TRIAL PROTOCOL

Oxy**B**utynin or venlafaxine for hot f**lush**es in women who cannot or choose not to use hormone replacement therapy: randomised trial and economic evaluation

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CI and Sponsor Approval 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 Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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 and serious breaches of GCP from the trial as planned in this protocol will be explained.

This protocol has been approved by:	
Trial Name:	Oxybutynin or venlafaxine for hot flushes in women who cannot or choose not to use hormone replacement therapy: randomised trial and economic evaluation
CI Name:	Professor Melanie Davies
Trial Role:	Chief Investigator
Signature and date:	
Date:	_____- _____-20 _____(dd-mmm-yyyy)

Sponsor approval	
Sponsor representative name:	University College London
Signature and date:	
Date:	_____- _____-20 _____(dd/mmm/yyyy)
Sponsor statement: Where University College London takes on the Sponsor role for oversight of protocol development, signing of the C**WOW** form by the Sponsor will serve as confirmation of approval of this protocol.	

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Protocol development and sign off

Lead and Co Applicants	
Name:	Affiliation and role:

Amendment number	Protocol version number	Type of amendment	Summary of amendment

Abbreviations

Abbreviation	Term
AE	Adverse Event
AR	Adverse Reaction
BNF	British National Formulary
CA	Competent Authority
CI	Chief Investigator
CACE	Complier Average Causal Effect
CPAS	Cancer Chemotherapy and Pharmacy Advisory Service
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CUA	Cost Utility Analysis
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EQ-5D-5L	Health related, quality of life questionnaire.
GCP	Good Clinical Practice
GP	General Practitioner
HFRDIS	Hot Flash Related Daily Interference Scale
IB	Investigator's Brochure
ICF	Informed Consent Form
ICECAP-A	Capacity and wellbeing
ICIQ-OAB	International Consultation on Incontinence Questionnaire Overactive Bladder
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MENQOL-I	Menopause-Specific Quality of Life Questionnaire- Intervention
MHRA	Medicines and Healthcare Products Regulatory Agency

NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Patient Information Sheet
PSQI	Pittsburgh Sleep Quality Index
QA	Quality Assurance
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
RSI	Relevant Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Products Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
WPAI	Work Productivity and Activity Impairment Questionnaire- general

Trial Summary

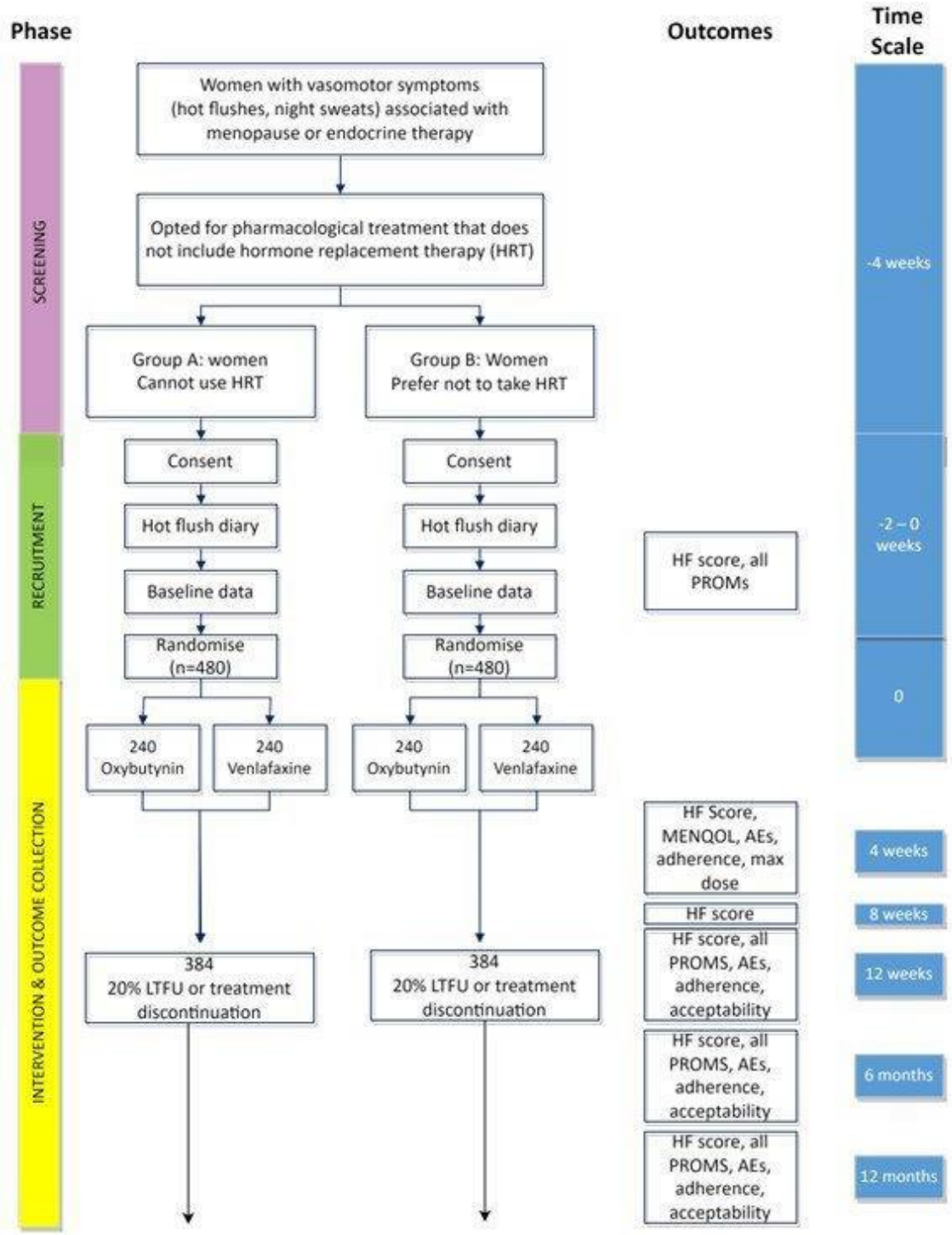
Trial Title	Oxybutynin or venlafaxine for hot flushes in women who cannot, or choose not to use hormone replacement therapy: randomised trial and economic evaluation
Internal ref. no. (or short title)	BLUSH trial
Clinical Phase	Category B – clinical phase IV
Trial Design	Multi-centre, randomised, open, parallel, superiority trial, within 2 populations, with equal allocation (1:1) to receive either oxybutynin or venlafaxine.
Trial Participant Population	Women with menopausal vasomotor symptoms (VMS) who are either unable to take (Group A) or prefer not to use (Group B) HRT.
Objectives	**Aim** To compare the relative clinical and cost-effectiveness of extended-release oxybutynin compared to low-dose modified-release venlafaxine in controlling VMS after 3 months of treatment, separately, in two populations of women with menopausal VMS: (a) those that are unable to take HRT, and (b) those who prefer not to use HRT. **Primary Objective** To compare the VMS, measured by weekly average Hot Flush (HF) score, at week 12, separately, in the two populations of women with menopausal VMS, after 3 months of treatment with extended-release oxybutynin or low-dose modified-release venlafaxine. **Secondary Objectives** • Compare the relative effectiveness of extended-release oxybutynin compared to low-dose modified-release venlafaxine in controlling VMS at week 4, week 8, and at 6- and 12-months post-randomisation. • Compare treatment discontinuation at 12 months. • Evaluate the cost-effectiveness of oxybutynin, compared to venlafaxine. • Determine the tolerability (continuation of allocated treatments) and participant-reported acceptability of oxybutynin and venlafaxine amongst women with VMS. • Assess the effectiveness of the trial treatments on quality of life, sleep quality, work and social productivity, mood, and bladder function.

Key Eligibility Criteria	Inclusion Criteria **Group A (HRT contraindicated)** • Women or transmen (who are not taking testosterone) for whom HRT is contraindicated, e.g., women with breast cancer treated with adjuvant endocrine therapy. • ≥5 moderate/severe menopausal hot flushes daily average, collected over a week, prior to randomisation. • Must provide written/electronic informed consent. **Group B (prefer not to use HRT)** • Diagnosis of menopause or perimenopause including transmen (who are not taking testosterone) • Age > 45 years at randomisation • ≥5 moderate/severe menopausal hot flushes daily average, collected over a week, prior to randomisation. • Not intending to use HRT within 12 months. • Must provide written/electronic informed consent.
	Exclusion Criteria **Group A (HRT contraindicated)** • Age >65 years • Contraindications to either trial treatment • Pregnant or planning on becoming pregnant or breastfeeding • Breast Cancer patients with advanced stage cancer • Taking other pharmacological treatment for VMS • Transwomen **Group B (prefer not to use HRT)** • Age >65 years • Contraindications to either trial treatment • Pregnant or planning on becoming pregnant or breastfeeding • Transwomen • Women already on HRT, or using hormonal treatment for gynaecological conditions or contraception* *Women already on HRT, or other pharmacological treatments for VMS, or using treatment for gynaecological conditions or contraception, who want non-hormonal

	treatment, are eligible if willing to stop their treatment for a ≥4-week washout period before entering the pre-randomisation eligibility screening phase.
Outcome measures	**Primary** The average Hot Flush (HF) score (frequency x severity) over one week, at week 12. **Secondary** All measured at baseline, week 12, and 6 and 12 months and additional stated timepoints: • Average HF score (also in weeks 4 and 8) • Frequency and severity (individually) of hot flushes/night sweats (also in weeks 4 and 8) • At least 50% reduction in the hot flush score from baseline • Individual domains and total score of MENQOL-I (also at week 4) • Hot Flush Related Daily Interference Scale (HFRDIS) (also at week 4) • Health related quality of life (EQ-5D-5L) and capability-wellbeing (ICECAP-A) • Participant acceptability and satisfaction with treatment (also at week 4) • Participant-reported global impression of change on VMS and overall health. • Urinary urgency, frequency and incontinence (ICIQ-OAB) • Sleep quality (PSQI) • Work Productivity and Activity Impairment Questionnaire- general (WPAI) • Pregnancy and pregnancy outcomes • Common known side-effects of each treatment. • Change or cessation of treatment, and for breast cancer population, continuation of endocrine therapy. • Resource Use
Planned Sample Size	Sample size calculation has been done separately for each participant group. 382 participants for analysis are required to detect a 4-point mean difference in HF Score (SD=12) at 12 weeks, with 90% power, 5% 2-sided significance and 1:1 allocation. To allow for ~20% loss to follow-up and treatment discontinuation, 480 participants will be recruited in each participant group (960 participants in total).
Treatment duration	12 months

Follow up duration	12 months concurrently
Recruitment duration	30 months
Randomisation and blinding	Eligible women who consent will be individually randomised on a 1:1 ratio, separately for the two participant groups, using an online randomisation system developed and maintained by the NCTU, minimised in a secure online algorithm by recruitment site, body mass index, and use of anti-oestrogens (group A) or recent hormone (HRT) use (group B), and retaining a random element. Access to the system will be granted by the NCTU in accordance with the roles delegated by the Principal Investigator on the Site Delegation Log. Blinding of investigators and participants is not practical.
Investigational Medicinal Product(s) And/or Intervention/Control	Oxybutynin: Extended release, oral, starting daily dose 5mg, max 15 mg Venlafaxine: Modified release, oral, starting daily dose 37.5mg, max 75mg
Statistical methods	Analyses will be performed separately for the two participant groups. Analysis of the primary outcome measure (HF score at 12 weeks) will be performed using a mixed effects model using all available follow-up data up to 12 weeks (weeks 4,8 and 12), adjusted for the baseline HF scores and minimisation variables, with recruiting site entered as a random effect. The model will include a treatment by time interaction to obtain the estimates of treatment effect at each follow-up time, with week 12 being the primary treatment comparison. For primary analysis, participants will be analysed according to randomised group regardless of treatment actually received. Between-group comparison of secondary outcomes will use an appropriate regression for the outcome (linear for continuous outcomes, logistic for binary, survival for time-to-event), adjusted for the minimisation variables and baseline outcome measure for continuous variables if available. For repeated measures, appropriate mixed-effect models for the outcome, adjusted for the minimisation variables, will be used.
Health Economics	From the perspectives of the NHS/social care, and of the wider society, cost-effectiveness will be evaluated using cost-consequence (including impact on individuals' capability and productivity) and cost-utility (incremental costs per QALY) analyses.

Trial Flow Chart



1. Background and Rationale

1.1. Background

Most menopausal women experience vasomotor symptoms (VMS), which include hot flushes and night sweats, lasting several years(1). Menopausal transition can cause difficulties for some women at work,(2)with hot flushes particularly difficult to manage and associated with an intention to stop working(3). Evidence for the menopause having an economic impact on women remains inconclusive, and no data on the personal economic margin costs for UK women exists(4). NICE guidelines do not consider personal and societal costs in their evaluations of treatments.

Hormone replacement therapy (HRT) is the most effective treatment for VMS and is recommended by the National Institute for Health and Care Excellence (NICE)(5). However, HRT is contra-indicated for some women, or they or their GP may be concerned about potential harms.(6, 7) VMS are a particular problem for women undergoing adjuvant endocrine therapy for breast cancer, HRT is contraindicated and there are limited options for their treatment. HRT is also contraindicated for breast cancer survivors because of an increased recurrence risk (8).

Early discontinuation of adjuvant endocrine therapy (tamoxifen or aromatase inhibitors) amongst breast cancer survivors is as high as 50% (9) and early discontinuation has been identified as a risk factor for recurrence and breast cancer death. Causes for discontinuation, which are multifactorial, include treatment-related VMS (10). Whilst there are no proven interventions that reduce the rate of discontinuation, the successful management of difficult side effects including VMS is likely to encourage women to persist with treatment.

Black women report more significant menopausal VMS (11) and a longer duration of symptoms than white women(12). Data on use of HRT and other pharmaceutical treatments across ethnicities is limited, but there is likely an unmet need for non-hormonal treatments. Socioeconomic status also influences the use of HRT, which is 18% lower in most deprived quintile of the population, compared with the highest (13), with such inequality suggesting another dimension of unmet need.

Use of complementary and alternative medicines is a further indicator of demand for non-hormonal treatment of VMS. A quarter of UK postmenopausal women in a large screening study reported trying alternatives, with higher levels of education, black ethnicity and previous use of HRT or oral

contraceptive pill being positive predictors of complementary/ alternative/ non-pharmacological interventions (14).

There is no standard non-hormonal treatment for VMS, as there is insufficient evidence on comparative efficacy (5, 15). Recommendations by NICE and other guidelines include selective serotonin reuptake inhibitors (SSRI), serotonin–norepinephrine reuptake inhibitors (SNRI), gabapentin and clonidine(16). All are less effective than HRT and are associated with side-effects(15, 17). An infrequently used treatment is oxybutynin, an antimuscarinic, anticholinergic agent licenced to treat urinary symptoms.

1.2. Existing Evidence

There is evidence from one randomised trial of oxybutynin of improvements in work, social and leisure activities from its use for VMS(18), but this is derived from single questions in one outcome measure(19). A more comprehensive assessment of capability, work productivity and personal costs associated with treatments for VMS is required.

Two RCTs, both placebo-controlled, of oxybutynin for the treatment of VMS were found in a systematic literature search. A phase 2, multicentre, RCT (148 women) with ≥7 hot flushes/day, used 15mg oxybutynin extended release (ER) for 12 weeks [20]. This trial found that flushes reduced in frequency from 13.24/day (standard deviation [SD] 5.54) by a mean of 9.61, and the HF Score (on a 3-point scale of severity) reduced from 32.51 (SD 13.03) by 25.02, both statistically significant reductions compared with placebo. The discontinuation rate was 6.8% in participants given oxybutynin. A further trial of 150 women with a minimum of 28 flushes/ week, two-thirds of whom were taking tamoxifen or aromatase inhibitors, compared standard oxybutynin at 2.5mg twice a day (BD) and 5mg BD doses, to placebo, over 6 weeks(18). (At baseline, flushes averaged ~9.1/day with an average reduction in frequency of 4.8 (SD 3.2) on 2.5mg BD and 7.5 (SD 6.6) on 5mg BD oxybutynin, both significant. The composite HF score (4-point scale of severity) reduced from a mean of 18.2 by 16.9 points (SD 15.6) on 5mg BD, 10.6 (SD 7.7) on 2.5 mg BD and 5.7 (SD 10.2) on placebo, both oxybutynin doses reducing the scores significantly more than placebo.

An RCT with 339 women with >2 hot flushes/ day, compared low-dose estradiol with up to 75mg venlafaxine modified release (MR) and placebo over 8 weeks (21). The average daily flushes reduced from 8.2 to 4.3 in the venlafaxine group, 15.2% less than low-dose estradiol. Only 5 out of 96 women discontinued venlafaxine due to side-effects(21). A further 4-arm RCT in 191 women with a history of

breast cancer compared placebo (n=56), venlafaxine MR 37.5mg (n=56), venlafaxine MR 75mg (n=55) and venlafaxine MR 150mg (n=54)(22). Reduction in HF scores from baseline at 4 weeks were 27% (95% CI 11–34), 37% (95% CI 26–54), 61% (95% CI 50–68), and 61% (95% CI 48–75) respectively. The frequency of side-effects including decreased appetite, nausea, constipation, and mouth dryness increased with dose, significantly so with respect to mouth dryness between 75mg and 150mg.

1.3. Trial Rationale and Design Justification

The BLUSH trial aims to answer whether Oxybutynin is more effective and better value for money than venlafaxine at controlling VMS in two groups of women: those with contraindications to HRT (Group A) and those who prefer not to use HRT (Group B).

1.3.1. Justification for participant population

Participants will fall into two distinct groups:

(A) those in whom HRT is contraindicated, which includes women who have a current or past history of breast cancer and other oestrogen-sensitive cancers, or venous or arterial thromboembolic disease.

(B) those who prefer not to take HRT, including women who are concerned about potential risks of HRT, for example those with a family history of cancer. Women who have previously used HRT will not be excluded.

In group B, only women over the age of 45 at randomisation will be included, because below that age there are potential health benefits to taking HRT. In both groups women over the age of 65 at randomisation will be excluded due to concerns about a possible effect of oxybutynin on cognition in older women.

The US Food and Drug Administration (FDA) guidance suggests a minimum of 7 to 8 moderate to severe hot flushes per day, or 50 to 60 per week, as the threshold for the treatment of moderate to severe menopausal VMS (23) whilst the European Medicine Agency (EMA) suggests a treatment threshold of at least 5 moderate to severe daily flushes (24). Studies in people with breast cancer tended to use an inclusion criterion of 1-4 hot flushes on average per day. To be consistent, to include participants with at least moderate symptoms, but acknowledging that thresholds are arbitrary, the BLUSH trial has chosen a minimum of 5 hot flushes on average per day.

1.3.2. Justification for design

The trial design is an open label pragmatic design to make the trial attractive and convenient to both participants and site staff (clinicians, research nurses). Although published evidence is lacking, it is anticipated that the two groups of women (those whom HRT is contraindicated (Group A) and those who prefer not to take HRT (Group B)) may not respond to the trial treatments in the same way and to the same extent, and acceptability may differ. To run one trial and treat these two populations as sub-groups (with an interaction analysis to determine sub-group effects), would require substantially more participants within each subgroup than if two trials were run in parallel. For example, to detect with the same power an interaction of the same magnitude as the main effects, a fourfold increase in sample size would be required(25). Therefore, the latter approach has been chosen. This would also enable a clearer interpretation for each group. Running the two groups in parallel, under a single master protocol, will be more efficient than sequentially, as many procedures will be common to both, and recruitment and retention strategies can be shared. Finally, running the two groups in parallel, under a master protocol, allows us to make separate decisions on trial discontinuation for effect, harm, futility, or poor recruitment within each individual trial.

Participants, site staff and principal investigators will not be blinded, for the following reasons: to represent real world effectiveness data, the onset of symptom relief differs between the two treatments (18, 21), it is unlikely women will report their hot flushes differently due to their knowledge of their treatment and blinding would require a dummy double design and a complicated dose-escalation schedule, prone to error.

1.3.3. Choice of treatments

Oxybutynin formulations include oral (immediate and extended release) and transdermal patch. All are licensed for urinary frequency and urgency, from which all cited safety data is obtained(26). Oral doses are titrated up to a maximum of 20mg/ day over 4 weeks, whereas the patch delivers 3.9mg/day. Although diarrhoea is common for all preparations, dry mouth is much more frequent for immediate release users (94%) than extended release and patch users (29% and 32%)(27, 28). Amongst patch users, 8% had erythema and 18% pruritis (27). Therefore, to try and reduce side effects the extended-release oral formulation has been selected for this trial.

Equivalent daily doses of 5mg, 10mg, and 15mg oxybutynin have reported efficacy for treatment of hot flushes. Direct comparison is not possible due to variation in HF frequency at baseline. There is

clear evidence of greater efficacy at 10mg and 15mg than 5mg. However, the incidence of anticholinergic side-effects is greater at higher doses (27, 28). Therefore, a maximum dose of 15mg once a day has been set. Treatment will be initiated at 5mg once daily for a week, increased by 5mg daily after one and two weeks, if tolerated. This regimen should maximise efficacy, improve tolerability and trial continuation and is in keeping with the British National Formulary (BNF) dosing recommendation.

The comparator, the SNRI venlafaxine, was selected as it is the single most commonly prescribed anti-depressant for VSM treatment, and also has the most evidence for its effectiveness (9). Some SSRIs are contraindicated in women taking the endocrine therapy tamoxifen for breast cancer treatment, because of treatment interaction. Specifically, there is evidence that they accelerate tamoxifen metabolism, thereby potentially reducing its efficacy (21, 29).

Venlafaxine is prescribed as a once daily modified-release (MR) tablet. Previously published studies showed maximum efficacy with venlafaxine MR 75mg once daily. At higher doses greater side-effects are seen (21, 30). Therefore, a maximum dose of 75mg once a day will be used. The treatment will be prescribed as 37.5 mg once daily for a week, being increased to 75 mg once daily, if tolerated**.** This regimen should maximise efficacy, improve tolerability and trial continuation and is in keeping with the BNF.

2. Aims, Objectives and Outcome Measures

2.1. Aims

To determine whether oxybutynin is more effective and better value for money than venlafaxine at controlling menopausal VMS in the short and medium term, in two groups of women: those with contraindications to HRT (Group A) and those who prefer not to use HRT (Group B).

2.2. Primary Objectives and Outcome Measures

Table 1 Primary objective and outcome measure

Objective	Outcome Measure	Time Point	Method of Collection
To determine whether oxybutynin is more effective than	Average Hot flush (HF) score over one week at 12 weeks.	12 weeks post-randomisation	Online diary via the following options; an app, text, email, or

venlafaxine at controlling menopausal VMS after 12 weeks of treatment, in two groups of women: those with contraindications to HRT (Group A) and those who prefer not to use HRT (Group B)	The HF score combines frequency and severity into one score. Mild, moderate, and severe hot flushes are scored 1,2 and 3, respectively, multiplied by the number of flushes reported per day and summed to provide one score.		paper form. Any missing data may be collected by site staff.

Frequency and severity of hot flushes will be reported and used to calculate the HF Score, a composite of frequency and severity of hot flush/night sweats, as the primary outcome (31). Accepted definitions of severity (23) are shown in Table 2. Hot flushes will be captured daily over a period of a week, the frequency multiplied by severity and the daily score aggregated so that each data point comprises a weekly mean. At least 4 days of data in a 7-day window, up to each timepoint, will be required for a valid mean HF score, to allow for some inevitable missing data and the burden of daily reporting.

Table 2 Hot Flush Score definitions and scoring

Grade	Definition	Score
Mild	sensation of heat without sweating	1
Moderate	sensation of heat with sweating, able to continue activity	2
Severe	sensation of heat with sweating, causing cessation of activity, night sweats that cause awakening	3

2.3. Secondary Objectives and Outcome Measures

A core outcome set for VMS has now been developed and includes six outcomes (32) : 1) frequency of VMS, 2) severity of VMS, 3) distress, bother or interference caused by VMS, 4) impact on sleep, 5) satisfaction with treatment, and 6) side-effects of treatment. All of these will be reported.

Table 3 Secondary objectives and outcomes measures

Objective	Outcome Measure	Time Point	Method of Collection
To compare the relative clinical effectiveness of oxybutynin compared to venlafaxine, on a range of secondary outcomes at, 4 ,8, 12 weeks, 6 and 12 months post-randomisation.	Average HF score. The frequency and severity (individually) of hot flushes/night sweats	Baseline, week 4, week 8, week 12, 6 and 12 months post randomisation	Online weekly diary via an app, text or email, or paper form. Any missing data may be collected by research staff at week 12 during clinic appointments.
	At least 50% reduction in the HF score from baseline		
To evaluate the cost-effectiveness of oxybutynin, compared to venlafaxine.	Health related quality of life using EQ-5D-5L and capability-wellbeing using ICECAP-A, WPAI	Baseline, week 12, 6 and 12 months.	App, text or email, or paper form. Any missing data may be collected by research staff at week 12 during clinic appointments.
	Resource Use	Week 12, 6 and 12 months	
To determine the tolerability (continuation of allocated treatment) and participant reported acceptability of oxybutynin and venlafaxine amongst women with VMS.	Change or cessation of treatment, and for cancer population, continuation of anti-oestrogen therapy. Commonly known side effects of each treatment class.	Week 4, week 8, week 12, 6 and 12 months	
To assess the effectiveness of treatments on quality of life, sleep quality, work and social	• WPAI - general • Condition-specific quality of life, measured by individual domains and total score of the	Baseline, Week 12, 6 and 12 months.	

productivity, mood, and bladder function.	MENQOL-I questionnaire (also at week 4) (33) • The HFRDIS (also at week 4) • Health related quality of life using EQ-5D-5L and capability-wellbeing using ICECAP-A • Participant acceptability and satisfaction with treatment, also at week 4 • Patient reported global impression (PGI-C) of change on VMS and overall health. • Urinary urgency, frequency and incontinence, using ICIQ-OAB(34) • Sleep quality, using PSQI(35)		

The MENQOL (36) was used by 12 of the 15 trials that collected quality of life related outcomes in the review of HFs (31). This outcome measure will be used to provide a broad woman- centred assessment, acknowledging there is a small degree of overlap with the HF score, PSQI and the ICIQ-OAB. The HFRDI will also be used as it is a measure for assessing the impact, specifically of hot flushes, on daily activities (19). There are many measures of sleep quality, with 31 different self-reported tools being used in 42 RCTs of MHT.(37) The Pittsburgh Sleep Quality Index (PSQI) has been chosen, as it encompasses all seven sleep domains and is the most frequently used in HRT trials (35).

Oxybutynin is primarily used for the treatment of overactive bladder. To collect urinary symptoms, the International Consultation on Incontinence Questionnaire (ICIQ) Overactive Bladder module will be used, which captures frequency and bother of four symptoms(34).

3. Trial Design and Setting

3.1. Trial Design

Multi-centre, randomised, open, parallel, superiority trial with internal pilot, and a parallel economic evaluation. To be adequately powered to detect clinically meaningful effects in both of the two populations, two RCTs in parallel under a single master protocol will be conducted. This design will avoid the statistical and methodological challenges posed by subgroup analyses in a single trial.

3.2. Trial Setting

Potentially eligible participants are expected to be identified via the following routes:

- Participants attending specialist cancer and menopause clinics in the UK will be approached by trained members of the site research team about participating in the trial.
- Clinical database searches in the UK:
    - Hospital databases/clinic records will be searched by members of the clinical care team to identify participants ahead of their scheduled clinic appointments who have menopausal VMS and who may be eligible.
    - GP databases and oncology clinic records will be searched by practice staff using relevant clinical codes.
- Self-referral (UK): Participants may make contact with the research team as a result of trial advertising and promotional material (e.g. posters, leaflets and social media).
- Additional primary or secondary care settings may be set up as Participant Identification Centres (PICs) if required during the course of the trial.

There will be two main recruiting hubs which will set up dedicated research clinics. With the support of the research fellow (trial clinician) and team, it is expected that these hubs will contribute 40% of the total recruitment. It is expected that Group A will be easier to set-up and initially recruit to, as it follows a more traditional trial recruitment model mainly via hospital clinics, so recruitment for each trial will be monitored separately.

3.3. Type of Trial by Risk Category

This trial has been categorised as a Type B risk category. Both treatments have a marketing authorisation in the UK, but their use in this trial is outside the licenced indications listed in the

Summary of Product Characteristics. Oxybutynin is not recommended for VMS in any clinical guidelines but is used off licence in practice. Venlafaxine is recommended as treatment for menopausal symptoms in women with breast cancer in clinical guidelines and its use is mentioned in the BNF (26).

4. Eligibility

4.1. Inclusion Criteria

Group A (HRT contraindicated)

- Women or transmen (who are not taking testosterone) for whom HRT is contraindicated, e.g., women with breast cancer treated with adjuvant endocrine therapy.
- ≥5 moderate/ severe menopausal hot flushes daily average, collected over a week, prior to randomisation.
- Written/electronic informed consent.

Group B (prefer not to use HRT)

- Diagnosis of menopause or perimenopause, including transmen (who are not taking testosterone)
- Age > 45 years
- ≥5 moderate/ severe menopausal hot flushes daily average, collected over a week, prior to randomisation.
- Not intending to use HRT within 12 months.
- Written/electronic informed consent.

4.2. Exclusion Criteria

Group A (HRT contraindicated)

- Age >65 years
- Contraindications to either trial treatment
- Pregnant or planning on becoming pregnant or breastfeeding
- Breast Cancer patients with advanced stage cancer
- Transwomen

- Taking other pharmacological treatment for VMS*

Group B (prefer not to use HRT)

- Age >65 years
- Contraindications to either trial treatment
- Pregnant or planning on becoming pregnant or breastfeeding
- Transwomen
- Women already on HRT or using hormonal treatment for gynaecological conditions or contraception*.

*Women already on HRT, or other pharmacological treatments for VMS, or who are using treatment for gynaecological conditions or contraception, who want non-hormonal treatment, are eligible if willing to stop their treatment for a ≥4-week washout period before entering the pre-randomisation eligibility screening phase. Women using a levonorgestrel-releasing intrauterine system (IUS), will not have to complete a washout or stop this treatment while in the trial, due to minimal systemic circulation of levonorgestrel.

4.3. Recruitment

It is anticipated that around 22 sites will be required, either gynaecology, oncology or multi-disciplinary clinics and recruitment will last 2.5 years. There will be virtual clinics at two recruitment hubs to remotely recruit participants who respond via the trial website.

All potentially eligible participants will be approached and provided with information about the trial. This information will be entered onto the participant screening/enrolment log at each recruiting site.

Potential participants that decline participation are not obliged to give a reason, however this will be recorded where this is given. Sites will be required to provide a summary of screening data on an ongoing basis during the recruitment period, which will be reviewed regularly by the Trial Management Group (TMG) and oversight committees.

4.4 Participant Identification

Potentially eligible participants will be identified by four pathways (Figure 1.) Each pathway will involve a two-step process to confirm eligibility.

Step 1: Participants reporting frequent hot flushes who fall into either trial group and do not meet any of the exclusion criteria will be provided with approved trial information (Participant Information Sheet (PIS)) and invited to join the trial according to standard procedures, including informed consent (written or electronic).

Step 2: Participants who consent to join the trial will be asked to complete a hot flush diary over a one-week period to confirm that they meet the minimum hot flush eligibility criterion.

If after the two-step process, the person is fully eligible, consent to the trial will then be reconfirmed verbally and randomisation will occur. To note, women who do not complete a hot flush diary due to illness or external circumstances, will be given a further opportunity to complete a weekly hot flush diary.

Pathway 1 –identification via oncology, menopause, or multidisciplinary clinics

The clinical care team will be able to identify potential participants by;

- Approaching potential participants about the trial when they attend routine appointments. Potential participants will be approached by a trained member of the sites research team about participating in the trial. If they are interested, they will be given the opportunity to learn more about the trial and given a PIS, if they haven't received one already.
- Using clinic database searches, potential participants may be sent (email/letter/text) a copy/link to the PIS and a trial invitation letter ahead of appointments. If potential participants don't have an upcoming appointment, the letter/email/text may ask interested women to contact the site research team or refer women directly to the trial website (to join pathway 2). If potential participants do not respond to invites, then the site research team may follow up with a phone call.

Pathway 2 – remote identification via social media adverts, trial website

Women may self-refer via the trial website after viewing trial advertisements with QR codes/links, for example social media adverts, posters, leaflets, newspaper adverts and hospital letters. Women will be required to complete a short pre-screening criteria webform to assess their initial eligibility. This form will also provide a link to trial information and the full PIS. Those who meet the criteria will be asked for consent to provide their personal details within the webform. Once this has been completed, the database will alert the research team at the recruitment hubs (trial clinician and team). They will call the potential participant to discuss the trial, confirm they understand the trial and give them chance to answer any questions. Initial eligibility will then be confirmed. At this point anyone found

not to be eligible, will not progress further, the reason for ineligibility captured and their personal details removed.

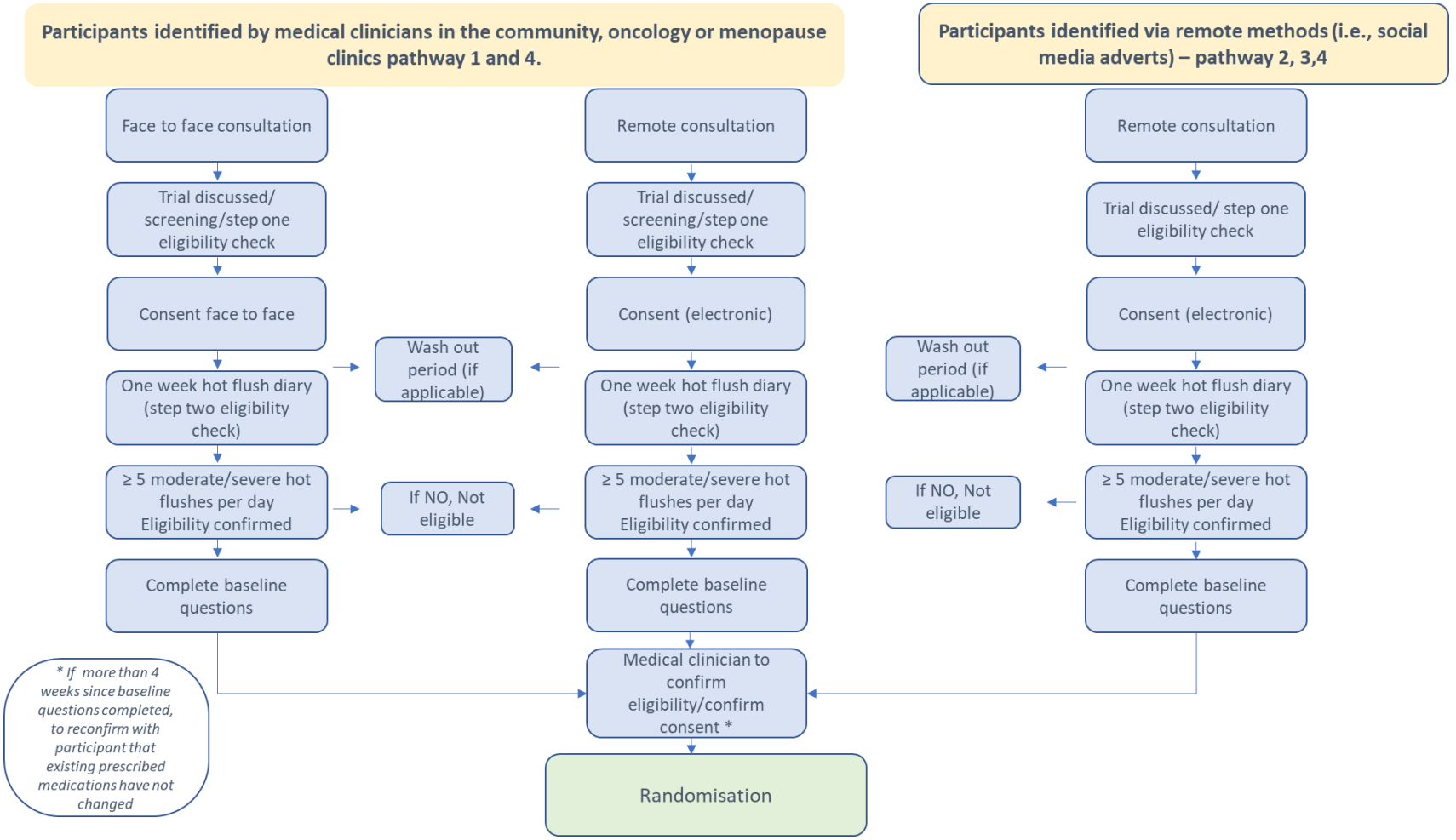
Pathway 3 – remote identification via GP database searches, or oncology database searches.

Oncologist and GP databases will be screened using appropriate SNOMED/ READ codes to identify women in Group A and B. Potential participants will be sent either an email, texts or letter informing them about the trial, with a link/QR code to access to the trial website and full PIS. Similar to pathway 2, those interested will be given the opportunity to complete a pre-screen webform to identify if they are potentially eligible for the trial.

Pathway 4 – identification via Community Heath clinicians and GPs

Clinicians in the community will inform potentially eligible participants about the trial, and those who express an interest will either be referred to a recruitment site, such as a local menopause/oncology site recruitment clinic, or to the trial website in order to find out more about the trial and to complete a pre-screening webform.

Figure 1 Participant Identification Pathways



4.5 Screening

Potential participants will be asked initial pre-screening criteria questions, either via a webform or trial clinician or nurse; the questions will screen for the following: whether participants are experiencing, on average, at least 5 moderate to severe hot flushes per day and use of prescribed (medical) treatment for hot flushes. Those who report they do not experience 5 or more hot flushes per day and are not taking prescribed treatments for hot flushes, will be informed they are not eligible for the trial. Those who experience less than 5 moderate to severe menopausal hot flushes per day, but are taking prescribed treatment (eg. Gabapentin) to specifically treat menopausal symptoms, will be asked if they are potentially willing to stop current treatment, to identify if they are eligible to take part in the trial. They will be asked to sign a consent form. After stopping existing treatment (washout period), will be asked again about the number and severity of their hot flushes.

Potential participants will also be asked their age (anyone 65 or over will be informed they are not eligible), whether they are pregnant, planning a pregnancy or breastfeeding (anyone who states 'yes' will be informed they are not eligible).

Following completion of the pre-screening criteria and if potentially eligible (≥5 hot flushes (or willing to stop menopausal medication), <65 years, not pregnant/planning/breastfeeding), a trial clinician or nurse will discuss the trial with the participant and assess their eligibility further. If after discussion, the participant wants to take part in the trial, the research staff will confirm potential eligibility, and determine whether women have contraindications to HRT (Group A) or if they would prefer not to use HRT (Group B). A full eligibility check by a medically qualified clinician will then proceed, relevant to the group they have been allocated to.

5. Consent

All identified as being potentially eligible for the trial, subject to the minimum hot flush eligibility criteria (after the washout, if applicable), will be given a paper ICF where face to face, or provided with a link to an electronic ICF. Potential participants will complete the consent either face to face or via an electronic consent method. All consent taking will be in accordance with trial approvals, applicable regulatory policies, and NHS guidelines. The potential participant will also be given the trial contact details so that they can ask any questions they may have before or after providing consent.

Informed consent for each participant must be obtained prior to performing any trial related activities, for example the hot flush diary or washout, and consent will be reconfirmed verbally prior to randomisation and this will be recorded on the e-CRF. The potential participant will be given the

opportunity to ask questions throughout the consent process. Where a participant is currently receiving treatment with HRT or other prescribed treatments for their hot flushes and wishes to take part in the trial, they will be asked to stop treatment for a 'washout' period of a minimum of 4 weeks prior to randomisation. Consent will be obtained prior to the washout and reconfirmed verbally prior to randomisation, if the participant is eligible.

Consent for the trial will be taken in person where possible during site recruitment. In light of the COVID-19 pandemic, alternative methods (e.g. electronic consent) may be used where a baseline face-to-face visit is not possible, or if women request further time to think about trial participation. Women recruited via remote identification methods (Database searches/direct participant marketing/via the trial website) may be consented electronically. Potential participants will be emailed or text a link to an electronic copy of the PIS and consent form. They will then be able to select the items on the consent form they agree to and sign their signature with a finger, stylus or mouse drawn signatures.

Consent will be obtained by a trained member of the research team in accordance with the delegation of responsibilities authorised by the Principal Investigator on the site delegation log. This will usually be by a medically qualified clinician, or where local trust policy allows, this may be by a research nurse. Eligibility for the trial must always be confirmed by a medically qualified clinician via the eligibility checklist. The consent documentation will also inform participants that their General Practitioner (GP) will be made aware of their participation in the trial. For participants recruited via remote methods i.e., social media adverts, a member of the research team will make contact via videocall rather than telephone, so participants can verify their identity, by showing a driving licence, passport or any other identification. For participants recruited in a hospital setting, or referred via their GP, it will not be necessary to verify the participants identity via a video call.

It remains the responsibility of the Principal Investigator to ensure informed consent is obtained appropriately. A Participant Information Sheet (PIS) will be provided to facilitate this process. Investigators or delegates will ensure that they adequately explain the aim, trial treatment, anticipated benefits, and potential hazards of taking part in the trial to the potential participant. They will also stress that participation is voluntary and so the potential participant is free to decline participation and may withdraw from the trial at any time. If the potential participant is being recruited while attending routine clinic appointments, they will be given the time they require to read the PIS and to discuss their participation with others if they wish (i.e., family members, GP or other

healthcare professionals outside the site research team). For online participation the research team will ensure the potential participant has read the PIS and has had enough time to think about trial participation and ask any questions they may have.

The Investigator or delegate will sign and date the form. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes for hospital recruited participants, and the original placed in the Investigator Site File (ISF) (a downloaded copy if electronic). A letter will be sent to the GP and oncologist (if applicable) to inform them about trial participation and treatment allocation. Once the participant has been randomised into the trial, the participant's unique trial identification number will be entered on the Informed Consent Form. In addition, a copy of the signed Informed Consent Form will be sent to the NCTU for review or uploaded into a secure area of the trial database. Finger, stylus or mouse drawn signatures used on e-consent forms will be stored within a secure area of the trial database. Receipt of consent forms will be used to perform in-house monitoring of the consent process.

The participant must give explicit consent for the regulatory authorities, members of the research team and representatives of the Sponsor to be given direct access to the participant's medical records. Details of the informed consent discussions will be recorded in the participant's medical notes.

Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, they will be given time to consider and if happy to continue will be re-consented. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the NCTU. Details of all participants approached about the trial will be recorded on the Participant Screening/Enrolment Log at site, and the NCTU will collect the data on the number of women screened and enrolled via online methods.

Participants previously on treatment who complete a washout period and are subsequently found to be ineligible or non-contactable, will not be randomised but their consent documentation will be retained and reasons for ineligibility or lack of randomisation, will be recorded.

5.1. GP Notification

Following randomisation, the participant's GP will be informed that the participant is taking part in the trial. The GP will be informed of the treatment allocated at randomisation.

6. Enrolment and Randomisation

6.1. Enrolment/Registration

After being consented into the trial, but before randomisation, participants will complete a hot flush diary over the course of 1 week, those who experience ≥5 moderate/ severe menopausal hot flushes daily average, will be asked to complete baseline questions, and participants will be contacted to be randomised into the trial. Once a full eligibility check has determined the participant is suitable for the trial, the participant will be enrolled using the online trial randomisation system. An authorised member of the site research team will then log into the secure randomisation system and randomise the participant. Any baseline information which is missing will be collected during the randomisation contact.

Those who have less than 5 daily average flushes, will not be eligible to enter the trial and will either be referred back to usual care for support in managing their symptoms or informed to contact their GP/hospital clinician for further support.

6.2. Randomisation

Eligible participants who consent will be individually randomised on a 1:1 ratio, separately for the two trial groups, using a secure online randomisation system developed and maintained by the NCTU. Dynamic randomisation will use a probabilistic minimisation algorithm to balance across groups by recruitment site, body mass index (<25, 25-30, >30), and use of anti-oestrogens (tamoxifen, aromatase inhibitors, gonadotrophin-releasing hormone agonist [GnRHa] (mono/combination) or none) (group A) or recent hormone (HRT) use (group B) and retaining a random element.

Unique log-in usernames and passwords will be provided to research staff to use the online system and who have been delegated the role of randomising participants into the trial as detailed on the BLUSH Delegation Log. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

BLUSH trial Randomisation Forms will be provided to trial clinicians via an online platform and should be completed and used to collate the necessary information prior to randomisation. The BLUSH trial Randomisation Form must be signed by a trial clinician to indicate that all of the eligibility criteria have been confirmed. It should also be noted in the medical records that the investigator has checked all

of the eligibility criteria and that the participant meets all of the inclusion criteria and none of the exclusion criteria.. If minimisation variables are missing, randomisation will be suspended, but can be resumed once the information is available. Following randomisation, a confirmatory email will be sent to the randomising clinician, local Principal Investigator, the named research nurse and the local pharmacy.

6.3. Blinding and concealment

This trial is open labelled and blinding of principal investigators, site staff and participants is not required, please see justification in design section 1.3.2.

Table 4 Blinding status per role

	Blinding status	Comments
Participant	Not blinded	Not practical (see justification of design)
Principal Investigator and other site staff	Not blinded	Not practical (see justification of design)
Chief Investigator(s)	Blinded	The Chief Investigators (CI) will remain blinded to treatment allocation overall (knowledge of treatment allocation is limited to participants at their own site). In instances where serious adverse events are reported, the CIs will become unblinded to complete the full causality assessment.
Database Programmer	Not blinded	The database programmer will be responsible for the management of the randomisation system and will have access to unblinded datasets within the trial database.
BLUSH Trial Management staff within NCTU	Not blinded	BLUSH Trial Management staff within NCTU will have access to the unblinded datasets within the trial database including information on treatment adherence.
Data Management	Not blinded	Data management staff will have access to the unblinded datasets within the trial database to ensure data quality and undertake central monitoring activities.
Trial Statistician and Senior Trial Statistician	Blinded	The trial and senior trial statistician will not have access to treatment allocations or data which has the potential to unblind until after the first database lock for the analysis.

Independent Statistician	Not blinded	A statistician independent to the trial team will be responsible for the generation of closed reports for the Data Monitoring Committee (DMC) and other potentially unblinding data and will therefore be unblinded to trial treatments.

7. Trial treatments

7.1. Treatments

Participants will be randomised to the drug oxybutynin or venlafaxine for treatment. Both treatments are considered to be investigational medicinal products (IMPs). No specific brand of drug will be used for this trial, once participants commence the trial treatment, sites will be advised that efforts should be made to use the same brand for the treatment period, but this won't be compulsory.

Table 5 Treatment arm

ARM	***TREATMENT***	***FORMULATION, ROUTE OF ADMINISTRATION AND DOSE***
INTERVENTION	*Oxybutynin Extended Release*	**Starting dose 5mg- max 15mg (if tolerated) daily oral*
CONTROL	*Venlafaxine Modified Release*	*Starting dose 37.5mg- max 75mg (if tolerated) daily oral*

*all doses stated refer to the dose of oxybutynin hydrochloride

Trial-specific labelling and dispensing will be carried out by site pharmacies. Participants being recruited via online routes by the trial team clinician, will be prescribed medication from the lead recruitment hubs. Repeat medications may be posted (using a trust courier service) to participants to avoid hospital visits or participants can pick up the treatment from the hospital pharmacy, as per local trust polices. The trial treatment charges will be dependent on local trust policies.

Randomising clinicians will be advised to issue a 3-month prescription supply at randomisation, however this can be for a shorter period if required by the clinician, future follow up appointments should occur around 3, 6, 9 months post randomisation (telephone or face to face). At the final follow

up visit (month 9) prior to reaching the trial end date, the research team will discuss the continuation or discontinuation of the trial treatment once the trial has ended. The trial clinician will contact the GP of those wishing to continue trial treatments, recommending treatment continues. Participants wanting to stop trial treatment will be advised to stop treatment at 12 months post randomisation. Oxybutynin will not require tapering. Venlafaxine may be tapered if the participant is taking a higher dose (75mg) and if deemed appropriate by the treating clinician.

Side effects of Venlafaxine	Side effects of Oxybutynin	Frequency
Dry Mouth, nausea, headaches, constipation, insomnia (Unable to sleep), dizziness, sedation, hyperhidrosis (sweating).	Dry Mouth	Very common (≥1/10)
Diarrhea, vomiting, visual impairment ,blurred vision, dilation of pupil, confusion/nervousness/agitation, dysgeusia (taste disorder), urinary changes (retention/hesitation/frequency), palpitations, shortness of breath, tachycardia (fast pulse), dry skin/rash/itchy, fatigue/tiredness/weakness/chills, libido decrease, abnormal dreams, decreased appetite/ weight changes, anorgasmia (delayed, infrequent or absent orgasms), blood cholesterol increase, tinnitus (ringing or other noises in ear), hypertension, cough, dry throat/nasal passages, gastroesophageal reflux, chills, abdominal pain, hypertonia (stiff arms and legs due to muscle tone), menorrhagia (menstrual bleeding >7 days), metrorrhagia abnormal bleeding between regular menstrual periods, paraesthesia (burning/prickly sensation), hot flush, inability to remain still, tremors, dyspnoea (breathlessness) and yawning, depersonalisation (feeling of being outside yourself)..	Urinary tract infections, insomnia (unable to sleep), fatigue/tiredness/drowsiness, dizziness, blurred vision, dry eye, palpitations, headache, dysgeusia (taste disorder), cough, oropharyngeal pain (soreness at the back of throat) dry throat/nasal passages, gastroesophageal reflux, indigestion, abdominal pain, diarrhea, flatulence (wind), constipation, nausea, dry skin/itchy, urinary changes (retention/hesitation/pain/frequency)	Common (≥1/100 to <1/10)

7.1.1. Oxybutynin dose and escalation schedule

Extended-release oral oxybutynin is prescribed at a starting dose of 5mg once daily, increasing by 5mg each week, if tolerated, to a maximum dose of 15 mg, according to the schedule in Table 6. The dose should be escalated every week until the participant perceives they are gaining benefit, or reported side effects (e.g. dry mouth) (26) precludes further dose increases. If necessary, the participant can reduce their dose to the last tolerated dose. Participants will be advised to take the best tolerated dose until week 52, unless the participants choose to stop treatment. Refer to the Summary of Product Characteristics (SmPC) for further details of contraindications, interactions and special warnings.

Table 6 Dose escalation for Oxybutynin

Week	Dose if escalating	Daily dose
1	1 x 5mg once daily	5mg
2	2 x 5mg once daily	10mg*
3	3 x 5mg once daily	15mg*
4 onwards	3 x 5mg once daily	15mg*

*unless intolerant and participants can reduce their dose back down

7.1.2. Venlafaxine, dose and escalation schedule

Modified-release oral venlafaxine, is prescribed at a starting dose of 37.5mg once daily, increasing by 37.5mg at week 2 if tolerated, to a maximum dose 75mg according to the schedule in

Table 7. The dose should be escalated if the participant perceives they are gaining benefit, or reported side effects (e.g. dry mouth(26) precludes further dose increases. If necessary, the participant can reduce dose to the last tolerated dose. Participants will be advised to take the best tolerated dose until week 52, unless the participant chooses to stop treatment. Refer to the SmPC for details further details of contraindications, interactions and special warnings.

Table 7 Dose escalation for Venlafaxine

Week	Dose if escalating	Daily dose
1	1 x 37.5mg once daily	37.5mg
2	2 x 37.5mg once daily	75mg*
3 onwards	2 x 37.5mg once daily	75mg*

*unless intolerant and participants can reduce their dose back down

7.1.3. Drug Interactions, contraindications and special warning

Refer to the SmPC and BNF for further details on interactions, contraindications and special warnings of the IMP, which would exclude participants from the trial. Also refer to adverse events reporting section 10.2.

If a participant develops a contraindication or a special warning situation arises during the trial, as defined in the SmPC, which results in a permanent or temporary change, or cessation of treatment, the participant should remain in the trial for the purpose of follow-up data collection and any required changes to the IMP documented in the participants notes and in the trial database.

At the follow up appointments (telephone or face to face), the trial clinician (or delegate) will ask about the use of other drugs and advise accordingly. The GP will also have received the trial letter, informing them about trial participation and randomised treatment. The letter will request that the GP does not prescribe any alternative or additional treatment that may impact vasomotor symptoms, unless requested by the participant. The GP will be given the trial contact details. Participants who stop taking trial treatment, will still be required to complete questionnaires.

7.1.4. Regulatory Status of Drugs

Both treatments have a marketing authorisation in the UK, but their use in this trial is outside the indications listed in the SmPC's. Oxybutynin is an anti-cholinergic treatment licensed for the symptomatic treatment of urge incontinence and overactive bladder. It is not recommended for VMS in any clinical guidelines but is used off licence in standard practice. Venlafaxine is licensed for treatment and prevention of major depression and treatment of anxiety and panic disorder. It is recommended as a treatment for menopausal symptoms in women with breast cancer in clinical guidelines and this off-label use is listed in the BNF(26).

7.1.5. Product Characteristics

A SmPC for each treatment in this trial will be included in the regulatory submission and referred to in this protocol.

7.1.6. Dose Modifications

Trial treatments should be taken continuously for 1 year if no contraindications arise. In the initial weeks, the dose escalation schedules described in Section 7.1.1 for oxybutynin and in Section **Error! Reference source not found.** for venlafaxine, should be followed. The participant will decide whether to escalate, maintain or reduce the dose according to the appropriate schedule during this phase. Trial treatment guidance on the dose escalation schedule will be provided to participants via a treatment leaflet, together with contact details for advice on trial treatment dosing.

The brand formulations (e.g., tablet or capsule) of the trial treatments can be modified at the discretion of the randomising clinician. Participants will be routinely contacted at week 12, month 6 and 9-months post randomisation.

Participants will be able to contact the research team if they have any concerns or questions about their treatment while in the trial. Any changes must not result in doses exceeding the maximum dose. If a participant decides to discontinue the trial medication because of unacceptable side effects, they will be advised to call the trial nurse/clinician. Participants wishing to discontinue medication because of perceived lack of benefit should be encouraged, whenever possible, to complete the course of prescribed treatment, particularly in the first 12 weeks, to enable the full effect of the treatment to be evident. Participants wishing to use HRT should consult their GP before stopping trial treatment, and report any change to HRT in the subsequent follow-up questionnaire.

8. Drug Storage and Supply

There are no trial-specific requirements for the storage of any of the treatments used in this trial. All treatment prescribed and dispensed for the purpose of the trial will originate from standard pharmacy stock which will be stored in accordance with the manufacturer's storage instructions as detailed in the applicable SmPC and their own local policies for storage of medication. Prescriptions will be from the randomising clinician's hospital as the trial treatments requires trial labelling. Repeat medication may be posted to participants from the site pharmacy or by the research site team, to avoid hospital visits. If hospitals do not have policies in place to post treatments, participants will be asked to collect treatment from the hospital site.

8.1.1. Preparation and Labelling of Drugs

In accordance with the Medicines and Healthcare products Regulatory Agency (MHRA) risk-adapted approach to the management of CTIMPs(38), BLUSH is categorised as a medium risk Type B trial and because the IMPs are being used outside their licenced indication and current practice, they require trial specific labelling. The label will comply with EU GMP Annex 13 requirements, which remain applicable until UK legislation replaces it. A clinical trial label will be applied by the site pharmacy. Individual site pharmacies will be trained to use trial labels which will be applied alongside the dispensary label. No packaging for blinding is required

Sites will be provided with a pharmacy manual and site file containing the essential trial documents, such as the protocol and confirmation of ethical approval.

8.1.2. Dosing Schedules

Participants will be instructed to start their allocated treatment on the day they receive their drug. Participants will be informed how to use their treatment by the prescribing clinician. All participants will be given a treatment leaflet explaining the dosing schedule and what to do if they experience side effects. See sections 7.1.1 and 7.1.2

8.1.3. Concomitant Medications

Participants should not be receiving, or have used, pharmacological treatment for VMS or hormone treatment for gynaecological conditions or contraception (other than the levonorgestrel-containing intra-uterine system) within the 28 days prior to randomisation. Those who have, will be asked to complete a washout for 28 days, as described in section 4.2.4.

After joining the trial, participants will be asked to complete follow up questionnaires about their use of prescribed medications that might impact the hot flushes, such as SSRIs or SNRIs, gabapentin, pregabalin, clonidine, HRT or contraception containing hormones. Participants will also be asked about non prescribed products such as herbal natural treatments and psychological therapies for their hot flushes.

8.1.4. Pregnancy during the trial

Women who are post-menopausal will not get pregnant, and women in the perimenopause will have an extremely low chance of getting pregnant. Some cancer drugs are contraindicated in pregnancy.

Nonetheless there will be fertile participants and they will be advised by the site research staff and PIS not to become pregnant while in the trial. Non-hormonal forms contraception will be discussed: it will be explained that trial treatments are not intended to be used in pregnancy or while breastfeeding. If any participant does become pregnant, trial medications should be immediately stopped. Participants will be told to inform the trial team immediately and stop medications if they become pregnant. Participants will not be expected to complete further questionnaires, but pregnancy outcome data will be collected either from their hospital records or contacting participants directly.

8.1.5. Assessment of compliance with trial treatment

Adherence information will be collected at week 4 post randomisation, week 8, week 12, 6 and 12 months. Participants will be asked whether they are still taking their trial treatment, and if not, the date they stopped. For those continuing, they will be asked how often they take their treatment (daily, every other day, once a week, less than once a week).

9. Trial procedures and assessments

9.1. Summary of assessments

A summary of the trial procedures and assessments is shown below in Table 8.

Table 8 Summary of assessments

Outcome	**Screening**	**Baseline**	**Randomisation**	**Week**			**Month**	
			0	**4**	**8**	**12***	**6**	**12**
Pre and Enrolment								
Participant identification	x							
Informed consent	x							
Washout (if needed)	x							
Confirm eligibility	x							
Baseline data		x						
Randomisation			x					
Treatment period			←	—	—	→		
Assessments		x				x	x	^x

Hot flush frequency		x		x	x	x	x	x
Hot flush severity		x		x	x	x	x	x
Condition specific Quality of life (MENQOL-I)		x		x		x	x	x
Hot Flash Related Daily Interference Scale (HFRDIS)		x		x		x	x	x
Health Related Quality of life (EQ-5D-5L)		x				x	x	x
Resource Use		x		x	x	x	x	x
Capacity-wellbeing (ICECAP-A)		x				x	x	x
Acceptability and satisfaction with treatment				x	x~	x	x	x
Patient Global impression (PGI – C)						x	x	x
Urinary symptoms (ICIQ-OAB)		x				x	x	x
Sleep quality (PSQI)		x				x	x	x
Work productivity (WPAI)		x				x	x	x
Adverse effects of therapy				x	x	x	x	x
Change/ cessation therapy				x	x	x	x	x

***Note: outcomes at timepoint marked with * may be collected during an appointment with clinician at the 12 week follow up appointment. All others will be reported directly by the participant.**

^ Assessments (follow up appointments) to take place at 3-, 6-, and 9-months post randomisation, but this is subject to the medical clinician's opinion, and can take place more frequently if required.

~ only satisfaction with treatment will be asked at the week 8 timepoint.

9.1.1. Enrolment and identification

At sites who are recruiting face to face, information about the numbers approached will be entered onto the participant screening/enrolment log for each recruiting site. All pre-screen forms completed via the trial website will be recorded within the trial randomisation system. Details of all participants who meet the pre-screen criteria will be recorded and all information regarding their potential participation (ICF completed, hot flush diaries completed) will be recorded. Information on where the

participant found out about the trial (social media advertising, search engine, GP search etc) will also be recorded as part of the randomisation system screening data, which is part of REDCap. Those that decline participation are not obliged to give a reason, however this will be recorded where this is given.

All screening information will be reviewed regularly by the Trial Management Group (TMG) and oversight committees.

9.1.2. Informed consent

Informed consent will be obtained as described in section 5. If a participant requires a washout period, then eligibility will need to be re-confirmed prior to collecting baseline data.

9.1.3. Washout

Eligible women who are already on HRT, other prescribed treatments for their VMS, or hormone treatment for gynaecological conditions or contraception (other than the levonorgestrel-containing intra-uterine system) are required to stop treatment for a washout period of a minimum of 4 weeks. This is to ensure a return to pre-treatment levels before performing baseline assessments.

9.1.4. Confirm Eligibility

Eligibility will be confirmed by the principal investigator or delegated trial clinician using the eligibility checklist form once informed consent and all baseline data has been obtained.

9.1.5. Baseline Data Collection

After informed consent, medication washout if applicable, and completion of the hot flush diary and if ≥ 5 moderate/severe hot flushes per day, then participants will be asked to give/complete the following:

Site team will ask the following questions after consent has been received;

- Participant demographics
- Body Mass Index
- When (approximate date) hot flushes started
- Hysterectomy (with/ without bilateral salpingo-oophorectomy)
- Reason for contraindication to HRT e.g. breast cancer, endometrial cancer (Group A)
- Lifestyle factors e.g. smoking, alcohol
- Use of medication e.g. prescribed (including cancer treatment), complementary and supplements.

Participants will complete the below questionnaires once the hot flush diary has been completed and if they have ≥ 5 moderate/severe hot flushes per day-

- Condition specific Quality of life (MENQOL-I)
- Hot flush disturbance (HFRDIS)
- Health Related Quality of life (EQ-5D-5L)
- Capacity-wellbeing (ICECAP-A)
- Urinary symptoms (ICIQ-OAB)
- Sleep quality (PSQI)
- Work productivity (WPAI) general

Baseline questionnaires will be provided to participants either in an online or paper format. Where paper questionnaires are used, these will be entered into the eCRF by the site staff. Any missing data will be collected from the participant during the randomisation process.

9.1.6. Randomisation

Randomisation of participants will occur as described in section 6.2

9.1.7. Prescribing of interventions/treatment

Following randomisation and treatment allocation, prescriptions for the randomised treatment will be initiated by the randomising clinician, with repeat prescriptions generated from the site pharmacy. Prescribing clinicians will be advised to prescribe further supplies at 3, 6 and 9 months, but the length of prescription will be the trial clinician's decisions. Treatments will then be delivered to participants or participants can collect, as per local trust policy. The trial database will keep a record of the doses participants have been prescribed and questionnaires will ask about their dose and adherence of trial treatment while in the trial.

9.1.8. Follow up

Prescriptions will be requested and dispensed according to local practice, ideally without the participant needing to visit the hospital for collection. Prescriptions will be issued post follow up appointment. Participants will be required to give their consent for collection of contact details for the purpose of follow-up data collection and important trial communications (e.g. reminder messages) as part of the eligibility assessment and informed consent process.

9.1.8.1. Recording hot flushes

Women will be required to record their daily hot flushes/night sweats over a week, before randomisation and in week 4, 8 and 12 of treatment, and again at 6 and 12 months. They will record this by using a trial app (MyCap), paper diaries, or text. The trial MyCap app has a direct interface to the REDCap database and participants can download this on to a device to register hot flushes in real time. An offline paper diary will also be available for women without access to a smartphone recruited via pathway 1. Participants will be informed to complete the diary at the same time each day, in order to capture a 24 hour period.

9.1.8.2. Other participant reported outcomes

Validated questionnaires and questions about treatment dose, adherence, side-effects, quality of life, health related quality of life, health wellbeing, acceptability, impression of treatment, sleep quality, urinary symptoms and work productivity will all be completed either online, using the trial app, or paper alternatives for those without smartphones. See Table 8 Summary of assessments.

9.1.8.3. Supporting follow-up

At the 3-month (or sooner if required) routine follow-up appointment with the clinician (or delegate), adherence to the trial treatment, with adjuvant endocrine therapy (where applicable), and side-effects will be reviewed. This will corroborate the direct reports or capture missing data. This appointment will also act as a checkpoint to schedule when the repeat prescriptions are required.

To maximise data completion, personalised text messages and automatic push reminders may be sent if data is more than 1 week late. After two reminders, participants may be contacted by phone by a trained member of the research team to answer research questions. Paper questionnaires and prepaid postage return options will also be offered, for women who find questionnaires difficult to complete on a device, or don't have access to a smart phone. If we cannot get a response to reminders, we may attempt contact via the participant's via GP. Contact will all be carried out as per the consent form.

Throughout the trial, reminders and updates will also be shared with participants via a range of media such as newsletters, websites, text message reminders and social media platforms.

9.2. Withdrawal and discontinuation Procedures

Participants are free to withdraw from the trial at any time and for any reason, the site investigator can also withdraw participants at their discretion. Participants who stop taking trial treatments, including those who start using HRT, will be asked to continue to complete follow-up hot flush scores

and all other questionnaires and will not be considered to have withdrawn from the trial. The actions following a withdrawal request, and consequences for the data, are shown in Table 9.

Table 9 Withdrawal categories

Withdrawal type	**Withdrawal procedure**	**Use of data**
Withdrawal of consent before randomisation	Participant requests to withdraw from trial via randomising clinician or trial website.	No identifiable or baseline data will be retained. Reason for withdrawal recorded where available.
Unable to be contacted during or after washout or baseline diary phase	Any participant unable to be contacted after providing consent but before randomisation within a reasonable timeframe will be considered withdrawn and will not be randomised	No identifiable or baseline data will be retained. Reason for withdrawal recorded as uncontactable.
Discontinue follow-up questionnaires	Any participant that requests to discontinue from trial questionnaires will be marked as withdrawn from questionnaire collection on the trial database and no further contact will be made with the participant for the purpose of obtaining questionnaire follow-up data.	Any data collected prior to participant withdrawal will be retained and used.
Discontinue trial treatment (e.g. side effects, no reason given)	Participants who wish to stop trial treatment, will still be required to complete research data	Research data will continue to be collected.

Discontinue trial treatment due to pregnancy	Participants who become pregnant will need to stop trial treatment. Consent will be obtained to collect data on pregnancy outcomes.	Any data collected prior to participant withdrawal will be retained and used.
Discontinue trial related communication e.g. newsletters, trial summaries.	Any participant that requests to discontinue receiving trial communications e.g. newsletter, results summaries, will be marked as withdrawn from trial related communication on the trial database.	Research data will continue to be collected.
Full trial withdrawal	Any participant that requests to have no further involvement in the trial will be marked as withdrawn on the trial database.	Any data collected prior to participant withdrawal will be retained and used.

9.2.1. Withdrawal prior to randomisation

Any participants that request to withdraw their consent **prior to randomisation** will be withdrawn completely from the trial; they will not be randomised, and follow-up questionnaires will not be issued. Their contact details will be removed from the trial database but we will retain a copy of their consent form.

9.2.2. Discontinuation and withdrawal post randomisation

Participants may withdraw their consent for follow-up and/or other trial-related activities /receiving trial-related communications. The NCTU must be informed of all requests by participants to stop their involvement in the trial; appropriate action will be taken to ensure that the participant's wishes are followed.

Sites will be trained to determine which activities participants may wish to withdraw from. If site staff are made aware of a participant's withdrawal of consent for any trial activities, the PI or delegate

should record this in the CRF as soon as possible (and within 24 hours), the database will then notify the NCTU team to ensure the correct procedures are followed. Participants will be asked their reason(s) for withdrawal but are not obliged to provide these.

Withdrawn participants who have been randomised will not be replaced. Data collected prior to withdrawal will be retained and used in the analysis. It should be made clear to any participant withdrawing consent for further data collection, that any serious adverse events that occur after withdrawal, will be reported by the trial clinician or her GP and will be included in the analysis. In addition, if any significant new information becomes available with regard to the treatment they received in the trial, it may be necessary to contact them in the future.

If contact cannot be made despite multiple attempts to contact the participant, including via their GP, and the participant has not withdrawn their consent to participate in the trial, then the participant will be designated as lost to follow-up for the primary outcome.

9.3. Post-Trial Care

Randomising hospitals, if able to, should continue the treatment post-trial if the patient wishes to continue. However, if this is not possible, at the 9 month follow up appointment, a letter from the randomising clinician will be sent to the participant's GP to recommend continuation on an off-label basis at 12 months (post-trial). Participants may incur a prescription charge for future treatment, but this will depend on local policy and if the participant has an exemption. Whether the GP continues to prescribe the treatment post-trial, will depend on their local prescribing policies. Participants will be informed about this in the PIS and during the discussion with the trial team, prior to joining the trial. Participants will be advised to discard of any unused or unwanted medication at any pharmacy if they discontinue trial treatments or stop treatments at the end of the trial.

10. Adverse Event Reporting

10.1. Reporting Requirements

Table 10 Definitions of adverse event and reactions

Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this drug. Comment: An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction (AR)	All untoward and unintended responses to an IMP related to any dose administered. Comment: An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that: • Results in death • Is life threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Or is otherwise considered medically significant by the Investigator** The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria.

	* Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. ** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.
Serious Adverse Reaction (SAR)	An Adverse Reaction which also meets the definition of a Serious Adverse Event
Unexpected Adverse Reaction (UAR)	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Summary of Product Characteristics (SmPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 (and subsequent amendments). Definitions of different types of AEs are listed in Table 10 Definitions of adverse event and reactions'. AEs will be reported by the participants on the 4, 8, 12 weeks, 6 months and 12-month questionnaire. The Principal Investigator will assess the seriousness and causality (relatedness) of all SAEs reported by the participant. Reference Safety Information (RSI) (Listed as Undesirable Effects in section of the current approved SmPC), which will be documented on the participant SAE form, eCRF and medical notes. Any updates to the RSI will be reviewed annually in line with the Development Safety Update Report (DSUR).

10.2. Adverse Events and reporting requirements/procedures

Adverse events are collected on the participant questionnaires. Only specified adverse events will be collected and this data will collect via questionnaires and during follow up consultations. Many of the adverse events are also associated with menopausal symptoms. Therefore, participants will be asked to only report if the adverse event is new and participants think they are related to drug treatment.

The adverse events will include the following:

- Dry Mouth
- Insomnia
- Headaches
- Rashes/dry skin
- Nausea
- Constipation, diarrhoea, abdominal discomfort
- Dizziness
- Anxiety/agitation
- Palpitations
- Urinary Infection
- Blurred vision
- Tinnitus
- Cough, dry throat/nasal region
- Hypertonia

Where any of the above events result in an admission to hospital or prolongation of a hospital stay this will also require reporting on a SAE form by the Principal Investigator or delegate. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) as per NCTU standard practice.

10.3. Serious Adverse Events and reporting requirements/procedures

AEs defined as serious, and which require expedited reporting as an SAE, will be reported on an a paper SAE Form. When completing the form, the Investigator will be asked to define the causality and the seriousness of the AE.

Causality of an event will be categorised as one of the following:

- Definitely related
- Probably related

- Possibly related
- Unlikely to be related
- Unrelated

10.3.1. Identification of SAE via participant questionnaires

As adverse events are participant reported via questionnaires, where participants have confirmed that they have had a hospital admission, a review of the participant's completed questionnaire will be conducted by the trial management team at NCTU within 1 working day of becoming aware of the potential SAE. The recruiting site may be asked to contact the participant to obtain further information to determine whether an event has occurred that fulfils the SAE criteria. Where an SAE has been experienced, the Principal Investigator (or delegate) must report the SAE on a paper SAE form and email this to the NCTU. Planned hospital admissions will not be reported as SAEs.

10.3.2. Identification of SAE via recruitment site

The NCTU will also request that sites perform a check of medical notes or check with the participants at 12 weeks consultation, to identify if there has been a SAE. The paper form should be emailed to NCTU as soon as possible and no later than 24 hours after first becoming aware of the event:

FOR SAE REPORTING ONLY: nctu-sae@nottingham.ac.uk

On receipt, NCTU will allocate each SAE a unique reference number which will be forwarded to the site as a confirmation of receipt within 1 working day. If confirmation is not received within 1 working day sites should contact NCTU to check whether the SAE was received. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the original SAE in the ISF and TMF.

Sites

For SAE Forms completed by a delegated individual other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and seriousness assessments. The form should then be returned to NCTU and a copy kept in the Site File. Investigators should also report SAEs to their own Trust in accordance with local practice.

NCTU

On receipt of an SAE Form, seriousness and causality will be reviewed independently by a medical monitor (which can also be the Chief Investigator) responsible for determining final causality assessment. An SAE judged by the Investigator or medical monitor responsible for determining causality assessments to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The medical monitor responsible for determining expectedness assessments will also assess all SARs for expectedness. If the event meets the definition of an SAR that is unexpected (i.e. is not defined in the Reference Safety Information (RSI)) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The documents used as RSI for the trial are:

- SmPC Oxybutynin hydrochloride prolonged- release 5mg Tablets (Accord-UK Ltd) – Section 4.8: Undesirable Effects
- SmPC Efexor XL 75 mg prolonged-release capsules, hard (Upjohn UK Limited) – Section 4.8: Undesirable Effects

10.3.3. Provision of follow-up information

Participants should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a new SAE Form/directly within the REDCap.

10.3.4. Events that do not require expedited (immediate) reporting

Participants receiving adjuvant therapy may require admission to hospital for appropriate medical intervention following development of some of the more severe known side effects of their treatment for their existing condition, which is not related to the trial treatment. For this reason, SAEs that relate to a pre-existing condition or treatments, do not require expedited reporting by the site or the participant and are not regarded as unexpected for the purpose of this trial.

10.3.5. Events that do not require reporting on a Serious Adverse Event Form

The following are regarded as expected SAEs for the purpose of trial and should not be reported on an SAE form as they are related to a previous condition.

- recurrence of cancer
- diagnosis of secondary tumours
- death from primary cancer
- inpatient chemotherapy and/or radiotherapy.

10.3.6. Monitoring pregnancies for potential Serious Adverse Events

There is no requirement to monitor pregnancies for potential Serious Adverse Events. There isn't strong indication that either trial treatment causes miscarriage or birth defects, however studies are limited(39).

If a participant does become pregnant, a pregnancy notification form in REDCap will be completed, participants will be asked via the consent form at the beginning of the trial, to collect the following information directly or via medical records (should they become pregnant during the trial): date pregnancy confirmed, expected date of delivery, and pregnancy outcomes. However, if the participant reported they had stopped trial treatments at least 1 week before conception, then we would not collect congenital anomalies information.

10.4. Reporting period

Details of AEs, SAEs, SARs, SUSAR's, will be documented and reported from the date of commencement of protocol defined treatment until 12 months after randomisation, as long as they are still on treatment and haven't withdrawn.

10.5. Reporting to the Competent Authority and Research Ethics Committee

10.5.1. Suspected Unexpected Serious Adverse Reactions

On becoming aware of a SUSAR, the Trial Manager (or delegate) will notify the sponsor as soon as possible. The NCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSARs to the Medicines and Healthcare products Regulatory Agency (MHRA) within 7 days. Detailed follow-up information will be provided within an additional 8 days. All other events categorised as SUSARs will be reported within 15 days.

10.5.2. Serious Adverse Reactions

The NCTU will report details of all SAEs and SARs (including SUSARs) to the MHRA annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

10.5.3. Adverse Events

Details of all AEs will be reported to the MHRA on request.

10.5.4. Other safety issues identified during the trial

If any urgent safety measures are taken the CI (or delegate) shall immediately and, in any event, no later than 3 days from the date the measures are taken inform the MHRA by phone of any urgent safety measures taken, and the circumstances giving rise to those measures.

The CI (delegate) must also email the NCTU and Sponsor within 3 days of the date the measures were taken, detailing the USM and stating what was discussed and agreed with the MHRA on the call.

The NCTU will submit a written notification to the MHRA via IRAS within 3 days of the measure being taken. The CI/PI or another designated member of the local site team should respond to any queries raised by the central trial team and/or Sponsor as soon as possible.

10.6. Reporting to Investigators

Details of all SUSARs and any other safety issues which arise during the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File.

10.7. Reporting to Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

10.8. Reporting to third parties

No reporting of adverse events to third parties is expected. Any safety issues identified during the course of the trial will be notified to the MHRA and REC.

11. Data Handling and Record Keeping

11.1. Source Data

To allow for the accurate reconstruction of the trial and clinical management of the participant, source data will be accessible and maintained.

Source data is kept as part of the participant's medical notes generated and maintained at site. Each site will record the location of source data at their site using a source data location log prior to commencing recruitment. Data that are not routinely collected elsewhere may be entered directly onto the eCRF; in such instances the eCRF will act as source data and this will be clearly defined in the source data location log and recorded. Some recruiting centres may initially record trial information into a source data worksheet; where this has been used this will be noted.

For this trial, source data refers to, though is not limited to, the participants' medical notes, data recorded directly into the eCRF, source data worksheets and questionnaires. Questionnaires

completed by participants on paper will be considered source data, if questionnaires are completed online by the participant, the data in the eCRF will be considered source data.

Where paper follow-up questionnaires are issued to participants these will be entered into the eCRF by a member of the research team at site, or by a member of the NCTU DM team, for data entry and will be considered source data. Where follow-up is obtained via telephone, this data will be entered directly into the eCRF or collected on paper proforma (where direct eCRF entry is not possible) by a member of the NCTU and will be considered source data.

11.2. CRF Completion

Data reported on each electronic Case Report Form (eCRF) will be consistent with the source data and any discrepancies will be explained. Staff delegated to complete eCRFs will be trained to adhere to ICH-GCP guidelines and trial specific guidance on the completion of the eCRF.

In all cases it remains the responsibility of the site's Principal Investigator to ensure that the CRF has been completed correctly and that the data are accurate. Where applicable for the trial this will be evidenced by the signature of the site's Principal Investigator on the CRF.

11.3. Data Management

Details about data handling will be specified in the Data Management Plan (DMP). This will include the agreed validation specification which will validate data for consistency and integrity as it is entered.

REDCap (Remote Electronic Data Capture) is a freely available Clinical Trial Management System (CTMS) widely used by Clinical Trials Units (CTUs) (https://www.project-redcap.org/). REDCap proves secure, role-based access to data entry forms with all data changes automatically audited. Other functionalities include electronic signatures, eConsent framework, data validation, randomisation, SMS & email alerts and reporting. Validation of computer systems ensures data and result integrity and the protection of the rights, safety and wellbeing of trial subjects.

The NCTU REDCap service is hosted on servers provisioned by the University of Nottingham. These servers are virtual machines (VMs) run by the University of Nottingham (UoN) Digital Technology Services (DTS). Only members of the NCTU programming team have administrator privileges on the live REDCap service. Senior members of the Data Management (DM) team have some administration rights on the development and test REDCap service as the DM team take a lead role in forms building. All trial project work on the live server is carried out by users assigned roles with permissions limited

to what is required to carry out their duties for the individual trial projects. University of Nottingham (UoN) staff use their UoN accounts to authenticate on the system. External REDCap users use table-based accounts. Access to the VMs by remote desktop is limited to the programming team accounts, and DTS administrators. DTS automatically save images of all VMs every date. System administrators may access these through the DTS portal should files need to be retrieved for a system restore.

All trial data will be entered onto a trial specific database through the eCRF with participants identified only by their unique trial identification number and initials. The database will be developed and maintained by NCTU. Access to the database will be restricted and secure. Any missing or ambiguous data will be queried with the site via the eCRF; sites should respond to the data queries in a timely manner, ideally within 2 weeks of the query being raised. All access and data transactions will be logged in a full audit trail.

Participant's eCRF data will be reviewed and soft-locked on an ongoing basis once they are deemed to have a complete set of data that has passed data validation checks (i.e. there are no data queries outstanding). Once all participant data have been soft-locked and the statistical analysis plan has been finalised, the trial database will be hard-locked (set to read only). This will be done prior to the data analysis.

11.4. Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source documents (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, participants' medical records, copies of CRFs etc.) at their site are securely retained for at least 5 years.

The Trial Master File and trial documents held by NCTU on behalf of the sponsor shall be archived at secure archive facilities (either physical or on electronic servers), which have been assessed as appropriate for storage of clinical trial data. This archive shall include all trial databases and associated meta-data encryption codes.

Documents are archived according to any regulatory requirements and any local procedures. No documents will be destroyed without prior approval from the Sponsor.

11.5. Data Sharing

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol.

Participants' contact details, including name, address, telephone/mobile number and email will be shared between participating sites, NCTU and third parties (where required) for the purposes of issuing questionnaires and electronic reminders (text/email) for the trial.

Any personal data will be held in a secure database using encryption, with restricted password protected access. Only appropriate members of the participating site team and NCTU research team will have access to these data. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in computer files. Data generated as a result of this trial will be available for inspection on request by University College London, NCTU, the REC, local R&D departments and the regulatory authorities.

12. Quality control and quality assurance

12.1. Site Set-up and Initiation

All participating Principal Investigators will be asked to sign the necessary agreements and supply a current CV and GCP certificate to NCTU – the CV should be signed within the last 2 years and GCP training completed within the last 3 years. All members of the site research team will also be required to sign a site delegation and training log. Prior to commencing recruitment all sites will undergo a process of initiation and will have completed any necessary training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documents, instructions, and other documentation required for the conduct and reconstruction of the trial. NCTU must be informed immediately of any change in the site research team.

12.2. Monitoring

Monitoring will be carried out as required following a Risk Assessment and as documented in the Monitoring Plan. NCTU will be in regular contact with the site research team to check on progress and address any queries that they may have. The trial team will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies On-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, lower than expected SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required, NCTU will contact

the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow NCTU trial staff access to source documents as requested.

Sites will be requested to send/upload copies of signed Informed Consent Forms and other documentation for in-house review for all participants providing explicit consent. This will be detailed in the monitoring plan and the Participant Information Sheet.

12.3. Audit and Inspection

The Principal Investigator will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up. Sites are also requested to notify NCTU of any MHRA inspections.

The Trial Master File and evidence of audits will be made available upon request for regulatory inspections.

12.4. Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and its amendments) the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial. Sites are therefore requested to notify NCTU of any suspected trial-related serious breach of GCP and/or the trial protocol. Where NCTU is investigating whether a serious breach has occurred, sites are also requested to cooperate with NCTU in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action. Serious and persistent non-compliance with the protocol and/or GCPcould potentially meet the criteria of a Serious Breach and sites may be suspended from further recruitment. Any major problems identified during monitoring may be reported to the TMG, Trial Steering Committee (TSC), the REC and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

13. End of Trial Definition

The end of trial will

This is when the final participant has completed the 12-month data collection time point and all attempts to chase this data have been exhausted. This will allow sufficient time for the completion of protocol procedures, data collection and data input. NCTU will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Should the trial terminate early (e.g. following recommendations by the DMC or regulatory authorities), NCTU will inform the MHRA and REC within 15 days of the end of trial. NCTU will provide them with a summary of the clinical trial report within 12 months of the end of trial.

14. Statistical Considerations

14.1.1. Power Calculations / sample size calculation

Sample size calculation has been done separately for each participant group using same parameters and assumptions. The trial has been powered to detect a 4-point mean difference in HF Score between oxybutynin and venlafaxine at 12 weeks post-randomisation, equivalent to an average of two moderate hot flushes experienced per day, deemed to be clinically meaningful from previous research (31) and supported by our participant questionnaire.

The SD of HF Score varies between 8 and 12 points.(20, 40) To be conservative, we have used SD of 12.(20) A total of 382 participants (191 per group) will be required to detect the between–group difference of 4 points on the HF Score (a small standardised effect size of 0.333) with a 90% power, 5% two-sided significance level and 1:1 allocation. To allow for ~20% loss to follow-up and treatment discontinuation, 480 participants will be recruited in each participant group. As the statistical analysis will adjust for the baseline HF scores and account for the correlation in HF scores between time-points, this will increase precision and offset any uncertainty in the parameters used in sample size calculation.

Our estimate of 20% missing primary outcome data is based on previous trials(20) where 82% (121/148) of participants completed all 12 weeks of treatment and had primary outcome data, whilst another trial found that had 75% (113/150) of the participants evaluable for the primary endpoint (18), however, 9% withdrew consent before treatment initiation. We have allowed for a maximum of 20% loss to follow-up and missing primary outcome data, but we will make every endeavour to collect data regardless of adherence and monitor both.

14.2. Definition of Outcome Measures

14.2.1. Primary outcome measures

The primary outcome is the mean number of HF score over a 7-day period at 12 weeks post randomisation.

14.2.2. Secondary outcome measures/exploratory endpoints

The secondary outcomes will be measured at different stages throughout the trial. Further information can be found in section 2.3.

14.3. Analysis of Outcome Measures

The analysis and reporting of the trial will be in accordance with CONSORT guidelines. A full statistical analysis plan (SAP) will be developed and agreed with the TSC prior to database lock.

The primary comparative analysis will be based on intention-to-treat, analysing participants in the groups to which they were randomised regardless of treatment received. The evaluation of the primary outcome will use a mixed-effects model using all available follow-up data up to 12 weeks, adjusted for the baseline HF scores and minimisation variables. The model will include a treatment by time interaction to obtain the estimates of treatment effect at each follow-up time, with week 12 being the primary treatment comparison. The estimated between-group effect will be presented using the difference in means, with a 95% confidence interval. To aid interpretation of trial results and for comparison with other studies, the following supplementary analyses will be performed for the primary outcome: (i) examining an overall time-averaged between-group effect over the 12 weeks (if no significant treatment-by-time interaction), (ii) analysing percent change from baseline, and (iii) analysing proportion of women with at least a 50% decrease in HF score. Further supplementary analysis will investigate potential effects of compliance with allocated treatment using complier average causal effect (CACE),if identified, or per-protocol analysis. The definition of the per-protocol population will be detailed in the SAP and will be defined differently for the two participant populations. Sensitivity analyses on primary outcome for effect of missing data will use multiple imputation by chained equations. The imputation model will be broad enough to incorporate all the variables in the analysis model as well as any significant predictors of the incomplete variable to make MAR (i.e. missingness depends only on the observed values) more plausible. At least 20 imputations will be performed, and the results combined using Rubin's rule.

Between-group comparison of secondary outcomes will use an appropriate regression for the outcome (linear for continuous outcomes, logistic for binary, survival for time-to-event), adjusted for the minimisation variables and baseline outcome measure for continuous variables if available. For repeated measures, appropriate mixed-effect models for the outcome, adjusted for the minimisation variables, will be used.

14.3.1. Planned Interim Analysis

There is no planned interim analysis of treatment effectiveness. However, an internal pilot phase has been built into the trial to allow a feasibility assessment which will examine recruitment, retention and adherence. The stop-go criteria are shown in Table 9 Stop Go Criteria' and will be used to determine the progression of the trial unless agreed otherwise with the funder. Assessment will occur 8 months after the first site opening. At month 8 of the recruitment time window, at least 77 women should have reached the 12-week timepoint and provided the primary outcome data and reported adherence to the randomised allocation. It is expected that there will be valid primary outcome responses (≥4 days HF scores over a 7-day window) in at least 80% of participants. Continued reminders will be sent to participants via a text message system, and possibly phone calls, until a valid response is achieved. Adherence to trial treatment is >80% in previous trials, albeit over a shorter timeframe. Screening and recruitment data for the pilot phase will be presented to the TSC and DMC around 8 months post recruitment for consideration, and their recommendations referred to the HTA.

Table 9 Stop Go Criteria

	Green – proceed	Amber – improve	Red – stop
Recruitment - % of projected randomised participants at month 8	100%	70-99%	<70%
Adherence – % of randomised participants taking the majority of their treatment, of all attending 3-month appointment	100%	70-99%	<70%
Data completion - % of randomised participants providing valid primary outcome data of all reaching 12 weeks.	100%	80-99%	<80%
Site opening - % of 22 projected sites	100%	90%	<90%

Site recruitment per month -% of recruitment target for site tier	100%	70-99%	<70%

14.3.2. Planned Final Analyses

Analysis of the primary outcome and secondary outcomes up to 12 months will be performed after all data up to the 12-month point has been collected and cleaned and the SAP finalised.

14.3.3. Planned Subgroup Analyses

Subgroup analyses for the primary outcome will be performed according to body mass index, use of anti-oestrogens (group A) or prior hormone use (group B), by including appropriate interaction terms in the mixed effect model. The trial is not powered to detect any interactions hence the subgroup analyses will be treated as exploratory.

15. Health Economics

15.1. Aim

In line with the trial design, separate evaluations will be conducted for each of the two populations. The aim of the health economic evaluations is to determine the impact and cost-effectiveness of oxybutynin compared with venlafaxine, in women with VMS associated with menopause who prefer not to take HRT and those who cannot use HRT. The evaluations will adopt the perspectives of the NHS and Personal Social Services in line with the current NICE guidance,(41) and of the wider society over a 12-month time horizon (alongside the trial).

15.2. Outcome and resource use measurement

Data on healthcare resource and work productivity will be collected over the course of the trial to inform the estimation of direct and indirect costs. It has been widely established that women often have substantial care responsibilities. Therefore, both paid and unpaid care work will be measured and valued. Data from EQ5D-5L and ICECAP-A will also be collected during the trial to inform the estimation of women's health utilities and capability.

15.3. Conceptual model

A conceptual model will be developed with input from clinical experts within the TMG and from the Patient Advisory Panel (PAP). The purpose of this model is to understand and illustrate trial mechanisms (e.g. biological, clinical or behavioural) that may be associated with key economic components (e.g. treatment cost, non-treatment cost, health related quality of life), so as to guide the data analyses.(42) Further, the conceptual model will also serve as a communication tool to aid stakeholders' understanding of the process of economic evaluation.

15.4. Analysis

A cost utility analysis will be conducted alongside the BLUSH trial, and cost effectiveness will be expressed as incremental cost per quality adjusted life year (QALY) gained and net monetary benefits. Missing data will be addressed using multiple imputation by chained equations, where appropriate. Generalised linear model (GLM) will be used to analyse costs with appropriate adjustments of baseline cost and minimisation variables, in line with statistical analysis described above. The area under curve approach will be used to estimate QALYs by adjusting life years gained by the health utilities reported over the trial period. Similar to the cost analysis, a GLM will be used to estimate mean QALYs with appropriate adjustments for baseline health utilities and minimisation variables. Difference in mean costs and outcomes will be estimated between arm, and non-parametric bootstrapping will be used to estimate confidence intervals around these estimates. A cost-consequence analysis will be conducted, reporting disaggregated and aggregated costs alongside consequences comprising the primary and secondary outcomes.

Uncertainty will be presented using the scatterplot on the cost-effectiveness plane and cost-effectiveness acceptability curve. Further, an uncertainty analysis with a conceptual model guided analysis will be completed. The potential associations will be validated between trial mechanism and key economic components in a regression framework. As an example: the conceptual model may suggest that average HF score predicts health related quality of life and non-treatment costs. If this were to be validated by the regression analysis, this will be included as nested equation, informing the bootstrapped estimates. This has potential to reduce the uncertainty around the estimates of the cost utility analysis and aid interpretation of the overall findings.

There is no planned interim analysis of impact and cost-effectiveness. The NICE guideline on menopause advised that cost-effectiveness of treatments was driven primarily by differences in short-

term symptom relief. Therefore, a proposed cost-effectiveness of oxybutynin vs venlafaxine beyond 12 months in this proposal has not been estimated.

16. Trial Organisational Structure

The roles and responsibilities for each organisation are documented in Contractual Agreements and the responsibilities of the Sponsor, CI, and NCTU specifically are detailed in the collaboration agreement.

16.1. Sponsor

The trial is sponsored by University College London (UCL).

16.2. Trials Unit

The trial is co-ordinated by the Nottingham Clinical Trials Unit (NCTU)

16.3. Trial Management Group

The TMG will be responsible for the day-to day management of the trial. Membership includes (but is not limited to) the CI, Co-Investigators, Trial Statistician, Trial Manager and Data Manager. Other relevant members of the trial team will be invited to TMG meetings as required. The TMG will ensure high quality trial conduct, to time and within budget, monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of trial itself. The TMG will also be responsible for ensuring project milestones are achieved. The TMG will meet regularly throughout the duration of the trial.

16.4. Trial Steering Committee

A TSC will be established and will include an independent chair, independent and non-independent members, and a participant representative. The CI will also be a member of the TSC. The role of the TSC is to maintain oversight of the trial, monitor progress and provide advice to the research team.

The TSC will provide independent oversight of the trial and will meet at least annually or more often as required, either face-to-face or by tele- or videoconference. The TSC will consider and act, as appropriate, upon the recommendations of the DMC, and in accordance with the TSC Charter, and ultimately carries the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy.

16.5. Data Monitoring Committee

Reports will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet initially during the trial set-up period to agree the protocol and content of the DMC charter and then annually unless there is a specific reason for additional meetings. After completion of the 12 month follow up, the meeting frequency will be reviewed by the DMC and if agreed reduced further.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the chair of the TSC who will convey the findings of the DMC to the TSC, TMG, funders and Sponsor as applicable.

16.6. Finance

This trial is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme (funding award number NIHR133461).

16.7. Participant gratitude and stipends

Participants will not be paid to participate in the trial. However, small financial incentives up to £20, in the form of an online shopping vouchers, will be offered for completion of a valid 12-week HF diary.

17. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care 2018, the applicable UK Statutory Instruments, which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 2018 and Guidelines for Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in

accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the REC and MHRA prior to circulation.

18. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participant names and contact details will be collected for the purpose of contacting participants to obtain follow-up information and to send important trial communications (e.g. reminder messages for trial questionnaires) in accordance with the schedule outlined in this protocol. Participants will always be identified using only their unique trial identification number and initials on the CRF/eCRF and in correspondence between NCTU and the participating site.

Finger, stylus or mouse drawn signatures used on consent forms will be stored within a secure area of the trial database. Receipt of consent forms will be used to perform in-house monitoring of the consent process. Sites may also use paper versions of the informed consent form; these will then be uploaded into a secure area of the trial database.

The Investigators must maintain documents not for submission to NCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

NCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g., competent authority, Sponsor). Representatives of NCTU and Sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

19. Insurance and Indemnity

University College London (UCL) will act as sponsor for the trial. Delegated responsibilities will be assigned to the NHS Trusts taking part and NCTU.

UCL hold insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should be advised to do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office. Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

The University of Nottingham and University College London has appropriate insurance coverage in place (including, but not limited to Clinical Trials, Professional Indemnity, Employer's Liability, and Public Liability policies) in relation to the Institution's Legal Liabilities arising from the University's activities and those of its staff, whilst conducting University business and research activity.

UCL (the sponsor) is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

20. Publication Policy

The dissemination of the proposed research findings will be via a published HTA monograph, research papers for publication in peer reviewed journals, presentation at scientific conferences and communication of the findings to groups involved in guideline development. Manuscripts will be prepared by the CI, deputy CI and TMG and authorship will be determined by mutual agreement. The TSC and DMC will be given opportunity to comment on the manuscripts prior to submission.

Any secondary publications and presentations prepared by Investigators must be reviewed by the CI, deputy CI and NCTU. Manuscripts must be submitted to either party in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues.

Authors must acknowledge that the trial was performed with the support of University College London.

All publications will acknowledge the support of the NIHR in funding this trial.

Trial participants will be asked whether or not they would like to receive a summary of the research findings, following the publication of the results. The research summaries will also be provided to the PPI partners, who can circulate to their membership.

Publications arising from further research conducted using shared trial datasets should appropriately acknowledge the trial investigators and funder.

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