# Premature Ovarian Insufficiency Study of Effectiveness of hormonal therapy (POISE)

(Hormone therapy for premature ovarian insufficiency: randomised trial and long-term evaluation)

## Site Initiation Training

Version 1.4, 31 Jul 2023



University of Nottingham UK | CHINA | MALAYSIA

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FUNDED BY NIHR | National Institute for Health and Care Research



NOTTINGHAM CLINICAL TRIALS UNIT at the University of Nottingham

# Agenda

- Welcome and Introductions
- Trial Organisation
- Trial Background & Rationale
- Trial Design
- Protocol
- Sub-study (only applicable for selected sites)
- Trial Process Breakdown
- Safety
- Data
- Roles and Responsibilities
- Monitoring
- Trial Administration
- Thank you and Question session

# Welcome and Introductions

# Trial Management & Key Contacts

## NCTU Team

Jane Daniels – Deputy CI
Clare Upton – Senior Trial Manager
Damini Mistry – Trial Manager
Wendy Daunt – Trial Coordinator
Jay Seale – Trial Administrator
Data Manager – Richard Swinden
Data Coordinator – Hollie Harvey

## UCLH Team

Melanie Davies – Chief Investigator
Zach Nash – Sub-study Lead / co-applicant

**poise@nottingham.ac.uk**

# Before we start...

## Sub-study

There will be references to the sub-study in this presentation. Please note this will only be applicable to sites: UCLH, Imperial College and Guy's and St Thomas'.

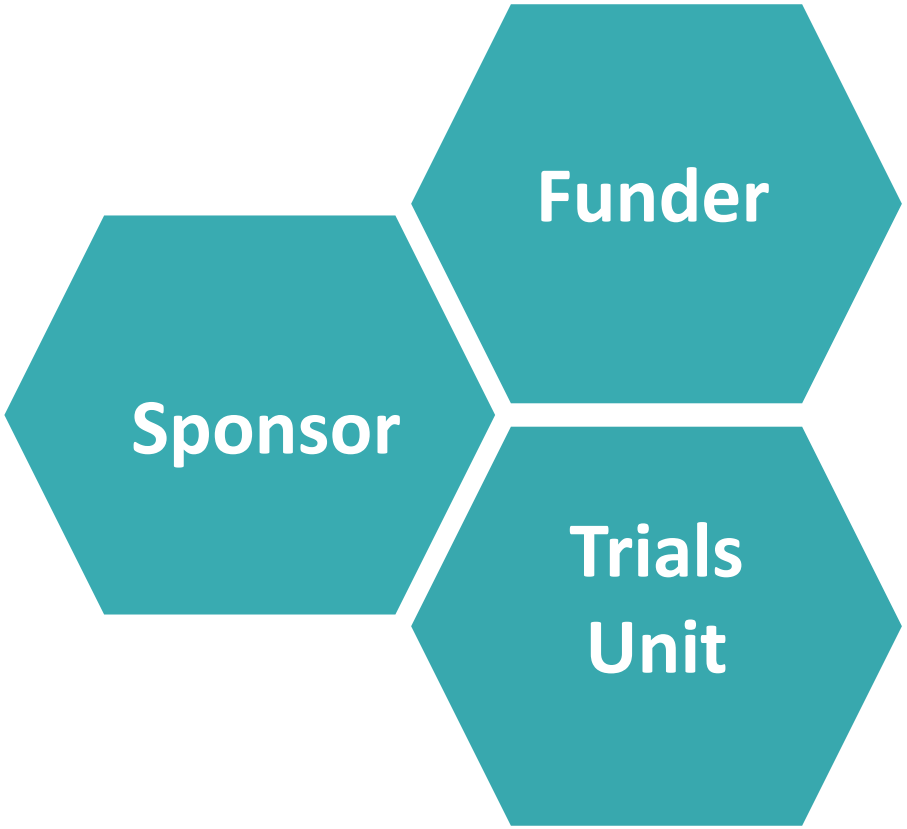
## Scottish sites only

HRT Prescription Costs– please note any references to HRT prescription costs/voucher compensation to participants will not apply to your site.

# Trial Organisation

# Trial Organisation

POISE

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# Oversight Committees

## Trial Management Group

Day to day management

Review recruitment, retention, compliance and data quality to ensure efficient study conduct

Report to the Trial Steering Committee (TSC)

## Trial Steering Committee

Provide independent oversight of the study

Approve trial protocol

Approve changes to protocol based on considerations of feasibility and practicability

Review data reports

Resolve problems

Ensure publication

## Data Monitoring Committee

Assess safety and efficacy of the intervention during the trial

Monitor overall conduct

Protect validity & credibility

Monitor evidence of treatment differences

Monitor safety data

Review Stop-Go data

# Trial Background & Rationale

# Background and Rationale

- The cause of Premature Ovarian Insufficiency (POI) is often unknown, can be caused by genetic conditions such as Turner's syndrome, as well as immune disorders, treatments for cancer, or surgery involving the ovaries.

- Women with POI are treated with either the combined oral contraceptive pill (COC) or hormone replacement therapy (HRT). Both are recommended treatments.

- The trial aims to find out what is the most effective hormone treatment for women with POI, in both the short and long-term.

# POI and oestrogen depletion

POI is associated with low levels of circulating oestrogen. Ovarian function can fluctuate in some women prior to complete cessation

Symptoms of oestrogen deficiency include;

**SYMPTOMS**

**Hot flushes &/or night sweats**

Vaginal atrophy (dryness) causing painful intercourse

**Low libido**

Low energy levels/fatigue

**Sleep disturbances**

Lack of concentration/brain fog

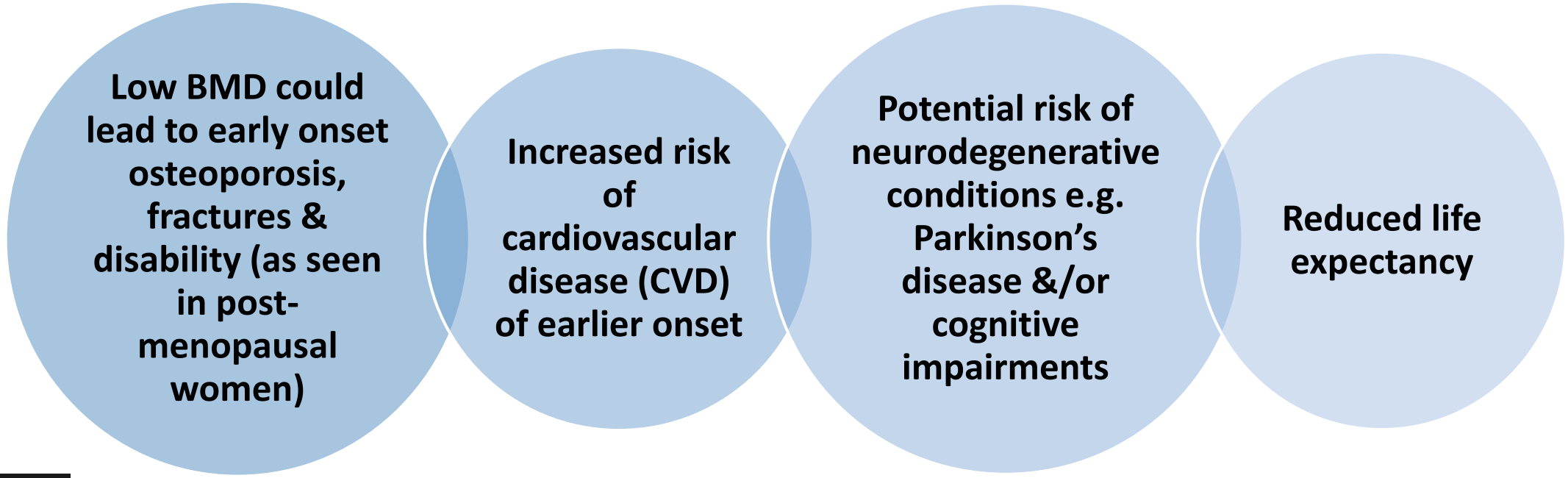
**Muscle & joint aches/stiffness**

Skin/hair changes

**Labile mood**

# Long-term outcomes of POI

- Long-term health issues can be widespread and severe:



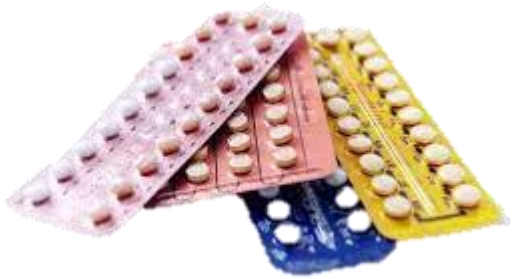
# Current treatment

Two preparations widely prescribed in the UK as oestrogen replacement for women with POI

**COC** seen as socially acceptable by younger women, may reduce stigma associated with menopause

Contraceptive cover (5-10% of POI women able to conceive)

Free of prescription charges



**HRT** provides physiological replacement of oestrogen

Likely to sustain long-term health benefits

Different oestrogen formulations and may have different benefits & risks

Some evidence HRT is superior to COC in increasing/maintaining bone density but not sufficient to change clinical practice at the moment

Currently a lack of robust data to aid women's decision making on treatment – causes variations in clinical practice and advice creating confusion

# Equipoise

***"A true state of equipoise exists when one has no good basis for a choice between two or more care options."***

- Important that clinicians are in equipoise
- We do not know which hormone treatment, HRT (any route), or COC is better for treating POI
- That is why we are conducting the study!

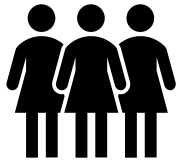
# Trial design

# Trial Design

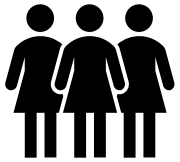
Multi-centre, open, two-group parallel, randomised controlled trial

- 24 Gynaecology clinics in the UK
- Hormone Replacement Therapy (HRT) vs Combined Oral Contraceptive Pill (COC)
- 1:1 ratio

# Recruitment



**We aim to recruit <u>480</u> women**



- **Require 480 participants overall, 100 within first 12 months**
- **Recruitment target of 1 participant per month if possible**
- **36 months recruitment July 2022 - June 2025**
- **All follow up activities are coordinated by site and monitored by NCTU**

# Primary Outcome

Absolute BMD ($g/cm^2$) at 2 years from the date of randomisation, assessed by a standard dual energy X-ray absorptiometry (DEXA) scan of the lumbar spine.

# Secondary outcomes

- **Absolute BMD (g/cm$^2$) in lumbar spine** at 1 and 5 years.
- **Absolute BMD (g/cm$^2$) in hip** at 1, 2 and 5 years.
- **T-score category** (≤-2.5, > -2.5 to ≤ -1, > -1) **for BMD at lumbar spine** at 1, 2 and 5 years.
- **T-score category for BMD at hip** at 1, 2 and 5 years.
- Individual domains (vasomotor, psychosocial, physical and sexual) and summary score of Menopause Specific Quality of Life **(MENQOL)-Intervention questionnaire** at 3, 6 and 12 months then annually.
- Sexual function (pleasure, discomfort and frequency) measured by the **Sexual Activity Questionnaire (SAQ**) at 3, 6, 12 months then annually.
- Work Productivity (absenteeism, presenteeism, work productivity loss and activity impairment), using the **Work Productivity and Activity Impairment (WPAI) Scale (Specific health Problem)** at 3, 6, 12 months then annually.
- **Weight** (kg) at 3, 6, and 12 months then annually.
- **Systolic blood pressure** (mm Hg) at 3, 6 and 12 months then annually.
- **Diastolic blood pressure** (mm Hg) at 3, 6 and 12 months then annually.
- **Pregnancy and pregnancy outcome**.

# Secondary outcomes (cont'd)

- **Satisfaction with treatment**, on a 5-point Likert scale at 3, 6 and 12 months then annually.
- **Change or cessation of treatment** at 3, 6 and 12 months then annually.
- **Adverse events** at 3, 6 and 12 months and then annually. Specific minor-side effects collected will include breast pain, nausea, headaches, skin or hair changes and unscheduled bleeding as well as more serious events such as venous thromboembolism. All serious adverse events will be collected and causal relationship with treatment considered.
- **Diagnosis of cancer, cardiovascular disease, cognitive impairment, bone fractures and mortality** will be collected from routine data sources at 5 years.

**Sub-study sites only:**

- **Bone metabolism markers**, liver function tests, bone profile, and 25 OH Vitamin D. Blood and urine samples will be collected in a subset of participants from selected sites, at baseline, 3 and 12 months (not reported until the end of the study).
- **Cardiovascular markers**. Fasting lipids, fasting glucose, HBA1c, insulin like growth factor and, renal function. Blood samples will be collected in a subset of participants from selected sites, at baseline, 3 and 12 months and then annually up to and including 5 years.

# Pharmacy

- HRT or COC will not be supplied to sites from the NCTU or Sponsor
- No additional trial specific labelling/accountability needed
- Sites will prescribe as per standard care and ask GP to prescribe repeats (6m scripts encouraged for HRT)
- Sites should maintain local accountability and dispensing records as per routine practice

# Blinding

- This is an open label trial, so no emergency unblinding procedures are necessary
- Participants, site-staff, NCTU trial management and data coordinators **will not be blinded**
- NCTU - Trial Statistician and Trial Steering Committee **will remain blinded** to treatment allocations

# Protocol

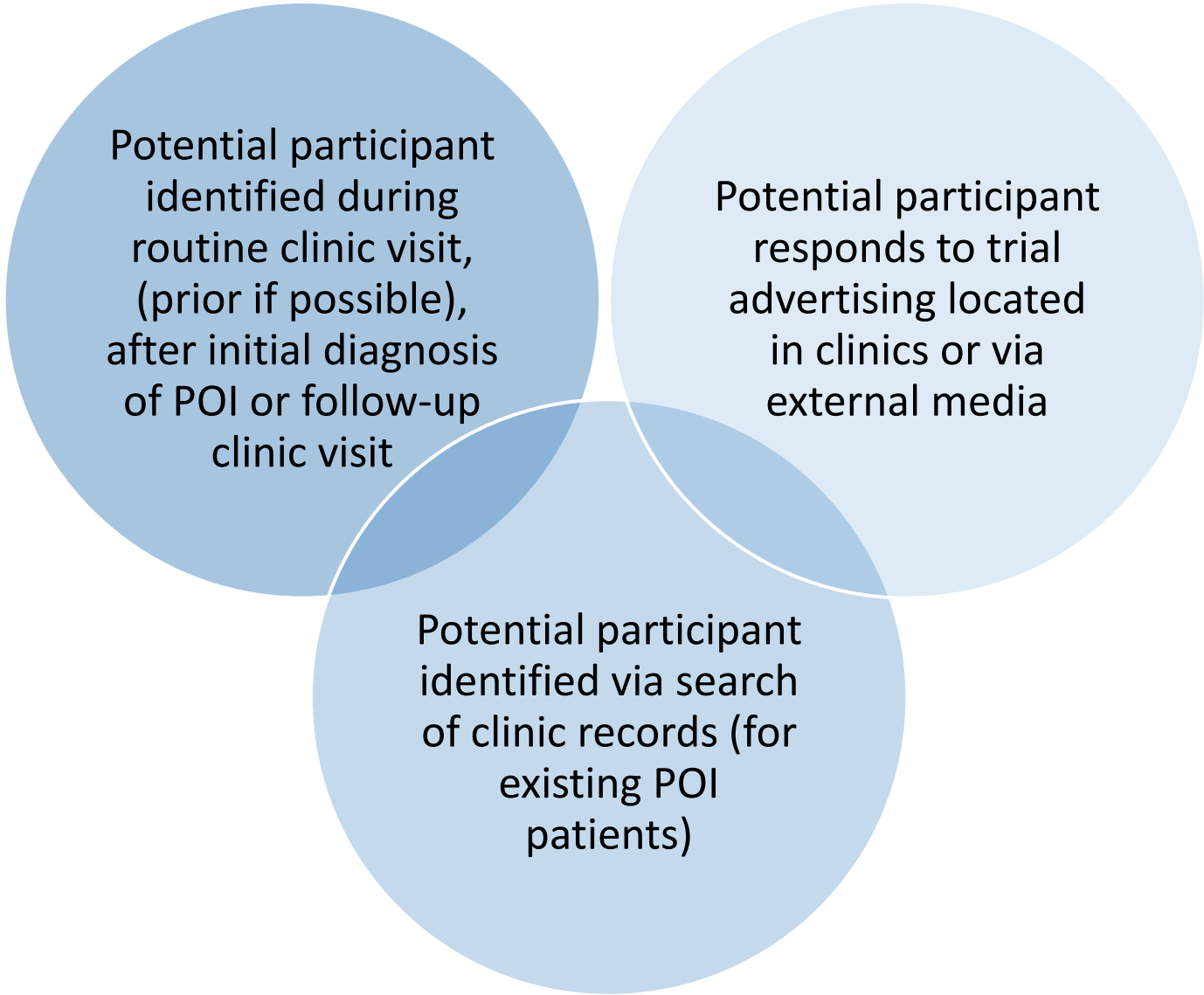
# Inclusion criteria

- ✓ Diagnosis of POI (based on NICE guidelines) or with established diagnosis of POI (e.g., Turner Syndrome, surgical menopause)
- ✓ Aged ≥ 18 years up to <40 years at randomisation
- ✓ Not intending to become pregnant within 12 months
- ✓ Not taken any HRT, COC or testosterone treatment in previous 4 weeks or agree to washout period of 4 weeks prior to randomisation (for accurate baseline measures data collection)
- ✓ Must provide written/electronic informed consent

# Exclusion criteria

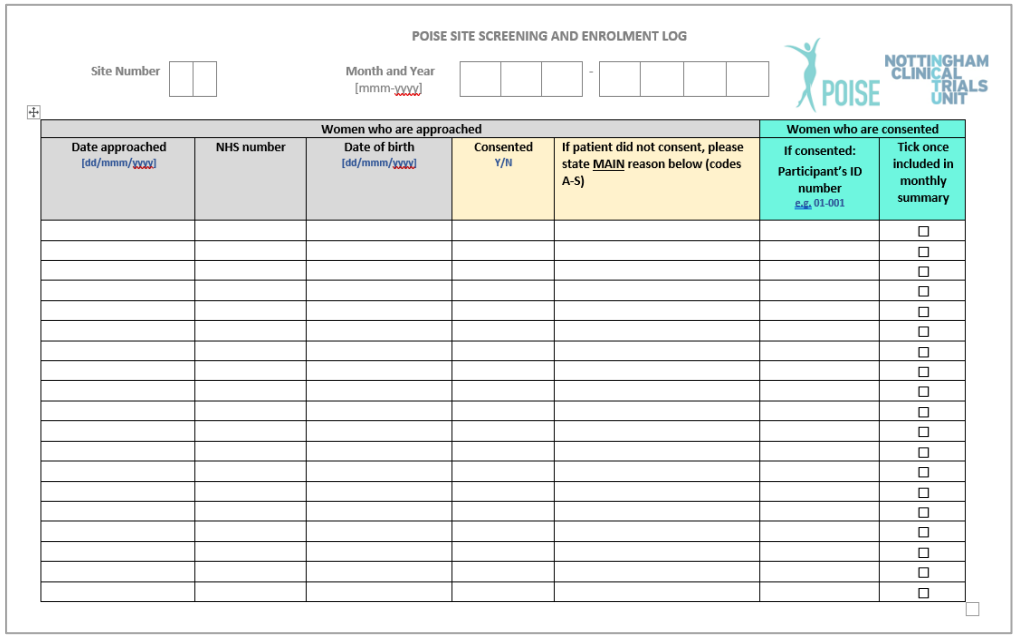
- × Contraindications to HRT or COC
- × Taking other drugs affecting BMD e.g. bisphosphonates, systemic corticosteroids (dietary supplements e.g. vit-D, calcium & short course corticosteroids are permitted)
- × Receiving estrogens for puberty induction
- × Participation in a clinical research study (currently or in the last 3 months) involving testosterone treatment or novel HRT formulations

# Participant Identification



# Screening

- You should record details for all patients who have been approached about the POISE study.
- If patient does ***not*** want to consent, please record **main** reason for not consenting.
- Sites are required to provide a summary of screening data on an ongoing basis which will be reviewed regularly by the TMG and oversight committee.
- Screening information will be recorded on the screening log and then transferred into the trial database.



POISE SITE SCREENING AND ENROLMENT LOG

Site Number

Month and Year [mmm-yyyy]

| Women who are approached | | | | | Women who are consented | |
|---|---|---|---|---|---|---|
| Date approached [dd/mmm/yyyy] | NHS number | Date of birth [dd/mmm/yyyy] | Consented Y/N | If patient did not consent, please state MAIN reason below (codes A-S) | If consented: Participant's ID number e.g. 01-001 | Tick once included in monthly summary |
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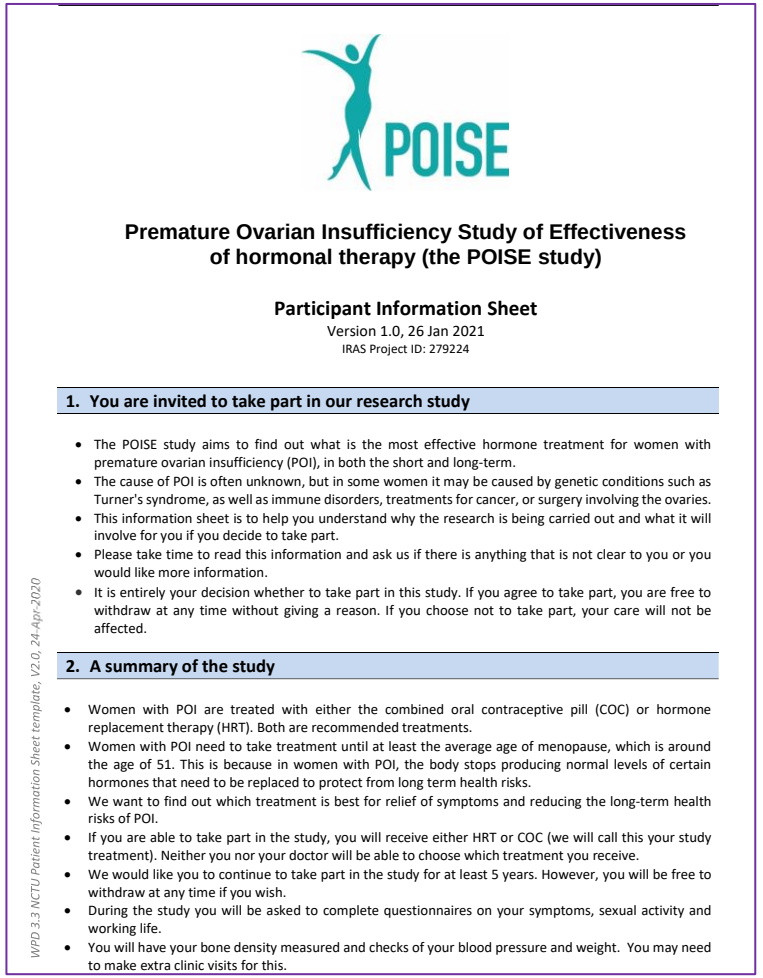
- Paper screening logs are in site file and electronic version will be emailed to your site team

# Participant Information Sheet (PIS)

- Eligible patients will be provided with a PIS and given time to consider participation
- The PIS will be sent to participants electronically once their contact details are entered and saved in the trial database (REDCap)
- Participants identified via database searches will be sent a personalised letter (introducing study and research staff contacts) and a copy of the PIS
- The same PIS is used for all sites including those taking part in the sub study



POISE

**Premature Ovarian Insufficiency Study of Effectiveness of hormonal therapy (the POISE study)**

**Participant Information Sheet**

Version 1.0, 26 Jan 2021

IRAS Project ID: 279224

**1. You are invited to take part in our research study**

- The POISE study aims to find out what is the most effective hormone treatment for women with premature ovarian insufficiency (POI), in both the short and long-term.
- The cause of POI is often unknown, but in some women it may be caused by genetic conditions such as Turner's syndrome, as well as immune disorders, treatments for cancer, or surgery involving the ovaries.
- This information sheet is to help you understand why the research is being carried out and what it will involve for you if you decide to take part.
- Please take time to read this information and ask us if there is anything that is not clear to you or you would like more information.
- It is entirely your decision whether to take part in this study. If you agree to take part, you are free to withdraw at any time without giving a reason. If you choose not to take part, your care will not be affected.

**2. A summary of the study**

- Women with POI are treated with either the combined oral contraceptive pill (COC) or hormone replacement therapy (HRT). Both are recommended treatments.
- Women with POI need to take treatment until at least the average age of menopause, which is around the age of 51. This is because in women with POI, the body stops producing normal levels of certain hormones that need to be replaced to protect from long term health risks.
- We want to find out which treatment is best for relief of symptoms and reducing the long-term health risks of POI.
- If you are able to take part in the study, you will receive either HRT or COC (we will call this your study treatment). Neither you nor your doctor will be able to choose which treatment you receive.
- We would like you to continue to take part in the study for at least 5 years. However, you will be free to withdraw at any time if you wish.
- During the study you will be asked to complete questionnaires on your symptoms, sexual activity and working life.
- You will have your bone density measured and checks of your blood pressure and weight. You may need to make extra clinic visits for this.

*WPD 3.3 NCTU Patient Information Sheet template, V2.0, 24-Apr-2020*

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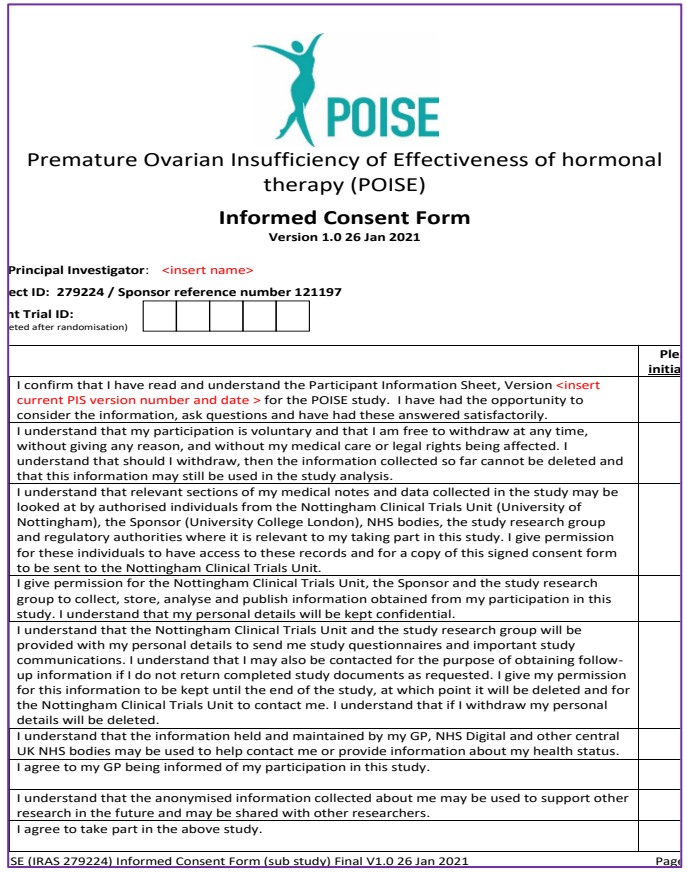
# Informed Consent Form

- All patients must provide written or electronic informed consent (preferred).
- When the eligibility form is completed in the trial database (REDCap) the patient is emailed a link to the consent form which they can complete online.
- Consent must be obtained prior to performing any trial related activities.
- There is a different version of the consent form for sub-study sites.



POISE

Premature Ovarian Insufficiency of Effectiveness of hormonal therapy (POISE)

**Informed Consent Form**

**Version 1.0 26 Jan 2021**

**Principal Investigator**: <insert name>

**ect ID: 279224 / Sponsor reference number 121197**

**nt Trial ID:**
eted after randomisation)

| | Ple initia |
|---|---|
| I confirm that I have read and understand the Participant Information Sheet, Version <insert current PIS version number and date > for the POISE study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. | |
| I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw, then the information collected so far cannot be deleted and that this information may still be used in the study analysis. | |
| I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the Nottingham Clinical Trials Unit (University of Nottingham), the Sponsor (University College London), NHS bodies, the study research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and for a copy of this signed consent form to be sent to the Nottingham Clinical Trials Unit. | |
| I give permission for the Nottingham Clinical Trials Unit, the Sponsor and the study research group to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. | |
| I understand that the Nottingham Clinical Trials Unit and the study research group will be provided with my personal details to send me study questionnaires and important study communications. I understand that I may also be contacted for the purpose of obtaining follow-up information if I do not return completed study documents as requested. I give my permission for this information to be kept until the end of the study, at which point it will be deleted and for the Nottingham Clinical Trials Unit to contact me. I understand that if I withdraw my personal details will be deleted. | |
| I understand that the information held and maintained by my GP, NHS Digital and other central UK NHS bodies may be used to help contact me or provide information about my health status. | |
| I agree to my GP being informed of my participation in this study. | |
| I understand that the anonymised information collected about me may be used to support other research in the future and may be shared with other researchers. | |
| I agree to take part in the above study. | |

SE (IRAS 279224) Informed Consent Form (sub study) Final V1.0 26 Jan 2021 Page

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**Please note: PIS and ICF's are in English language only**

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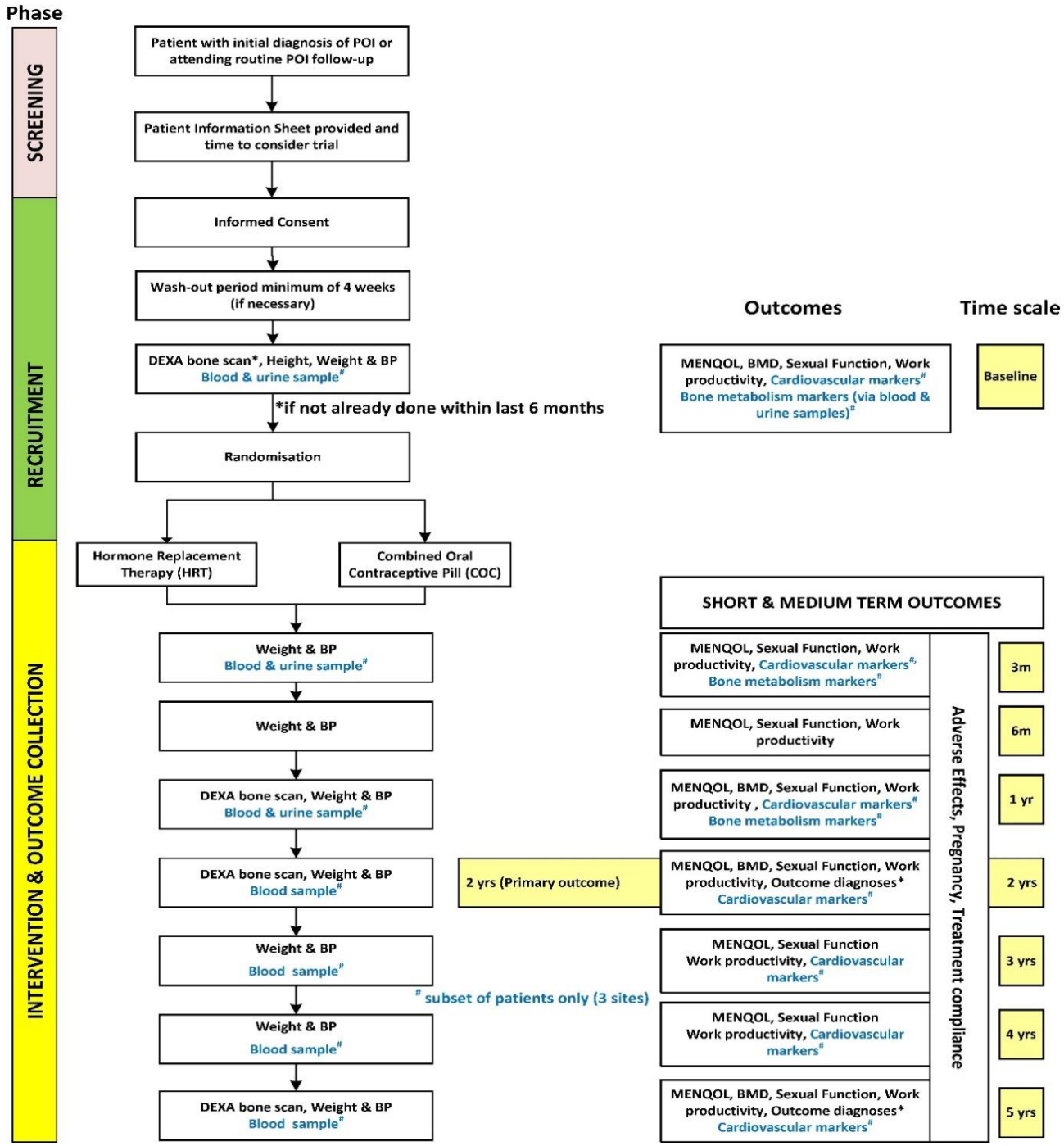
# Consent for sub-study

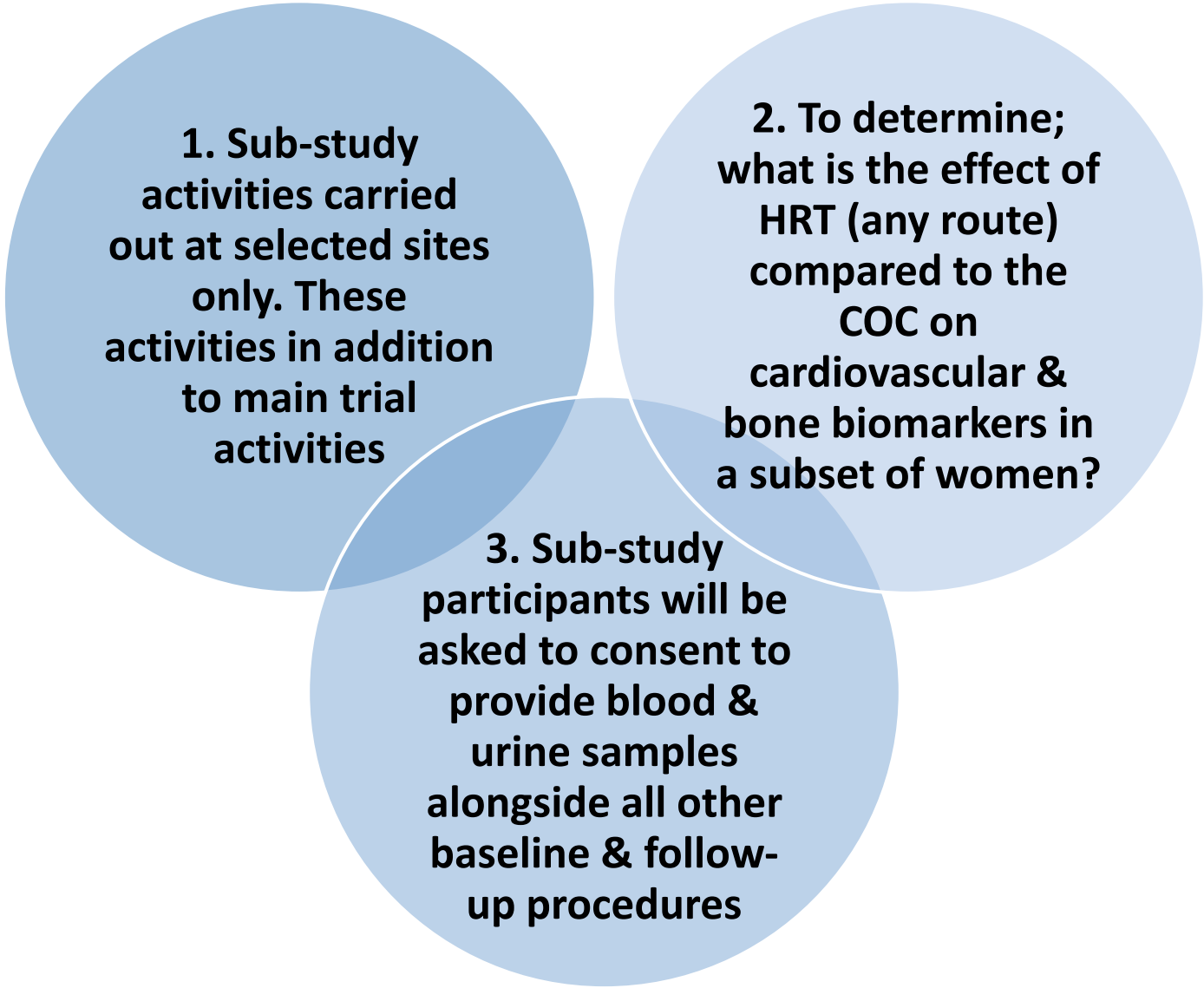
- Consent for the sub-study is optional
- If participants consent, they agree to provide blood and urine samples for bone metabolism and cardiovascular biomarker analysis
- Participants will be asked to consent to storage of some of their samples for future analysis. Including additional specific consent for genetic analysis

# POISE Flowchart



# Sub-Study
# (only applicable for selected sites)

# Sub-study information



# Sub-study continued…

Blood samples for cardiovascular and bone biomarkers will be collected. Some will be analysed immediately following the same process as routine samples using local laboratories. Others will be collected, stored and processed at the end of the sub-study.

**Please remember: all bloods must be taken fasted**

Locally analysed blood sample results will be entered into the trial database by site staff

Full sample collection and handling instructions are in the sample processing manual.

Sample tracking for individual participants blood & urine samples will be entered into a separate trial database via a barcode tracking system.

Samples can only be stored at -20°C for 28 days. After which samples will require -80 °C storage facilities or courier to UCLH.

# Sub-study continued…

## Please remember:

- It is preferable, though not mandated, that sub-study blood tests are taken on a day that the participant takes both oestrogen and progestogen in women taking cyclical HRT or on a day that the participant takes the combined oral contraceptive, rather than hormone free interval.

# Trial Process Breakdown

# Baseline assessment main study

**After informed consent, DEXA scan (within previous 6 months), & washout if applicable, baseline visit data will be collected by a member of the site research team & will include:**

- Patient characteristics, demographics, smoking, alcohol & exercise habits
- Quality of life (MENQOL questionnaire) –*sent electronically when eligibility confirmed*
- Sexual function (SAQ) – *sent electronically when eligibility confirmed*
- Work productivity (WPAI questionnaire) – *sent electronically when eligibility confirmed*
- Blood pressure (BP) & weight (refer to details in upcoming slide for BP measurement)
- Height

# Baseline assessment sub-study

**After informed consent, DEXA scan (within previous 6 months), & washout if applicable, baseline visit data will be collected by a member of the site research team & will include:**

Undergo all activities of the main study (detailed in previous slide) and the following additional activities

- Blood samples for bone & CVD biomarkers (selected sub-study sites only)
- Urine samples for bone biomarkers (selected sub-study sites only)

**Please refer to sample processing manual for full details of sample handling, storage, & data entry**

# Blood pressure

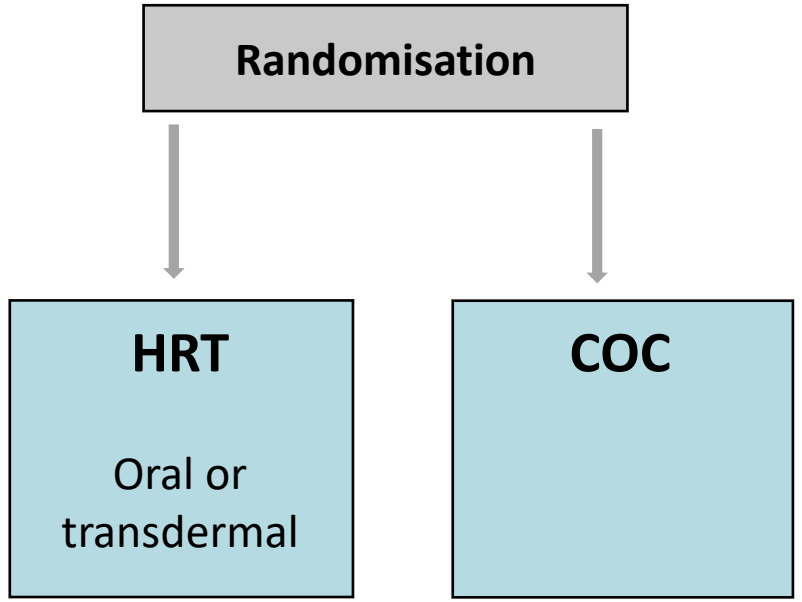
- All blood pressure measurements must be performed after the participant has been lying down at 45° for at least 5 minutes
- 3 measurements should be taken
- 3 separate blood pressure readings should then be entered into trial database (REDCap)

# Points to remember

- Availability of DEXA scan appointments may result in time delays, specifically if the participant requires a baseline scan.
- If the participant has not had a DEXA scan in the 6 months prior to the date of the baseline appointment & randomisation, then baseline assessment & randomisation should be delayed until a scan is performed.
- If possible all the DEXA scans for one participant should be performed on the same machine
- Eligible women who are already on COC/HRT treatment are required to stop treatment for a washout period of a minimum of 4 weeks.
- Participants will have the option to complete questionnaires via access to an electronic format or on paper where requested. If requested these will be provided to participants by site staff. Where paper questionnaires are used these will be entered into the eCRF by the site staff.

# Randomisation

- Patients will be randomised via the study database
- **Randomised** to either HRT (any route) or COC (1:1)
- For women randomised to HRT, patient preference will be taken into account when deciding which route of administration, oral or transdermal, to be used.
- Where there is no preference, the route will be randomly selected using the combined online database/randomisation system.




1:1

HRT v COC

# HRT treatment

**HRT**

- Women randomised to receive treatment with HRT should be prescribed oestradiol in a **daily dose** of 2mg orally, or a 50µg patch, or 1.5mg of gel, given continuously.
- Women with a uterus will also be prescribed progestogen, taken cyclically or continuously. The formulation is not mandated.
- The preferred oral formulation is oestradiol 2mg with dydrogesterone 10mg (Femoston 2/10)
- The preferred transdermal formulation is oestradiol 50µg with norethisterone 170µg patch (Evorel Sequi).
- Alternative formulations can be prescribed if required but must contain oestradiol as mandated above, for example oestradiol gel with micronised progesterone or LNG-IUS.
- Women who are not using the LNG-IUS will be advised to use non-hormonal contraception if required.

# COC treatment

**COC**

- Women allocated the COC should be prescribed 30µg ethinyloestradiol with 150µg levonorgestrel (Microgynon 30 or equivalent) as an extended regimen
- The suggested regimen is 63 days with 7 days hormone-free interval.
- Alternative formulations can be prescribed if required but must contain 30µg ethinyloestradiol in a monophasic formulation.
- Use of a contraceptive patch or ring is not permitted.

# Post-randomisation

- Patients GP will be informed that they are in the trial (template letter available).
- The GP will be informed of the treatment allocated at randomisation and asked to issue further prescriptions of their treatment.
- Participants randomised to HRT treatment can apply for a pre-payment certificate (annual payment of £19.30).

# Follow up assessments

- Follow-up time points will be timed to coincide with routine clinic visits
- Details of which procedures/ assessments are required at each time point are provided in following slides
- Clinician vs participant facing questionnaires:
  - Participants will be emailed links to complete their questionnaires online, (unless paper copies are requested)
  - Clinician facing forms will be completed during the face to face follow-up appointment

# 3 month follow up data collection

## Main study

- Study follow up form
- Problems with treatment questionnaire
- Quality of life (MENQOL questionnaire)
- Sexual function (SAQ)
- Work productivity (WPAI questionnaire)
- Face to face appointment for clinician facing forms, blood pressure and weight

## Sub-study only

- Sub-study samples form – Bloods and urine for CVD and Bone biomarkers

# 6 month follow up data collection

## Main study

- Study follow up form
- Problems with treatment questionnaire
- Quality of life (MENQOL questionnaire)
- Sexual function (SAQ)
- Work productivity (WPAI questionnaire)
- Face to face appointment for clinician facing forms, blood pressure and weight

## Sub-study only

**No sub-study samples are taken at 6 months**

# 12 month follow up data collection

## Main study

- Study follow up form
- Problems with treatment questionnaire
- Quality of life (MENQOL questionnaire)
- Sexual function (SAQ)
- Work productivity (WPAI questionnaire)
- Face to face appointment for **DEXA scan**, clinician facing forms, blood pressure and weight

## Sub-study only

- Sub-study samples form – Bloods and urine for CVD and Bone biomarkers

# 2,3,4 & 5 year follow up data collection

## Main study

- Study follow up form
- Problems with treatment questionnaire
- Quality of life (MENQOL questionnaire)
- Sexual function (SAQ)
- Work productivity (WPAI questionnaire)
- Face to face appointment for **DEXA scan (years 2 and 5 only)** clinician facing forms, blood pressure and weight

## Sub-study only

- Sub-study samples form – Bloods for CVD biomarkers (no urine samples)

# Pregnancy during treatment

- Women who become pregnant will remain in the study but should stop taking their allocated treatment for the duration of their pregnancy.
- After the birth, the allocated hormonal treatment should be resumed following the advice of the participants' doctor.
- At each follow up time point participants will be asked their pregnancy status, and if applicable, pregnancy outcomes via a clinician completed questionnaire.

# Retention

## Retention is just as important as recruitment

### Ways you can help us improve retention…

- ✓ Ensure participants are aware of the importance of us collecting follow-up data, completing questionnaires and attending clinic appointments
- ✓ Explain processes clearly to them
- ✓ Ensure correct contact details are recorded
- ✓ Remind them of the vouchers they will receive (HRT allocation only)

# Safety

# Safety reporting

**Adverse Events (AE):** any untoward medical occurrence in a patient administered a medicinal product which does not necessarily have a causal relationship with this treatment

**Serious Adverse Event (SAE)**: is an AE which:

- Results in death
- Life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity, or
- Congenital anomaly/birth defect
- Other medically important event

**'Important medical events' are considered serious if they jeopardise the participant's health or require an intervention to prevent any of the above consequences**

# Adverse Events (AEs)

**The following expected AEs will be participant-reported and collected via the problems with treatment questionnaire at 3, 6, 12 months, then yearly up to 5 years.**

- Unscheduled bleeding
- Breast pain
- Nausea
- Headaches
- Skin or hair changes (acne/facial spots, greasy or oily skin, hair loss/hair thinning, hirsutism (=excessive hair growth on face or body))
- Dysmenorrhoea (period pains)
- Menorrhagia (heavy periods)
- Premenstrual syndrome (PMS)
- VTE or pulmonary embolism (PE)
- Broken bone(s)

**NB: Where any of the events result in hospital admission or prolonged hospital stay this will require reporting on a SAE form**

# Serious Adverse Events (AEs)

Investigators will report AEs that meet the definition of an SAE.
An SAE is defined as an AE that meets at least one of the below criteria:

- results in death;
- is life-threatening;
- requires hospitalisation or prolonging of existing hospitalisation;
- results in persistent or significant disability or incapacity; and
- consists of a congenital anomaly or birth defect.

If a participant has an SAE The Principal Investigator (or delegate) must send a completed SAE form to the NCTU within 24 hours of obtaining the information. When completing the form, the PI will be asked to define the causality and the severity of the SAE

**To report an SAE, email the SAE Form to:** **nctu-sae@nottingham.ac.uk**

# Data

# Data Entry

- All data will be entered into the REDCap system (eCRF) including screening, enrolment, randomisation, treatment details, follow-up data etc

https://redcap01.nottingham.ac.uk/

# Data Collection

- Data will be entered directly into the trial database (eCRF).
- Paper CRFs can be provided to assist with the collection of trial data but only if this is requested or necessary.
- Completed paper CRFs MUST be retained at site.
  - Where paper CRFs have been used, data should be entered within 7 days of collection.

# Source data

- Source data is the first place data is recorded, this is considered source data and must be retained e.g.
  - **Paper questionnaires**
  - **Electronic CRF (REDCap)**
  - **Patient Medical Notes**
  - **DEXA scan results**
  - **Laboratory blood results (if applicable)**

- Source Data Location Log – should be completed to indicate where data is located. This should be filed in the POISE Site File, and a copy sent to NCTU.

- **Documents to be filed in Medical Records**
  - Copy of signed Informed Consent Form
  - Copy of Patient Information Sheet

# Protocol Deviations

- Treatment modification - the prescribed formulations can be modified at the discretion of the randomising clinician following discussion with the participant.
- If any dose modifications (increase or decrease) or formulation changes do occur these will be documented in the eCRF and will not be considered protocol deviations.
- Participants are encouraged to stay on allocated treatments. Any changes must remain within the constraints detailed above and not reduce the oestrogen dose.
- Irrespective of any modifications, the participant will remain in the study and will complete all remaining assessments and follow-up questionnaires as planned.

# Discontinuation

- If a patient withdraws their consent prior to randomisation, they will not be randomised, and no follow-up data will be collected.

- Participants may also withdraw their consent for follow-up &/or other trial-related activities /receiving trial-related communications any time after randomisation without giving a reason.

- **The NCTU must be informed of all requests by participants to stop their involvement in the trial as soon as possible;** appropriate action will be taken to ensure that the participant's wishes are fully established & followed.

# Treatment discontinuation

- Participants who discontinue the study treatment or change treatment for any reason will continue to be followed up in accordance with the trial schedule.
- Participants will continue to provide trial data, including completion of follow-up questionnaires for use in the analysis, unless they are unwilling to do so.
- All data collected to be used, any participants that discontinue study treatment will be reminded of the importance of continuing to complete questionnaires and assessments.

# Roles and Responsibilities

# Roles and Responsibilities

**Sites:**

- ✓ Medical care of participants, ensuring their safety and wellbeing
- ✓ Work in accordance with the approved protocol, Good Clinical Practice (GCP), UK Policy Framework for Health and Social Care Research and SOPs
- ✓ Comply with all ethical and legal requirements
- ✓ Ensure consistency and completeness of trial data
- ✓ Participant recruitment
- ✓ Participant baseline and follow-up assessments
- ✓ Keeping and retaining accurate records

**Nottingham Clinical Trials Unit:**

- ✓ Trial management
- ✓ Data management
- ✓ Study oversight and monitoring
- ✓ SAE handling and reporting

# Roles and Responsibilities

**PI or delegate responsibilities:**

- ✓ Legal responsibility for trial conduct & safety reporting at site
- ✓ Trial-related medical decisions
- ✓ Participant confidentiality
- ✓ Source document retention
- ✓ Investigator site file maintenance
- ✓ Safety reporting
- ✓ Protocol deviations
- ✓ Maintain a list of staff & delegated duties
- ✓ Ensure new staff are trained on the current trial protocol (document on training/delegation logs)
- ✓ Ensure staff changes are reported to the Trial Manager
- ✓ Ensure adequate lines of communication with the Trial Manager and NCTU
- ✓ eCRF final sign off
- ✓ Permit monitoring, audit & inspection
- ✓ Archiving (retain all documents & records; NCTU will communicate re archiving towards end of study)

# Research Nurse Responsibilities

- ✓ Maintain:
  - ✓ ISF and trial related documents
  - ✓ Patient identification/enrolment log/ entering details of potential participant contact into screening log
- ✓ Instruct participant with sample collection (if applicable)
- ✓ Completion of eCRFs
- ✓ SAE reporting
- ✓ Prepare for monitoring visits (if required)
- ✓ Manage and implement trial amendments and version control when/if applicable

# Monitoring

# Monitoring

- No routine onsite monitoring visits will take place (low risk)
- Triggered monitoring visits may take place if necessary
- Central monitoring of the following data will be performed remotely by NCTU continuously throughout the trial:
    - Screening data
    - Informed consent forms
    - Eligibility checklists
    - eCRF data
    - Sample results (if applicable)
    - Sample tracking (if applicable)

# Trial Administration

# Investigator Site File (ISF)

- You are provided with an ISF
- Maintenance of the ISF should be delegated on the site delegation log

- The ISF must contain all trial records for the site:
  - Protocol & Trial Manual
  - Patient facing documents (PIS & ICF)
  - Study logs (training & delegation)
  - Screening log
  - Approvals (local & trial)
  - Agreements
  - Staff CV's & GCP certification
  - Monitoring records
  - SAE documentation
  - Other important documents & correspondence

**GCP certificates and CVs**

GCP certificates (dated within 2 years) and signed and dated CVs must be collected for **all** members of staff listed on the delegation log.

# What happens next

Site file, documents to be signed/completed for the green light checklist:

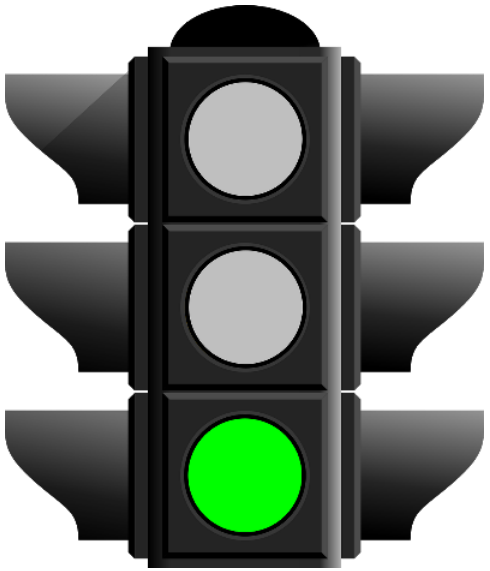
- Protocol signature page
- SmPC signature page
- Staff CVs / GCPs
- Source data location log
- Training log
- Delegation log
- Site visit log
- SIV report

# Green Light Approval

- When all documents and approvals are in place, NCTU will complete a **Green Light checklist**

- This is official notification that the site is open and can start recruiting participants

- NO TRIAL ACTIVITY can begin prior to receiving the Green Light checklist from NCTU



# Contacts

- Trial team: poise@nottingham.ac.uk
- Trial website: www.poise.nottingham.ac.uk
- Prof. Melanie Davies (CI): melanie.davies@ucl.ac.uk

## Social Media

Twitter: @poisestudy

Instagram: @Poise.Study

Join our WhatsApp group by scanning the QR code:

# Thank you, any Questions?