1. Full title of project

ESTEEM: Evaluating the clinical and cost-effectivenesS of TEstosteronE to improve Menopause-related quality of life

2. Summary of research (Abstract)

Research question: Is testosterone an effective and safe treatment for menopausal symptoms, beyond altered sexual function, when added to standard hormone replacement therapy (HRT) treatment?

Background: The menopause affects 51% of the population and is associated with multiple symptoms, which can negatively affect quality of life for some women. HRT is prescribed to relieve these symptoms by replacing the oestrogen the body loses during the menopause. The role of testosterone in HRT to manage symptoms, other than altered sexual function, is not clearly understood and poorly evidenced to date. There is no licensed testosterone for use in women available within the NHS. As a result, prescribing practices and access to 'unlicensed' testosterone across the UK are variable although demand for testosterone as part of HRT has increased.

Aims and objectives
Primary:
- To investigate whether testosterone is effective in reducing menopause symptoms beyond altered sexual function, using the Menopause-Specific Quality of Life Intervention questionnaire Scale (MENQOL-I).

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

Methods: Multi-centre double-blind parallel arm randomised controlled trial to compare outcomes for women aged >45 years with menopausal symptoms despite standard HRT, allocated at random to receive testosterone gel or matched placebo. 416 women will be recruited in person or remotely via NHS organisations and by self-referral, promoted via social media and community groups. Following eligibility screening, electronic consent will be taken, including agreement for long-term follow-up. Baseline and follow-up data will be collected using electronic case report forms (eCRF) using a trial app or by phone if preferred. The primary outcome of MENQOL-I will be measured over time up to 12 months (3, 6 and 12 months), and secondary outcomes at 3, 6 and 12 months, all analysed based on intention to treat. A health economic evaluation will assess relative costs and benefits of adding testosterone to standard HRT. Lay research partners and community groups will inform study design and conduct, and alongside a qualitative process evaluation will inform recruitment/retention and dissemination strategies.

Timelines for delivery: Complete milestones (by month): set up (8), pilot (14), assess progression criteria (17), main recruitment (32), follow-up (44), analysis/report (51).

Anticipated impact and dissemination: The trial will provide clarity to policy, practice and patients about efficacy and safety of testosterone when added to standard HRT, beyond altered sexual function. We will disseminate via academic pathways (eg journals), key training organisations and professional networks (e.g. RCOG, RCGP, FSRH) and NICE to update current guidance on Menopause management. We will co-develop summaries with PPI partners to feedback to trial participants, patient groups, and broader public.

3. Background and Rationale

The menopause is a part of the natural life course affecting 51% of the population and is associated with up to 34 different symptoms. 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. 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.[1] 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.[2-3] Under-representation of women with various protected characteristics in underpinning research is also recognised by policy.[4]

Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services? 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.[5] NICE recognise the lack of evidence supporting testosterone use beyond altered sexual function and the profound impact for women of the menopause.[6] Currently, testosterone gel for reduced sex drive remains unlicensed and access to care is often via specialist doctors/clinics.[7] More broadly, hormone treatment patterns in UK primary care indicate variability in menopausal care suggesting educational needs for patients and clinicians.[8] Therefore, it is essential that a new trial provides clear evidence for the use of testosterone when added to HRT for quality of life and a broad range of symptoms beyond sexual function.

Review of existing evidence - How does the existing literature support this proposal?

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.[9] There is also some evidence suggesting that testosterone may improve headache and migraine.[10-12] However, Islam and colleagues 2019 systematic review of testosterone for women found insufficient evidence of benefit for indications beyond altered sexual function.[13] 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 postmenopausal women or 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.[14] Davis' larger (n=89 postmenopausal women) single centre trial reported improvements at 26 weeks on measures of verbal learning and memory.[15] Considering mood and wellbeing, an RCT involving 34 women found transdermal testosterone therapy improved well-being and mood in premenopausal women with low libido and low testosterone.[16] 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. 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.[13]

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.[17] 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.[18]

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.[19] 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.[20]

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.[21] This study plans to recruit 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 muscle and bone strength. 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 three months (reflecting current clinical practice for prescription of testosterone) and our primary outcome measure is a broader measure which incorporates the wide range of symptoms experienced by women in the menopause.

Health economics: Although no published economic evaluations of testosterone 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.[22] The limited evidence of the cost implications surrounding menopausal symptoms is a considerable limitation for economic evaluation of potential treatments.

Safety: 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.[23]

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.[24] 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.[13] Long-term safety via this route remains unknown.

Why is this research needed now? It is well established that testosterone plays a critical role in the reproductive function and hormonal balance in women physiologically. But the role of androgens supporting the 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. 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 help to dispel the myths and misconceptions around the role and importance of androgens 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. 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, to provide high-quality evidence to inform policy, practice and patients about the benefits, potential harms and costs of testosterone treatment in women experiencing menopause symptoms despite standard HRT.

4. Aims and objectives

Research question: Is testosterone an effective and safe treatment for menopausal symptoms when added to standard HRT treatment?

Primary aim: to investigate, in menopausal women already receiving standard HRT treatment, whether testosterone is effective in reducing menopause symptoms 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.

Objectives, to:

1. Establish the effectiveness of testosterone for menopausal women already receiving standard HRT in reducing menopausal symptoms beyond altered sexual function as measured by a validated measure of menopause-specific quality of life

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. Confirm feasibility of adequate and equitable trial recruitment, retention and data quality in an internal pilot

6. Explore barriers/facilitators amongst service providers and women to future prescribing and uptake of testosterone

7. Work with lay research partners to design, deliver and report a trial that meets the needs of all women who may experience menopausal symptoms

PICO SUMMARY

• Population: 416 women aged >45 years with menopausal symptoms, despite standard HRT treatment

• Intervention: Transdermal testosterone gel 5mg, adjusted depending on response, once a day for 12 months, added to current HRT regime

• Comparator: Matched placebo gel, once a day for 12 months, added to standard HRT regime

• Outcome: Primary - self-reported menopause-related quality of life, using the Menopause-Specific Quality of Life Intervention Questionnaire Scale (MENQOL-I), measured at 6 months.[25]

5. Overview of research design

Pragmatic, 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 in women with menopausal symptoms, despite standard HRT, and assess for superiority over placebo. An internal pilot phase will assess recruitment, retention, and adherence with associated progression criteria. In person as well as remote (trial website or telephone call) screening, eligibility and consent procedures will be used. All women will have a discussion (in person or by telephone/video) from a medical professional to confirm eligibility prior to randomisation and a clinical review at 3 months. Women will be randomised after baseline assessment. Clinicians will be blinded to allocation. All outcomes will be assessed by individuals who are blind to allocation. Participants will be followed up at 3, 6 and 12 months with primary outcome comparison (menopause specific quality of life) measured over time up to 12 months. Consent will be sought for linkage to routine health care data to facilitate longer-term follow up subject to further funding.

Study population: Women aged >45 years with menopausal symptoms, despite standard HRT treatment

6. Internal pilot progression criteria

An internal pilot will examine recruitment, retention and adherence and assess against stop-go criteria using descriptive statistics.

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).

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

7. Health technology being assessed

Transdermal testosterone gel, once a day for 12 months. Both active treatment and placebo to match supplied free of charge by licensed manufacturer of testosterone gel. An MHRA licenced manufacturing unit will label, package and distribute trial medication directly to participants' homes.

8. Sampling

Several assumptions are required for a sample size using a repeated measures approach, that may result in an underpowered study. For this reason, the trial is powered to detect a clinically meaningful benefit of at least one point difference on the summary MENQOL-I questionnaire score at six months follow up. 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.[26] 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.[27]

9. Target population

Women aged >45 years, with menopausal symptoms despite standard HRT

10. Summary of patients/public as research participants

Details of protected characteristics such as ethnicity, age and gender will be captured at screening along with other data required to establish eligibility. We will work with our research partner co-applicants and lay advisory groups (see below) to establish the best format and presentation for capturing such data (e.g. to reduce burden and to avoid these questions becoming a barrier to participation for some potential participants). We have specified broad and inclusive eligibility criteria, allowing for variability in relation to age, HRT treatment, long-term physical and mental health conditions. This will ensure that the study group will reflect the greatest cohort of women who may benefit from addition of testosterone in practice, following the trial.

Standard HRT treatment broadly refers to both oral and transdermal preparations of HRT, given either in a continuous or sequential regimen. It also allows for women using a 52mg Levonorgestrel containing intra-uterine device as their progestogen of choice for endometrial protection to also be included in the trial. We have not specified a dose of standard HRT but would not exceed BNF recommended doses.

Premature ovarian insufficiency affects 1% of women in the UK <40 years old, with a shortened life-expectancy mainly due to the impact on cardiovascular health of lack of hormones. It is important to include this specific group of women in the study to ensure management is optimised.

Our recruitment method facilitates an opt-in approach where individuals are able to volunteer for trial participation. This removes the need for a gate-keeper 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 app), something recommended to us during our PPI consultation.

We consulted with a number of diverse groups (Talking Trials, SUPER, Fair Treatment for Women in Wales) to design an engagement strategy with participants (regular email/newsletter updates/ chat function on the app/clarity about rationale for methods, data collection etc.) to reduce potential for drop-out.[28-29] The strategy will be further refined in collaboration with our PPI advisory groups and co-applicant research partners, based on the early recruitment activity and interview feedback during the internal pilot phase.

During the process evaluation, we will be interviewing individuals who have dropped out of the study as well as those who are continuing with the study to better understand the reasons for this. Recommended modifications in the engagement strategy will be implemented based on this feedback.

The online portal will be the main hub for dissemination of progress and findings for study participants, but we will also use a multi-media approach, reflecting the ways our study participants have chosen to engage with the study. This will include social media channels (as used in recruitment) to facilitate dissemination of findings to public stakeholders.

11. Inclusion/Exclusion criteria

Inclusion criteria:

- Women receiving standard HRT for at least 3 months who remain symptomatic
- Willing to stay on current standard HRT for duration of trial
- Able/willing to provide informed consent, or their legal representative is willing to provide informed consent
- At any stage in perimenopause or menopause, including those with premature ovarian failure and medical/surgical menopause already taking standard HRT
- Able to receive transdermal testosterone
- Able/willing to adhere to a 12-month follow-up
- Able/willing to have blood tests

Exclusion criteria:

- Women with altered sexual function as their only menopausal symptom
- High baseline testosterone level
- Allergy to almonds
- Pregnant or breast feeding
- Active malignancy or treatment for malignancy (<6/12)
- Involvement in another clinical trial for investigational medicinal product (CTIMP)
- Androgen treatment (testosterone or tibolone) or antiandrogen therapy within the past 6 months

12. Setting and model of recruitment

Setting: Multi-centre trial recruiting participants in the community and NHS organisations. We will use electronic consent, and undertake baseline and follow-up data collection using electronic case report forms (eCRFs) in a decentralised trial model.

We will adapt a model of blended recruitment we successfully used in the PANORAMIC trial (co-apps NI, KHo) with patient self-referral (via social marketing and targeted underrepresented community engagement approaches) via an online hub for patients in Wales and some English sites (followed by remote clinical assessment) and recruitment in primary care in England (supported by research networks, selected to promote ethnic diversity / inclusion by deprivation indices). [30-31] Experiences from studies such as PANORAMIC emphasise the importance of adopting a flexible approach to recruitment rather than retaining a static approach across sites and over time. In this trial that could include identifying physical and virtual points for promoting visibility of the trial which evolve and iterate based on progress monitoring and PPI inputs (*physical* being community-based organisations such as primary care / health centres, pharmacists, community centres, places of worship and other social hubs; *virtual* being targeted social media advertising such as via google which target user searches for relevant terms such a menopause, treatment etc). Our three PPI advisory groups have provided important initial suggestions for both physical and virtual targeting. Additionally, ‘patient champion’ models we have used to support trial recruitment in deprived community settings to address health inequalities in trials will be adapted and used to strengthen the patient voice in reaching out to potential participants.

We will utilise the primary care teams within local Clinical Research Networks (CRNs) who will provide local intelligence (e.g. identification of “Deep End” practices) on the suitability of GP sites to act as primary care hubs based on local assessment of capacity and capability.[32] Participant Identification Centres will be established to feed into hubs. The primary care CRN agile research teams will be deployed to support site set-up training in conjunction with the central research team.

Potential participants can self-refer directly via the trial website or if preferred by telephone. An expression of interest can be completed. This will capture potential participants’ eligibility to enter the trial and an opportunity to ask any trial related questions prior to signing the consent form. The eligibility and consent can be self-completed by the potential participant, or completed during a telephone call with a member of the trial team with delegated responsibility at the recruiting sites. Thereafter, baseline, demographic and contact information can be entered directly onto the website or via the telephone with

the support of a member of the clinical team. All documentation will be collected using an eCRF in a decentralised trial model which will include electronic consent, baseline and follow-up data collection.

13. Data collection

Randomisation

Participants will be individually randomised on a 1:1 ratio to testosterone or placebo, using a secure, fully validated and compliant web-based randomisation system developed and maintained by the CTR. Treatment will be assigned using binary stratification for the following factors:

- Mode of oestrogen at baseline (oral or transdermal)
- Progesterone taken at baseline (yes or no)
- Premature ovarian insufficiency status (yes or no)

Research methods and data capture

We will utilise a bespoke trial eCRF for collection of standard clinical data at each visit which will be built by the Centre for Trials Research (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 (Figure 1). 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.

***Table 1**: Schedule of procedures*

Assessment	**Screen**	**Baseline**	**Month**											
			1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Invitation and PIS provision	X													
Assessment of eligibility	X													
Informed consent	X													
Randomisation		X												
Dispense IMP		X												
Questionnaires		X			X			X						X
Telephone call			X	X	X	X	X	X	X	X	X	X	X	X
Treat adherence monitoring (via App)		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood tests		X			X			X			(X)			X
(X) if required														

Data collection
Baseline data will include participant demographics, lifestyle factors (e.g. smoking, alcohol, exercise), medication used, weight and height.

We will ask participants to complete the following measures via questionnaires at baseline, 3 months, 6 months and 12 months. The menopause-related quality of life intervention (MENQOL-I) questionnaire is a validated questionnaire consisting of 32 items divided into 3 domains (vasomotor, psychosocial and physical functioning).[25] The MenoScores questionnaire was developed in Denmark and has not yet been validated for use in English.[33] It is a comprehensive questionnaire, consisting of 51 items, covering a broad range of symptoms experienced in the menopause. Although both these questionnaires attempt to cover the breadth of menopausal symptoms, we have also included questionnaires to look in more detail at cognition and memory; anxiety and depression; sleep, urinary incontinence, and headache and migraine; as well as satisfaction with treatment; and health related quality of life and capability for the

health economic assessment (details below). The MAC-Q consists of 6 questions, and the MFQ 64 questions, relating to cognition and memory.[34-35] The HADS questionnaire includes 14 questions about anxiety and depression. The PSQI includes 15 questions about sleep quality.[36] The ICIQ_OAB questionnaire includes 8 questions relating to urinary urgency, frequency and incontinence.[37] The MIDAS (migraine disability test) includes 7 questions about headache and migraine. The MS-TSQ is a questionnaire consisting of 8 questions which assesses satisfaction with menopause symptom treatment.[38] For the economic outcomes, the EQ-5D 5L consisting of the EQ5D descriptive system, 5 questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and the EQ Visual Analogue Scale, (Euroqol) will measure health-related quality of life; and the ICECAP-A questionnaire is a broader measure of wellbeing with 5 items - attachment, stability, achievement, enjoyment and autonomy.[39-40]

While the data collection model (i.e. completion by mobile phone app with telephone support for those who find that helpful) has been designed to be easier to complete than methods requiring visits or paper, we are keen to further reduce participant burden. This may include reducing the total number of items included. Consultation to date with our public co-applicants and our three lay advisory groups have provided some steer on this and a final list of outcomes to be measured will be subject to review by the same groups and the Trials Steering Committee.

Blood samples at baseline, 3, 6 and 12 months will include Free Androgen Index, total testosterone, SHBG, FBC, U+E, LFTs, Lipid Profile, HbA1c. Additionally, there will be a single Thyroid Function Test at baseline, to exclude differential diagnosis. At 9/12 months additional blood tests may be taken if dosing has been altered as part of the trial.

As part of the study protocol, we will allow 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 range 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. We will take advice from the steering committee as to this process.

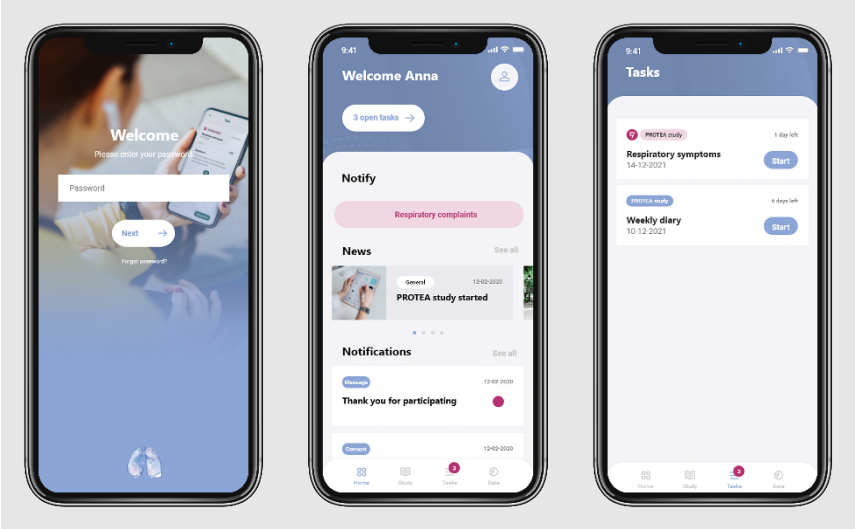
Participants will have the choice to learn the blinded treatment to which they were randomised at the end of the short-term follow-up data collection point (post 12 months follow-up). Unblinding will be important so that participants can make decision regarding their onwards use of testosterone. Unblinding after the short-term outcome data is collected (post 12 months) will not negatively affect the short-term study. However, unblinding will potentially change the composition of the randomisation allocation. We will explore the requirement of this approach and the acceptability or delaying unblinding in our currently on-going preparatory work with PPI stakeholders and through into study set-up.

The future use of IMP will be monitored via participant assessment, up to 5 years post randomisation. Outcomes will be based on the use of objective measures collected via routine health care data and therefore less likely to be affected by knowledge of the original allocation. Self-reported outcome data for example the primary outcome of Menopause-Specific Quality of Life Intervention questionnaire Scale (MENQOL-I), will be more subjective.

Adherence

Participants will be mentored by the central study team (Research Nurse and Data Manager) regarding completion of a weekly dosing summary to monitor adherence to the IMP. The RN will provide written and verbal information on use of the Trial App regarding recording of medication doses. The Trial App will provide frequent 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 Figure 1). 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 study 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.

Figure 1: Trial App Dashboard



14. Data analysis

Outcome measures:

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).

Primary outcome:
Mean summary score from validated Menopause-Specific Quality of Life-Intervention (MENQOL-I) questionnaire, self-reported at 6 months.

Secondary outcomes (Measured at baseline, 3, 6 and 12 months):

- Questionnaires (final selection to be confirmed through consultation with PPI partners):
  - Individual domains (vasomotor, psychosocial, physical functioning) and summary MENQOL-I score*
  - Danish MenoScores*[33]
  - Urinary urgency, frequency and incontinence (ICIQ-OAB)*
  - Sleep quality (PSQI)*
  - Hospital Anxiety and Depression Scale (HADS)*
  - Memory Complaint Quest (MAC-Q)*/Short Memory Functioning Quest (MFQ)*
  - MIDAS (headache & migraine disability questionnaire)*[41]
  - Satisfaction with treatment measure: Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ)*
  - Health-related quality of life (EQ-5D 5L)*
  - Capability (ICECAP-A)*
  - Self-reported weight (kg)
  - Adverse events
  - Adherence to treatment groups
  - Change in current HRT regime.

Measures (noted by *) were piloted by two of our public partners and one member of the study team and took on average a total of 22 minutes to complete. All were deemed to be important and reasonable to include.

Additional outcomes:

- *Blood samples (Measured at baseline, 3, 6 and 12 months):* Outcomes include Free Androgen Index, total testosterone, sex hormone binding globulin, FBC, U+E, LFT, lipid profile, HbA1c. 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.[42-44] The final version will be used in the internal pilot to assess response rate.

- *Individual patient-level linkage to routine health care data:* We will seek consent to access electronic health records e.g., Admitted Patient Care (APC) from NHS England and SAIL Databank (Wales) and link to trial data. Outcomes to include cancer, cardiovascular disease, stroke, cognitive impairment (e.g. dementia), bone fractures/osteoporosis, type 2 diabetes, deep vein thrombosis/pulmonary embolisms, and mortality. Funding will be sought separately to undertake linkage/analysis. Additional assessments could include measurement of participant weight.

Statistical analysis

Analysis and reporting of the main trial will accord with CONSORT guidelines. A statistical analysis plan will be developed and agreed prior to database lock for the analysis. 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.

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 (HRT mode, progesterone use, and premature ovarian insufficiency status) 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.[45] 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.[46-47] Similarly, changes to testosterone dosage will be adjusted for in the analysis. 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.

Secondary outcomes (measures and blood samples) 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 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 short-term final analysis 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.

The final analysis of the 5-year follow up 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.

Since the study drug will not be necessarily available on prescription at the end of the study, there is a potential that the randomisation allocation will be preserved for a short period, with no intercurrent events, and the intention to treat approach could still be valid. However, any further uptake will be self-selecting and may provide a more biased study cohort with a propensity to use testosterone after the initial 12-month treatment period. If we find that the composition of the arms has changed drastically, we will use causal modelling to analyse the long-term follow-up. The analysis approach will be detailed in the application for the follow-up study.

15. Measurement of costs and outcomes

A health economic evaluation will provide evidence of the relative costs and benefits 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.[48]

We will collect prospective information from trial records and a bespoke, participant-reported, 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.[42-44, 49] 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.[50] 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. 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.[51-53] 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).[54] 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).[55-56] If feasible, as a sensitivity analysis the MENQOL-I will be mapped to the EQ-5D 5L.[57]

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 (e.g. seemingly unrelated regressions, SUR) will be used to derive incremental costs and effects. Our primary incremental analysis will be QALYs gained in the intervention vs. comparator group at 6 months with secondary analysis at 12

months, with presentation of net benefit. 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). Consistent with the statistical analysis, a per-protocol/sub-group analysis will be conducted. A further analysis will be used to derive the incremental cost per years of full capability/years of sufficient capability at 6 and 12 months if the ICECAP-A is considered acceptable for the trial.[58]

Deterministic and probabilistic sensitivity analyses 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 QALY gain (NICE 2013) and £33,500 threshold per year of sufficient capability to estimate the probability of testosterone being cost-effective (Kinghorn 2019, Kinghorn and Afentou 2021).[59-61]

16. Process evaluation

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).[62] 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.[63] 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.[64] 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.[65]

Research in the US demonstrates diverse experiences of menopausal transition across different ethnic groups.[66-67] Disparities in discussing and managing menopause symptoms have also been identified.[68] 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 practitioners were less likely to recognise and address menopause issues in ethnic minority communities.[69]

The trial design incorporates NIHR guidance on inclusion and patient and public involvement and engagement to build equitable recruitment and retention strategies.[70] 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. To mitigate these recruitment challenges we will use an adapted Quintet recruitment intervention (QRI) methodology.[71] 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.[72]

Methods: We plan to conduct up to four recruiter workshops, based on 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.[71,73] 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.[74] We will

interview up to 15 research delivery staff (e.g. GPs, Pharmacists, clinical screeners) 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 those who are 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.[75-76] 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.

17. Dissemination, outputs and anticipated impact

To ensure visibility of the trial in progress we will register the trial on a suitable registry (e.g., ISRCTN). We will also establish a bespoke trial website which will be the hub for all trial activity and outputs, with dedicated sections for different stakeholder groups (e.g., trial participants, the broader public, trial researchers and clinicians, healthcare professionals). This will be used to provide information at different stages of the trial (e.g., participant facing materials at recruitment, study updates while the trial is open and in follow-up, summaries, and links for full reports of study findings). Information will be made available in a variety of written and visual formats to maximise access for the broadest range of stakeholders possible.

We will develop a comprehensive publication / output plan to establish the scope of intended outputs. While this is best practice and we will adopt our CTU template for this purpose, it is also essential to ensure timely and comprehensive dissemination of all findings regardless of findings (i.e. whether the trial supports or does not support the effectiveness of treatment). Within the plan we will also identify our plans for data sharing subsequent to the trial being reported, for both trial and process evaluation data, and where relevant coding.

The output plan will include a number of planned academic articles and conference presentations. These will include an initial protocol paper to raise the profile of the study with academic audiences and to assure delivery of the trial to its a priori analysis plan. Primary results papers will include those reporting effectiveness and cost-effectiveness. Key secondary outputs will include reports on the trial process evaluation, the approach to, and learning from the model of recruitment being developed for the trial and the development of the new comprehensive resource use measure for this clinical population. To best represent the role of our lay co-applicants and the lay advisory groups, we aim for a dedicated publication highlighting the lay role and impact on the study, including research partner self-reflections and impact upon them. We will report these results in high impact open access peer reviewed journals and in accordance with NIHR policies (including via the NIHR Journals).

Conference presentations will be used to raise the profile of the ongoing study to a national and international audience (given the potential to influence clinical practice beyond the UK) and to report principal study findings. Meetings will include the British Menopause Society ASC, and the International Menopause Society's World Congress.

We will send bespoke summary briefings directly to relevant bodies (e.g., NICE) to inform guidance for clinicians / commissioners, funders, ethics committee, NHS Trusts, and international conferences. Lay summaries prepared with our PPI group will be used for press releases and social media outputs. Public facing information will be available in various formats to support inclusive practice and rapid access. We

will work with national and international stakeholders (e.g., the trial's own lay advisory groups, Women's Health Concern) to identify the range of pathways to disseminate findings to lay audiences.

18. How will your outputs enter our health and care system or society as a whole

We plan to engage with the key organisations that support health care professionals with training in Menopause qualifications such as the Royal College of Obstetrics and Gynaecology, Royal College of General Practitioners and the Faculty of Sexual and Reproductive Healthcare, to embed up-to-date evidence from this research into training. We will ensure that evidence from this research will feed into the NICE guideline on Menopause diagnoses and management review (https://www.nice.org.uk/guidance/ng23).

Outcomes from this research will therefore support evidenced training and best practice guidance for those delivering the services within our health and care systems. We will engage with the UK Parliament Menopause Taskforce group, the Women's Health Ambassador for England and their equivalent in Scotland and Wales, to ensure that evidence informs policy in developing Women's Health services. The research group will work with our PPI contributors to create a toolkit of information appropriate for women seeking information about testosterone as part of HRT to inform consultations with their health care practitioners. Through our PPI networks we will ensure that this information is easily accessible and disseminated to menopause charities, support networks and other relevant patient facing groups to make them aware of the research and its key outcomes.

19. What further funding or support will be required if this research is successful

Our trial will obtain consent from participants for linkage to NHS data (e.g. via NHS England) to establish long-term clinical outcomes. This provides a cost-efficient method for maximising the utility of the trial cohort but will require additional funding to undertake. Given the likely evolution of approaches for healthcare data linkages over the next 5 years (e.g. increased growth in Trusted Research Environments for example by ONS) the model of linkage and cost of supplementing our trial dataset is still to be determined, but the latter is likely to reduce over time. The applicant team are well placed to exploit this potential as it includes leading researchers in the use of existing healthcare data in trials. For example, RCJ led the statistical design and analysis of the follow-up of a trial cohort subsequent to a major public health trial of specialist home visiting; MR is the lead for a 5 year work programme developing training resources for optimising use of healthcare data in randomised controlled trials.

20. Barriers for further research, development, adoption and implementation

A successful trial demonstrating the clinical advantage of testosterone will only fulfil its potential if women who are likely to benefit, actually present for and are supported in accessing care. Current disparities in access to HRT highlighted above, risk being reflected in populations of women who successfully gain access to subsequently approved testosterone therapy.

While this trial correctly focuses on establishing the effectiveness and cost-effectiveness of testosterone for menopausal symptom beyond libido, it can contribute to addressing such health inequalities in three key ways. First, by seeking to maximise diversity and reach in those recruited to the trial, it will establish a solid basis for generalising findings to the broadest possible population. This will be important for messaging about treatment benefits (and/or disbenefits) to both patients and to professionals alike. Secondly, learning to be obtained from the process evaluation during the pilot stage about why patients and professional engage with the trial (e.g. exploring personal beliefs about testosterone) can inform subsequent engagement work. For example, a greater understanding of what may promote or inhibit likelihood of accessing treatment can be built into messaging about trial findings to the wide range of planned stakeholder groups. Thirdly, we will extend the insights and products from our PPI engagement activities to further inform our engagement strategy. This involves our work with the Fair Treatment for Wales and the South Riverside / Talking Trials groups. We believe this will address strategies targeted at patient and professionals alike. Across each of these three opportunities we will address issues of acceptability, accessibility and feasibility.

It is also important to consider primary care contracting frameworks and the capacity within primary care to training opportunities in menopause qualifications as key challenges to adoption and implementation of key recommendations from this research. In 2022, the FSRH carried out a survey of its Welsh members (78 responses) which found 73% of respondents did not feel they had time to undertake training in menopause care as it was unsupported as part of their job plan, and those that did were doing so in their own time, unpaid. Respondents were specifically asked if they prescribed testosterone as part of HRT. The majority (73%) said they did not currently prescribe due to lack of knowledge/training (59%), lack of evidence to support its use (14%), and lack of guidance on its safety (39%). A survey by Newson Health (Delayed diagnosis and treatment of menopause is wasting NHS appointments and resources) of 5000 women who attended their GP with symptoms relating to the menopause found that only 37% were given HRT, with 44% having to wait at least a year to receive treatment.[77] Ensuring a trained workforce, supported to deliver menopause care will be paramount to ensuring implementation of key outcomes. At this time there is no incentivisation within the GMC contract for management of the menopause. A key recommendation from the All-Party Parliamentary Group on Menopause inquiry to assess the impacts of menopause and the case for policy reform (APPG-Menopause-Inquiry-Concluding-Report-12.10.22-1.pdf) was to include Menopause as an indicator within the GP Quality and Outcomes Framework (QOF).[78] Such change would ensure that Menopause care would be sustainably delivered in primary care, by trained healthcare practitioners.

The trial will produce IP relating to the effectiveness of testosterone in the treatment of the symptoms of menopause. Thus, the outcome of the study will be highly relevant to manufacturers of testosterone gel who may wish to extend product licences and/or bring currently non-UK licenced testosterone products to the market. We are in active negotiations with Lawley Pharm in respect of free-of-charge IMP supply and conditions around access to the trial data. The terms of the IMP Supply Agreement as between Cardiff University as Sponsor of the Clinical Trial and Lawley Pharma would reflect the above and comply with NIHR terms and conditions. A final draft of the IMP Supply Agreement would be provided to the NIHR.

21. Impact

We anticipate beneficial impacts for patients, practitioners, policy, research and the broader public. If testosterone is found to be effective, the trial results have the potential to improve patient quality of life and also reduce other menopausal symptoms. This may lead to improved productivity at work, reductions in time off work, greater likelihood of being promoted at work, reductions in attendance in primary and secondary care appointments for symptoms and increases in physical activity.

Impacts for patients, practice, policy and future research include:

- Results from the research will support best practice standards and guidelines on HRT prescribing i.e. NICE, BMS
- Nationally available qualifications in menopause care will be updated to include key recommendations on testosterone as part of HRT, ensuring appropriate training, and reducing variability in prescribing practices across the country
- Health care professionals will be better equipped to discuss with their patients the evidence to support testosterone as part of HRT and menopause management
- Service development so that testosterone is delivered in the most appropriate facility, by the most appropriate professional
- Women will be informed of the role of testosterone in the peri- and post-menopausal stage of their life, with information to support a shared decision-making consultation with their health care practitioner
- Removal of the stigma that testosterone is a ‘male hormone’ and support evidenced discourse around its role in women’s health
- Support the recommendations for licensed testosterone to be available on the NHS within the current prescribing schemes i.e. free in Wales and Scotland, and prescription prepayment certificate in England, allowing equitable access to testosterone
- A comprehensive resource use measure specifically for women experiencing the menopause that can be used to inform future economic evaluations

- Greater understanding of the health, social and personal costs related to menopausal symptoms.

22. Sharing progress and findings

The decentralised trial design will involve two mechanisms for engaging trial participants about ongoing progress and then study findings. First, we will design the online portal (being used for recruitment) to act as a key communication channel for study participants. Initially this will feature accessible information supporting recruitment and then as the study opens and proceeds through to follow-up and analysis stages, incremental news and updates about trial progress. As we know that trial allocation can have an impact on attrition, we will aim to ensure sufficient informative updates that will be engaging for all. Second, we will use the Trial app to foster the relationship between participants and the trial team, an approach we are currently adopting in another trial. Our public consultation activities to date have recommended this channel of communication as being especially useful for potential participants. This benefits in particular from the secure chat function built into the app. Although the primary purpose of the Trial App is to support medication adherence, adverse event monitoring and outcome data capture, the potential to foster the relationship with the trial team and study progress is substantial, especially when used in tandem with the online hub.

The online portal will then be the hub for dissemination about study findings, including for trial participants. We will draw upon existing guidance for developing study summaries including the HRA guidance (lead applicant Robling contributed to the development of this guidance) and frameworks such as from the RECAP project.[79-80] For example, we will adopt and where necessary adapt the RECAP framework for Plain Language Summary content ('What questions the trial set out to answer?', 'What did the trial find?', 'What effect have the trial results had and how should they change NHS/treatment?', 'How can I find out more?') in a co-production process with our research partners. We will work with our formal PPI partners groups (Fair Treatment for Women Wales and South Riverside Community Development Centre) to develop messages and formats for dissemination from the trial. This is an approach we have developed over a large number of diverse studies. These development meetings aim to have a particular focus on optimal and inclusive communication. This is likely to draw from a range of visual approaches (e.g. brief talking head videos, infographics) commonly used on our other trials. We would also be keen to support the patient voice in such materials (for example, by supporting our PPI co-applicants in voicing summaries). In designing our approach to providing feedback we will adhere to best practice in terms of informing participants about their options for receipt of study findings, including the opportunity to update their preferences over time.

23. Project timetable

We plan a 51-month project with a start date of August 2024 and end date of 31st October 2028

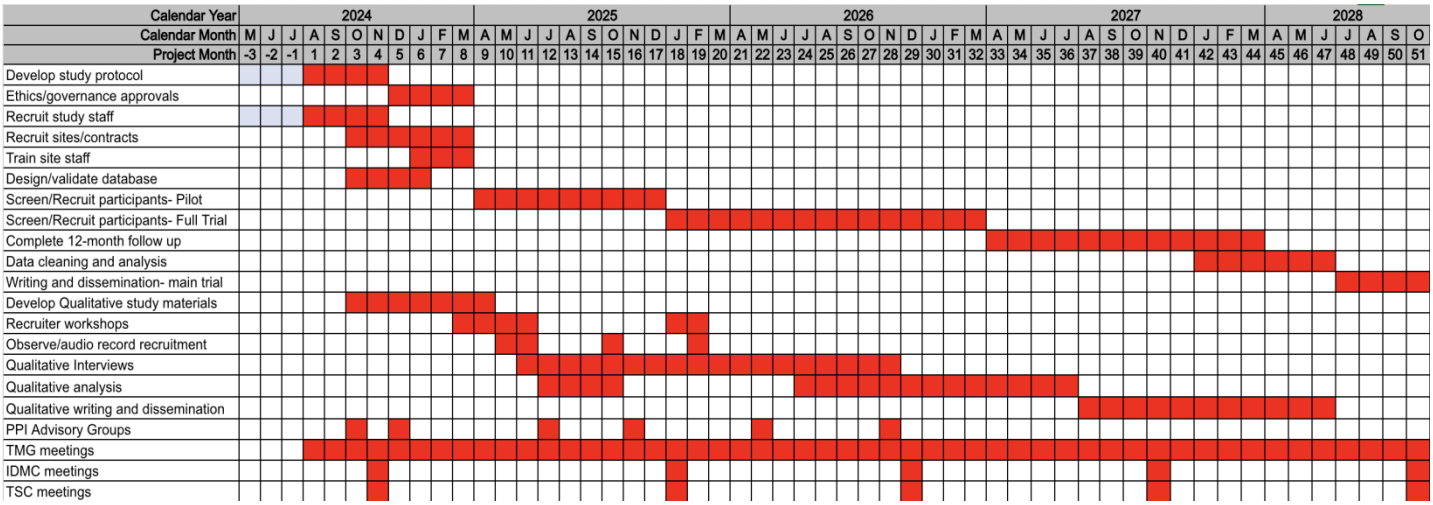
Table: Project timetable

Project month	Phase	Milestone
0-8	Set-up	Contracts, Finalise protocol, Ethics & MHRA submission, design data collection tools, site set-up and training.
9-14	Pilot recruitment	Internal pilot recruitment
15-17	Progression criteria	Assessment of progression criteria (recruitment continues during this period)
18-32	Stage 2 Recruitment	Stage 2 recruitment, test data linkage
33-44	Follow-up	Complete 12-month follow-up
42-51	Analysis and write up	Data cleaning, statistical analysis, prepare report, draft paper, stakeholder event

Longer-term follow-up via (i) patient survey / assessments and (ii) routine data up to 5 years (pending

further funding) would mean availability of results by 102 and 107 months respectively.

Gantt chart



24. Project management

The trial will be fully coordinated by Cardiff University Centre for Trials Research (CTR), a UKCRC registered Clinical Trials Unit (UKCRC registration ID = 63) and will be conducted according to CTR Standard Operating Procedures (SOPs), including those for data management, serious adverse event reporting, maintaining study documentation according to GCP, archiving and data sharing. Study specific SOPs will be developed as required. The trial manager and research nurse will be responsible for day-to-day running and coordination of the trial and will be accountable to the Chief Investigators (CIs). The CIs, trial manager, research nurse, statistician, administrator and other directly employed staff (Project Team (PT)) will meet weekly and take responsibility for the day-to-day conduct of the study. The PT will refer any key management decisions to the Trial Management Group (TMG).

The TMG (all co-applicants and PT members, including PPI co-applicants) will meet monthly to discuss key management issues and monitor milestones. TMG members will be required to sign up to the remit and conditions set out in the TMG Charter. With our public research partner co-applicants we have designed an approach which ensures that lay input into monthly TMG meetings is feasible while not expecting that each will attend every meeting. Arrangements for ensuring we support continuity of engagement is described above.

A Trial Steering Committee (TSC), consisting of an independent chair, and three other independent members including an independent PPI representative will meet four/five times during the trial to provide overall supervision for the trial. The frequency and timings of the meetings will be reviewed by the TSC and adjusted if required to enable timely oversight and critical input to the trial team. The two Co-CIs, trial manager and trial statistician will attend as observers. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter (developed from the CTR's standard template).

Similarly, an Independent Data Monitoring Committee (IDMC), consisting of an independent chair, and three other independent members, including one lay representative, will meet throughout the trial to review safety and other relevant trial data. Members of the IDMC will also be required to sign up to the remit and conditions as set out in their charter.

Our three public research partners will participate as members of the TMG, as described above. We will appoint separate lay representatives to the external governance committees (TSC, IDMC) to ensure independence from the trial management team.

25. Ethics

We have made early contact with our research governance team to discuss both sponsorship and contracting requirements for the study. A letter of sponsorship in principle is appended to the application. The trial will be conducted according to Good Clinical Practice (GCP) and the applicable data protection regulations. This project will require NHS REC, Health Research Authority and MHRA permissions, and also permission from each participating NHS organisation. The project is a clinical trial of an investigational medicinal product (IMP) and will require a CTA granted by the MHRA.
This Detailed Research Plan (DRP) is not an ethically approved document and precedes the submission of an ethically approved protocol.

26. Funding Statement

This study is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme (NIHR159538). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

27. Project expertise

MR/HM will co-lead the trial. HM has extensive clinical experience of delivering specialist menopause care, advising policy on menopause care and support, and is a senior UK leader in training health professionals in women's health. HM was awarded the prestigious Health and Care Research Wales Research Time Award (2023-26) and is the Theme 1 (Menstrual Health and Menopause) co-lead for the NIHR Reproductive Health Policy Research Unit (led by University College London, 2023-28). HM has been conferred Honorary Professor, Aberystwyth University, in recognition of her contribution to the field of Women's Health, and is the Vice President of the Faculty of Sexual and Reproductive Healthcare (FSRH) supporting 14000 healthcare professionals in SRH. MR has extensive experience in conducting large multicentre policy trials at the Centre for Trials Research (CTR) and has a focus on underserved communities, public involvement and routine data. MR has a substantial track record in mentoring clinical and methodological co-/lead investigators at senior grade in leading large clinical research projects (including several funded by NIHR and UKRI). In this study, MR will provide mentoring support to HM in her role of co-lead investigator.

The CTR team includes a trial manager (JL) who has significant experience in the design, management and conduct of clinical trials involving IMPs, senior statistician (RCJ), and experienced qualitative researchers (SC, DW) as well as data managers, information services, and PPI experts (DW). SC has led the process evaluations for several large trials and has substantial experience in women's health research. She was formally Director of the Research Design and Conduct Service for South East Wales and has considerable experience in supporting the development of studies being submitted to NIHR programmes. DW has extensive experience in public involvement through previous women's health projects and currently leads public involvement as academic lead in the Health and Care Research Wales Evidence Centre. Our three public partners (LM, LN, SM) are critical in developing our equitable recruitment strategy and plans. Our partners each have different lived experiences of menopause and HRT, ranging from surgical menopause, significant symptoms despite HRT, as well as testosterone use. Health economics expertise will be provided by KC, DF (Swansea Centre for Health Economics) who have significant experience in within-trial economic evaluations and development of resource use measures. Clinical skills: In addition to HM, co-applicants include clinicians from NHS primary care (KHu), and private care (LN, DR, KN), with extensive experience in caring for menopausal women. KHo and NI have experience in delivering decentralised trials during COVID – specifically the PANORAMIC Trial. Professor Hood is a professor of trials and Dean of Research and Innovation in the College of Biomedical and Life Sciences, Cardiff University and senior statistician with extensive experience of designing and delivering primary care trials, including the landmark PANORAMIC trial.

Our key study collaborators are Dr Louise Newson and colleagues from Newson Health Menopause and Wellbeing Centre. The Centre is the largest in the UK and possibly worldwide and brings together 118 clinicians with approximately 4000 consultations per month. In partnership with co-lead investigator Munro this provides extensive expertise in the study population, in testosterone therapy, its management and evaluation. Clinical input from the Centre will contribute to recruitment and prescription oversight,

safety monitoring and assessment. Along with lead applicant Munro, this collaboration will be pivotal in developing the trial's policy and practice engagement strategy utilising their extensive respective networks.

CTU involvement: CTR is a large CTU (UKCRC registration ID: 63) and has supported trial development from inception. CTR will fully co-ordinate the trial, governance/approvals, data collection and management, analysis, publication, data archiving and sharing. CTR have extensive expertise and track record in successfully collaborating with other HEIs, including the health economics team, to deliver clinical and cost-effectiveness trials. CTR is co-located with PRIME, Cardiff University which is a research centre focusing on primary and emergency care. Co-applicants Hughes and Williams are based in PRIME and provide substantial networking routes and intelligence for potential primary care research sites in Wales and England.

28. Success criteria and barriers to proposed work

Prior to set-up we will complete a full risk assessment using CTR's standard template which takes a full study lifecycle approach and incorporates a formal Data Protection Impact Assessment (DPIA). In developing this application, we have identified a number of potential risks and approaches to mitigation:

Study Set-up: We are aware of the timescales involved with set-up of Clinical Trials of IMPs. We will rely on our established Standard Operating Procedures and existing contract templates to rapidly develop the trial protocol with support from the TMG. We have actively engaged with Lawley pharma regarding sourcing of both active and placebo drug free of charge, and with our preferred IMP manufacturer who will label, package and distribute to patients. To ensure expediency with contracting we have opted to include dedicated time for a contracts officer and research governance administrator.

Recruitment: Timely and sufficient recruitment is a key risk to many RCTs. We have built in a pilot stage to allow testing (and refinement as necessary) of our recruitment strategy, with clear progression thresholds (described above). We have adapted the blended model of trial recruitment we successfully used in the PANORAMIC trial (co-applicants Hood, Ivins) which enables patients to self-refer as well as recruiting via more conventional routes (primary care hubs) while ensuring appropriate clinical oversight. We have worked with PPI partners to further develop our approach (which will continue into the set-up phase) including for how to ensure recruitment reaches patient populations who may be traditionally excluded from research. Strategies identified so far through such consultation include use of social media, targeted Google adverts, heterogenous community-based marketing of the trial (e.g. leaflets in pharmacies, social hubs, primary care venues). We will use targeted systematic process evaluation interviews in the pilot phase to understand the strengths and opportunities for improvement of our recruitment strategy.

Adherence with IMP, completeness of patient-reported outcome data and attrition: We appreciate the challenges of adherence for trials of a long duration in respect of adherence to treatment, completion of outcome measures and attrition. For example, as summarised in Islam and colleagues' systematic review, previous trials of testosterone have suffered from attrition of control group participants.[13] We will mitigate these risk through a) consultation with our PPI representatives around the perceived burdens on patients, constructing elements of the data collection to be as minimal as possible, and b) investment in a patient-facing Trial App which will provide daily reminders to the patients and also provide oversight for the CTR and RNs, as well as allow participants to conveniently report outcome measures without the need for paper forms or logging into a computer. Suggestions from our existing PPI consultations emphasise the need to provide accessible platforms for data collection (e.g. mobile devices), and recommendations regarding choice of presentation format for outcome measures.

Impact, engagement and value for money: A successful trial will inform policy, practice and public stakeholder alike regardless of findings (e.g. even if the intervention is found not to benefit patients). We will develop an engagement plan (alongside our dissemination strategy) and use the substantial networks offered via our team (including our collaborating partners, Newson and colleagues) to ensure findings have maximum impact. We will design the study to ensure data are shareable by design (i.e. that governance requirements for archiving and data sharing are addressed in initial study design) and can be updated with routine data over time thereby maximising value for public money.