-group analysis will be performed by headache classification: chronic migraine, episodic migraine and unclassified headache at baseline. The range of symptoms attributable to the menopause as measured by all the outcome measures used in ESTEEM (excluding MS QoL) will be described in the migraine/headache sub-group compared to the non-migraine/headache sub-group at baseline and end of study to explore association of symptoms attributable to the menopause with migraine.

21 End of Trial definition

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database.

Sponsor must notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

22 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 25 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

23 Regulatory Considerations

23.1 CTA

This CTIMP trial has Clinical Trials Authorisation (CTA) from the UK Competent Authority: MHRA.

The outcome of the trial will be reported to the MHRA within 90 calendar days of trial closure. In the event of the trial being prematurely terminated a report will be submitted to the MHRA within 15 calendar days. A summary of the results will be submitted to the MHRA within one year of completion of trial closure.

23.2 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol will be submitted through the relevant permission system for global governance review dependant on the location of the lead site e.g. HCRW/HRA.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

Any changes to the protocol will be made in the form of an amendment and communicated to stakeholders as required in line with organisational processes. Other changes in trial conduct not covered by an amendment will not be permitted. Any unforeseen changes will be recorded in the clinical trial report. Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be approved by the sponsor before implementation.

The Sponsor will provide an opinion on whether an amendment meets criteria to be considered substantial. All substantial amendments must be approved by the REC responsible for the trial, in addition to approval by NHS Research and Development (R&D). Non-substantial amendments will not require prior approval by the REC.

If the trial is stopped due to adverse events or an urgent safety measure it will not be recommenced without reference to the REC responsible for the trial, and will only resume following written MHRA approval of a substantial amendment permitting recommencement.

The outcome of the trial (e.g. completed) will be reported to the REC responsible for the trial within 90 calendar days of trial closure. In the event of the trial being prematurely terminated a report will be submitted to the REC responsible for the trial within 15 calendar days.

A summary of the results will be submitted to the REC responsible for the trial within one year of completion of trial closure.

There may be an opportunity for patients' data to be used in similar studies in the CTR. Patients will be asked to consent to be contacted separately for this and explicit consent would be sought from patients separately before any data that could identify them is shared with other researchers.

23.3 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016. The data custodian and the translational sample custodian for this trial is Cardiff University.

This includes collection of NHS number (or equivalent – e.g. CHI number in Scotland), name and postcode to register and trace participants with the HSCIC or SAIL.

23.4 Indemnity

- Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply. Cardiff University has Clinical Trial insurance in place for the design, management and conduct of the ESTEEM trial. Cardiff University is insured by UMAL.
- Negligent harm: Where studies are carried out in a primary care setting, the general practice continues to have a duty of care to a participant being treated within the general practice, whether or not the participant is participating in this trial. Cardiff University does not accept liability for any breach in the other general practice's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

For participants recruited at NHS sites, the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

Members of the CCRT will have clinical negligence indemnity in place, as confirmed by their NHS employer.

23.5 Trial sponsorship

Cardiff University will act as Sponsor for trial. Delegated responsibilities will be assigned to the sites taking part in this trial.

The trial is being sponsored by Cardiff University with responsibilities delegated to the CTR. The CTR shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments.
- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research.
- The Data Protection Act 2018.
- The Human Tissue Act 2004.
- Other regulatory requirements as appropriate.

The trial will be conducted in compliance with the protocol, regulations set by the Medicines and Healthcare products Regulatory Agency (MHRA) and Good Clinical Practice as required by these regulations.

23.6 Funding

This trial is funded by the NIHR's Health Technology Assessment Programme (funding reference NIHR159538).

24 Trial management

24.1 TMG (Trial Management Group)

Trial Management Group (TMG) members will be required to sign-up to the remit and conditions as set out in the TMG Charter. The TMG will meet monthly to review trial progress.

24.2 Independent Trial Steering Committee

The independent Trial Steering Committee (TSC) members will be required to sign-up to the remit and conditions as set out in the TSC Charter. The TSC will meet with frequency specified in the TSC charter.

24.3 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) members will be required to sign-up to the remit and conditions as set out in the IDMC Charter. The IDMC will meet with frequency specified in the IDMC charter.

25 Quality Control and Assurance

25.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the ESTEEM trial. A detailed monitoring plan will be generated specifying the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed, and monitoring frequency adjusted as necessary.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Where electronic health records (EHR) are being used, trial teams and monitors should check EHR process early in trial and periodically thereafter.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

25.2 Audits & inspections

The trial is participant to inspection by MHRA as the regulatory body. The trial and any of its sites may also be participant to inspection and audit by Cardiff University under their remit as Sponsor.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ Institutional Review Board (IRB) review, and regulatory inspection(s), providing direct access to source data / documents.

The sites and Sponsor-appointed laboratories and IMP manufacturers must inform the CTR of any MHRA inspections they are subject to.

26 Public Involvement and Engagement

The in-depth PI&E plan will be described in a separate document. Summary of plans presented below:

Two public partners will be part of the trial management group. Each has different lived experiences of managing symptoms attributed to the menopause / HRT and bring a unique personal perspective. They will be involved in all aspects of the project including advising on an equitable recruitment approach by reviewing recruitment plans and participant facing documents. The public partners will contribute to: analysis meetings (eg process evaluation), developing the resource use measure, reviewing and commenting on reports / scientific publications (as co-authors). An additional public partner will be recruited to sit on the trial steering committee.

To support inclusive opportunities that work best for our public partners, each partner has completed a 'Working Together Preferences', exploring preferences for communication, additional support required, other needs to be considered (eg caring responsibilities), and training needs. Public partners will complete Health and Care Research Wales Public Involvement Training and any specific training highlighted in the working together form (such as GCP training). Public involvement activities will adhere to the six UK standards of public involvement. To capture the involvement of public partners, a co-owned public partner log will be embedded in the PPI strategy. The log will be based on the PIRIT public involvement toolkit and will highlight the unique contributions made by public partners during the trial.

We established relationships with key community groups e.g. Fair Treatment for Women in Wales, Talking Trials Group and Bargoed Community Group. We will meet with them during the trial to inform trial processes and dissemination activities. Most meetings will take place during the start of the trial: four meetings in the early stages to advise on recruitment and process evaluation plans; two later meetings during the results phase and a final meeting towards the end of the trial to advise on modes of dissemination. All meetings will have a particular focus on optimal and inclusive communication and engagement with diverse groups in relation to recruitment, retention and dissemination.

27 Publication policy

Standard principles in accordance with the policy of the International Committee of Medical Journal Editors will be followed. The CI will co-ordinate dissemination and writing of data from the main trial. All publications and presentations relating to the trial will be authorised by the Trial Management Group in accordance with the trial specific publication policy.

The results of the trial will be disseminated regardless of the magnitude or direction of effect, via a full report to the funder as per their reporting requirements and in peer-reviewed journal publications. Participants will be able to view a summary of trial publications if they wish, which will contain full references on the trial website. The trial team will involve ESTEEM research partners in the development of tailored summaries of trial findings. ESTEEM results dissemination plan will ensure active promotion to participants and the broader public through a variety of optimal dissemination pathways.

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