Prolapse management: Effectiveness of PFMT plus PessarY

Randomised controlled trial of the clinical and cost effectiveness of supervised pelvic floor muscle training plus vaginal pessary compared to supervised pelvic floor muscle training alone for management of pelvic organ prolapse

PROTOCOL

A UK Collaborative Trial funded by the National Institute for Health and Care Research, Health Technology Assessment (HTA) Programme

This Protocol has regard for the HRA guidance and order of content.

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Funder

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Other

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Signatures

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, 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.

Suzanne Hagen: _____ signature

Date: 27/02/25

Prof Sharron Dolan _____ signature

Date: 27/02/25

VERSION HISTORY

Amendment no.	Protocol version no.	Description of changes (*incl. author(s) of changes*)	Date of document
	Draft Version 1.0	1st Draft to NIHR for approval	3/11/24
	Version 1.1	S Hagen made the following changes: • Change to wording as requested by HTA • Added Appendix B Consent Pathways • Changed from PISQ to ICIQ-VS Sexual Matters subscale as sexual function outcome measure • Changed time without a pessary before outcome measurement from 4 weeks to two weeks. • Added S. Cotton as replacement co-investigator • Updated detail about process evaluation consent processes • Changed Finance and Insurance section wording • Changed simplified POP-Q to full POP-Q measure • Flow diagram updated	22/11/24
	Version 2.0	• TSC and DMEC members added • References to informing participant's GP removed • Removed collecting ethnicity from un-consented patients • Figure 2 updated to show current plan for opening of centres • Updated scales used to measure prolapse severity for randomisation minimisation • Numbering of participant letters updated • Information added on insurance • Confirmation of handling of audio-recorded data in section 12.2.3 • Other minor edits to correct inconsistencies	21/01/2025
	Version 3.0	• Correction in section 5.1 Use of electromyography biofeedback, pressure biofeedback, and electrical stimulation as part of the PFMT programme will NOT be permitted in either trial group.	26/02/2025

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TRIAL SUMMARY

TRIAL TITLE	Randomised controlled trial of the clinical and cost effectiveness of supervised pelvic floor muscle training plus vaginal pessary compared to supervised pelvic floor muscle training alone for management of pelvic organ prolapse
Short title	PEPPY: effectiveness of PFMT plus pessary for prolapse
CT Clinical phase	Phase 3
Rationale	Pelvic organ prolapse causes distressing vaginal, bladder, bowel and sexual symptoms, and impaired quality of life. On examination, 40% of women over 50 years of age have prolapse, symptomatic prolapse affects 11% of women, and prevalence increases with age. Supervised pelvic floor muscle training (PFMT) is an effective non-surgical option for treating and preventing prolapse symptoms and is first line management. A vaginal pessary, a support device inserted vaginally to hold the prolapsed organs in place, also provides symptom relief, and two thirds of women try a pessary when offered. PFMT and pessary are used together in clinical practice by some healthcare professionals, however there is insufficient evidence supporting this practice, therefore NICE identified this as a research gap. Inserting a pessary may allow the pelvic floor muscles to be trained more effectively by reducing the obstructing prolapse, leading to a better treatment outcome. This research will establish effectiveness and cost-effectiveness of PFMT plus pessary, and also investigate intervention context and implementation, to inform evidence-based practice and service delivery.
Trial design	A pragmatic multicentre parallel group superiority randomised controlled trial with an internal pilot, parallel process evaluation and economic evaluation.
Eligibility criteria	We will include all women ≥18 years who have been referred for PFMT for prolapse of any severity, even if they have had previous prolapse treatment at any time (PFMT, pessary, surgery) as currently PFMT would be offered for all such women. If a woman has significant vaginal tissue atrophy, this will be treated according to the centre's usual practice, and will not be reason for exclusion or delay in randomisation. We will exclude: women for whom prolapse is not the main presenting problem; women currently using a vaginal pessary (unless they discontinue for 1 month); women who are pregnant or less than 6 months' postnatal; women having active treatment for pelvic cancer; women with severe vulval disease; women who have cognitive impairment affecting capacity to give informed consent.
Interventions	Supervised PFMT plus vaginal pessary as an adjunct (Intervention) and supervised PFMT alone (Control)
Randomisation and blinding	Individual women will be randomised to the trial groups 1:1, with minimisation on age, severity of prolapse and centre. It is not possible to blind women or treating clinicians to group allocation, however assessment of pelvic floor muscle function and prolapse severity at 12-month follow-up will be conducted by an assessor blinded to the participant's trial group.
Planned sample size	Five hundred and fifty-two women (276 per group) will be randomised to provide 90% power to detect a difference of 12 points in the PFDI-20 score at 12 months. This allows for a 40% pessary fitting non-success rate, which would potentially reduce the group difference in PFDI-20 from 20 (the upper limit of the minimal clinically important difference) to 12, which remains within the lower limit of 6.2. A standard deviation of 40 is

	assumed, two-sided alpha of 0.05, and 15% loss to follow-up.	
Duration of trial	42 months	
	Objectives	Outcome measures
Primary	1)To undertake a randomised controlled trial to establish if a supervised PFMT programme with the addition of a vaginal pessary, compared to supervised PFMT alone, is more effective in improving prolapse symptoms, prolapse-specific and general quality of life, adherence to, and self-efficacy for, treatment, perceived treatment benefit, sexual function, pelvic floor muscle function and prolapse severity at 12 months.	Pelvic Floor Dysfunction Inventory-20 (PFDI-20)
Secondary	2)To undertake an internal pilot to ensure the trial can recruit, randomise and retain sufficient numbers of participants, and deliver the intervention as planned. 3)To undertake an economic evaluation to establish whether supervised PFMT plus vaginal pessary is cost-effective compared to supervised PFMT alone. 4)To undertake a process evaluation (PE) to inform trial recruitment methods, and to explore and expand the proposed programme theory by understanding intervention context and implementation (fidelity, acceptability and adherence) within the trial.	• Condition-specific quality of life (PFIQ-7) • Generic quality of life (EQ-5D-5L) • Patient Global Impression of Improvement (PGI-I) • ICIQ-Vaginal Symptoms module (ICIQ-VS), Sexual Matters subscale • Uptake of other prolapse treatment • Pelvic Floor Muscle Exercise Self-efficacy Scale • Intervention adherence • Pelvic floor muscle strength / function (MOS) • Prolapse severity (simple POP-Q)
Statistical methods	Analyses will be conducted according to a pre-specified Statistical Analysis Plan. The main effectiveness analysis will be based on the intention to treat principle. The analysis of the primary outcome measure will estimate the mean difference in the PFDI-20 score at 12 months between the trial groups using a longitudinal ANCOVA model. Statistical significance will be at the 5% level. The missing at random assumption for primary outcome data will be assessed further in sensitivity analyses. A complete case analysis and a complier average causal effect analysis will also be conducted. Subgroup analyses will be carried out by age and prolapse severity. Secondary outcomes will be analysed using an appropriate generalised linear model. All models will be adjusted for minimisation covariates (age, prolapse severity and centre) and baseline score (where applicable).	
Co-ordination	Local: by local research teams Central: by Trial Office at Glasgow Caledonian University, Glasgow (Telephone tbc) Overall: by the Project Management Group and overseen by the Trial Steering Committee and the Data Monitoring and Ethics Committee.	

LAY SUMMARY

BACKGROUND TO THE RESEARCH

Pelvic organ prolapse is when the organs in a woman's pelvis descend into her vagina. Prolapse is very common, affecting 40% of women over the age of 50, and becomes more common as women age. It has distressing symptoms and negative effects on women's daily lives. One common treatment is pelvic floor muscle training (PFMT) where women are taught by a specialist physiotherapist or nurse how to exercise the muscles around their vagina. If this is done regularly, over time it can reduce the symptoms of prolapse. A vaginal pessary is another prolapse treatment. The pessary, which is a plastic or silicone device (often shaped like a ring), is inserted into a woman's vagina to lift and hold the pelvic organs in place.

UK guidelines recommend that women with prolapse consider PFMT treatment and separately that they can consider pessary treatment. The guidelines suggest that research is needed to find out if adding a pessary to PFMT would be more effective than PFMT alone. Some physiotherapists in the UK have told us they combine these treatments in their practice, and they think it can be beneficial as it holds up the prolapse during PFMT and this improves symptoms more. One study in a single hospital in Hong Kong has looked at this question but the study had some limitations, so a larger study with stronger methods is needed. If combining these two treatments gives better results, this knowledge can be used to improve the lives of women with prolapse. It may also reduce NHS costs if women do not then need further prolapse treatment, such as surgery.

AIMS OF THE RESEARCH

The aim of this research is to find out if wearing a vaginal pessary whilst exercising pelvic floor muscles is better at improving symptoms than exercising pelvic floor muscles without a pessary, for women with prolapse.

DESIGN & METHODS USED

We will invite women with prolapse who are starting PFMT treatment to take part in the study. Women that agree to take part will have an equal chance of receiving PFMT alone (group 1) or receiving PFMT and also having a pessary fitted (group 2). We will collect information on women's prolapse symptoms, the quality of different aspects of their life, whether they feel an improvement, how acceptable they found treatment and how confident they were in doing the exercises, whether they had to have other prolapse treatment and whether their pelvic floor muscles are stronger and the prolapse decreased. We will record this information after 6 and 12 months, and compare the two groups of women to see which treatment is best and which offers the NHS the best value for money. We will ask women in each group about their experiences and record any side effects. We will also ask NHS staff about their experiences of the study and the treatments. This will help us explain why the combined treatment did or did not work better for women.

PATIENT & PUBLIC INVOLVEMENT (PPI)

We have talked with many women who have experience of PFMT and pessary treatment in our previous research. Also, our research team includes three women who have experience of treatment for prolapse, two of whom are co-applicants. Their views have helped us design this study from the outset, and they will work with the research team throughout the study. They have contributed significantly to this summary, as did an independent PPI group at Glasgow Caledonian University.

DISSEMINATION

When the study ends, we will share our findings with those who took part in the research, with groups who support women with prolapse, with healthcare staff and people who plan health services.

GLOSSARY OF ABBREVIATIONS	
AE	Adverse Event
BNF	British National Formulary
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQol Group's 5-dimension/level health status questionnaire
GCP	Good Clinical Practice
GCU	Glasgow Caledonian University
GP	General Practitioner
HTA	Health Technology Assessment
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute for Health and Care Research
PI	Principal Investigator
PIL	Patient Information Leaflet
PFMT	Pelvic floor muscle training
PMG	Project Management Group
POP-Q	Pelvic organ prolapse quantification
NPT	Normalisation Process Theory
PPI/PPIE	Patient and Public Involvement/and Engagement
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration

TRIAL PERSONNEL

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3 Trial Manager: Catriona O'Dolan

4 Data Co-ordinator: Lynn Melone

5 Senior Trial Manager: Seonaidh Cotton

6 Senior IT Manager: Mark Forrest

7 Trial statistician: Catherine Best

8 Process Evaluation researcher: Melanie Dembinsky

Project Management Group (PMG)
This group is comprised of the grant holders, as listed above along with members of the Trial Office team and an additional PPI representative, Curie Freeborn.

Trial Steering Committee (TSC) Members
The membership of this committee comprises independent members, listed below along with the Chief Investigator (CI) (Suzanne Hagen) or a nominated delegate. The other PEPPY grant-holders and key members of the central office (e.g. the trial manager) may attend TSC meetings.

1.	Anu Dua	TSC Chair	Consultant Urogynaecologist
2.	Thomas Chadwick	Non-independent member	Clinical Trials Statistician
3.	Alison Smith	Independent member	Health Economist
4.	Paula Igualada-Martinez	Independent member	Clinical Lead for Perinatal Pelvic Health Service
5.	Reshma Punjabi	Independent member	PPI representative
6.	Bridgette Barrett	Independent member	PPI representative
7.	Sacha Newman	Independent member	Consultant Nurse Urogrynaecology
8.	Lyndsay McDade	Non-independent member	Senior Clinical Research Governance Manager

Data Monitoring & Ethics Committee (DMEC) Members
This committee is comprised of independent members, listed below and the trial statistician contributes as appropriate. The CI and / or a delegate may contribute to the open session of the meetings as appropriate.

1.	Julia Wilkens	DMEC Chair	Consultant Urogynaecologist
2.	Alex Wright-Hughes	Independent member	Clinical Trials Statistician
3.	Jo Dafforn	Independent member	Specialist Pelvic Health Physiotherapist

Role of the Trial Sponsor and Funder
The Sponsor has responsibility for the initiation and management of the trial as defined by the UK Policy Framework for Health and Social Care Research v3.3 07/11/17. This is further defined within an agreement outlining the roles and responsibilities of the parties involved in the research. Specific responsibilities delegated to another party are formally agreed and documented by the Sponsor.

The funder has oversight of the study through regular reports from the trial office. The funder appoints the independent members of the Data Monitoring and Ethics Committee and Trial Steering Committee and receives minutes from these. The funder is made aware of all outputs from the study but does not have a role in the decision to publish results from the study. In any publications, the funder is acknowledged, and appropriate disclaimer used to indicate that the views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

1. INTRODUCTION

1.1 Background

Pelvic organ prolapse is the descent of the female pelvic organs into the vagina. Forty percent of women over 50 years of age have prolapse on examination, and symptomatic prolapse affects 11% [1]. Prolapse prevalence increases with age, and in an ageing population [2] case numbers will rise. Prolapse causes distressing symptoms such as a feeling of something coming down in the vagina, bladder, bowel and sexual dysfunction, which negatively impact on women's quality of life [1].

Both surgical and non-surgical treatment options are available. An estimated 9.5% of UK women have prolapse surgery and 15.8% will have re-operation [3], with the annual cost in England alone being €81M [4]. The recent concerns relating to surgical mesh complications, the rate of prolapse recurrence following surgery and the ageing population have, in combination, increased the focus on non-surgical options such as pelvic floor muscle training (PFMT) and vaginal pessaries. Supervised PFMT delivered by a specialist pelvic floor physiotherapist is effective for strengthening and improving the function of the pelvic floor muscles to treat and prevent the symptoms of prolapse [5,6] and is first line treatment for women referred with prolapse [7]. A vaginal pessary, a support device inserted into the vagina to hold the prolapsed organs in place, also provides symptom relief [8], and two thirds of women try a pessary when it is offered [9]. Types of pessaries include ring, cube, shelf, donut and Gellhorn, which can be made of plastic or silicone, and come in a range of sizes. Medical staff, nurses and, more recently, physiotherapists can fit pessaries with appropriate training.

Both supervised PFMT and pessary are used together in clinical practice. We surveyed members of the UK Pelvic, Obstetric and Gynaecological Physiotherapy (POGP) network of the Chartered Society of Physiotherapy in preparation for this application (n=124 responses, 10% response rate). The vast majority (94%) reported that they had on occasion delivered PFMT for prolapse in women who had a pessary, and 15% had fitted a pessary as part of PFMT. Most believed that inserting a pessary could benefit the outcome of PFMT.

NICE identified that evidence to support this combined treatment is however insufficient [7]. Searches of the Cochrane Library and clinical trial registers (clinicaltrials.gov; WHO (World Health Organization) ICTRP) (searched 2/8/23) for "prolapse" AND "pessary" identified 846 records, of which one was a completed trial comparing PFMT plus ring pessary with PFMT alone [10]. This was also the only relevant trial identified in the Cochrane review on pessary management of prolapse [8]. This was a single-site trial in Hong Kong which NICE judged to be very low quality. Two hundred and seventy-six women were randomised, and the PFMT plus pessary group (n=139) had significantly better prolapse symptoms at 12-month follow-up than the PFMT group (n=137). Unfortunately, there was no "washout" period after pessary removal prior to outcome assessment, therefore the between group difference could have been due to the residual effect of the pessary rather than an additional improvement in pelvic floor muscle function brought about by pessary support during PFMT. Only a ring pessary was available to women in the trial although other pessaries may be more effective for some women depending on their anatomy and type of prolapse.

One small feasibility and randomised pilot study compared pessary plus PFMT with pessary alone [11]. Due to recruitment issues encountered, meaningful conclusions could not be drawn from the limited data, but feasibility issues were identified, and potential solutions found which have informed this application. One trial has compared pessary with surgery [12] and another pessary with PFMT for prolapse [13]. An ongoing trial of pessary plus PFMT versus pessary plus resistance exercise was registered in April 2022 by Silva in Brazil, with a target of randomising 122 women with prolapse (https://ensaiosclinicos.gov.br/rg/RBR-8qnmdpm). None of these studies provide evidence about the effect of pessary as an aide to making PFMT more

effective. A trial evaluating the combination of these established prolapse treatments is needed, and previous research and current practice confirm that such an evaluation is feasible.

1.2 Rationale for the trial

It is hypothesised that, by reducing a woman's prolapse using a pessary the pelvic floor muscles can be trained more effectively, leading to a better treatment outcome than PFMT alone (https://www.jla.nihr.ac.uk/priority-setting-partnerships/pessaries-for-pelvic-organ-prolapse/priority-13-from-the-pessary-use-for-prolapse-psp.htm). The proposed research will generate robust trial evidence regarding the effectiveness and cost-effectiveness of this combined intervention, and also investigate the delivery context to refine the proposed programme theory [14]. In turn, this will inform evidence-based practice and service delivery, leading to optimal outcomes for women. Implementation of the trial findings across the NHS would be supported via updates to the existing NICE guidelines.

The importance of this research for women's health is recognised by many national and international organisations. NICE guidance [7] and the UK clinical guideline for pessary use [15] discuss the possibility of combining PFMT and pessary but highlight the lack of robust evidence. The International Consultation on Incontinence [1] concluded that the combined use of PFMT plus a pessary, rather than PFMT alone, could be recommended for treatment of prolapse although this was based on evidence from one single-site randomised controlled trial in which only ring pessary was used [10]. The NHS England Long Term Plan [16] emphasises the importance of PFMT for prevention and treatment of post-natal prolapse, and undertakes to improve access to pelvic floor physiotherapy. Evidence about the optimal PFMT programme, and the role of pessary as an adjunct, is particularly important for this population of younger women who are unlikely to want surgery.

This pragmatic trial which will provide clear evidence about the clinical and cost benefits, or lack of benefits, of offering women supervised PFMT plus pessary, while also establishing a robust programme theory to explain the influential contexts and mechanisms of any benefit. It has relevance to recent national guidance, addressing an identified uncertainty, with the potential to improve women's outcomes and reduce their need for surgery and the associated costs.

1.3 Assessment and management of risk

The CI will ensure, through the TSC, that adequate systems are in place for monitoring the quality of the study (compliance with GCP) and appropriate expedited and routine reports of adverse events, to a level appropriate to the risk assessment of the study.

Trial participants will be informed of possible benefits and known risks (including known complications) of both interventions in the trial by means of a Participant Information Leaflet (PIL 01), and discussion with the local Research Nurses and clinical team members. Both interventions (PFMT and pessary, and in combination) are routinely used within the NHS. We do not anticipate that participants will run additional risks by participating in the PEPPY trial. They will sign a consent form approved by the Ethics Committee. They will be consented to participating in the trial with follow-up, being randomised, being contacted in the future about this and (optionally) other relevant research. Participants who are not able or not willing to be randomised will not be recruited. Participants will be consented separately for other parts of the study (for example, women will be consented separately if taking part in process evaluation interviews).

2. TRIAL AIM AND OBJECTIVES

The research aims to determine whether supervised PFMT with vaginal pessary as an adjunct is more effective and cost-effective than supervised PFMT alone at reducing symptoms at 12 months for women with pelvic organ prolapse.

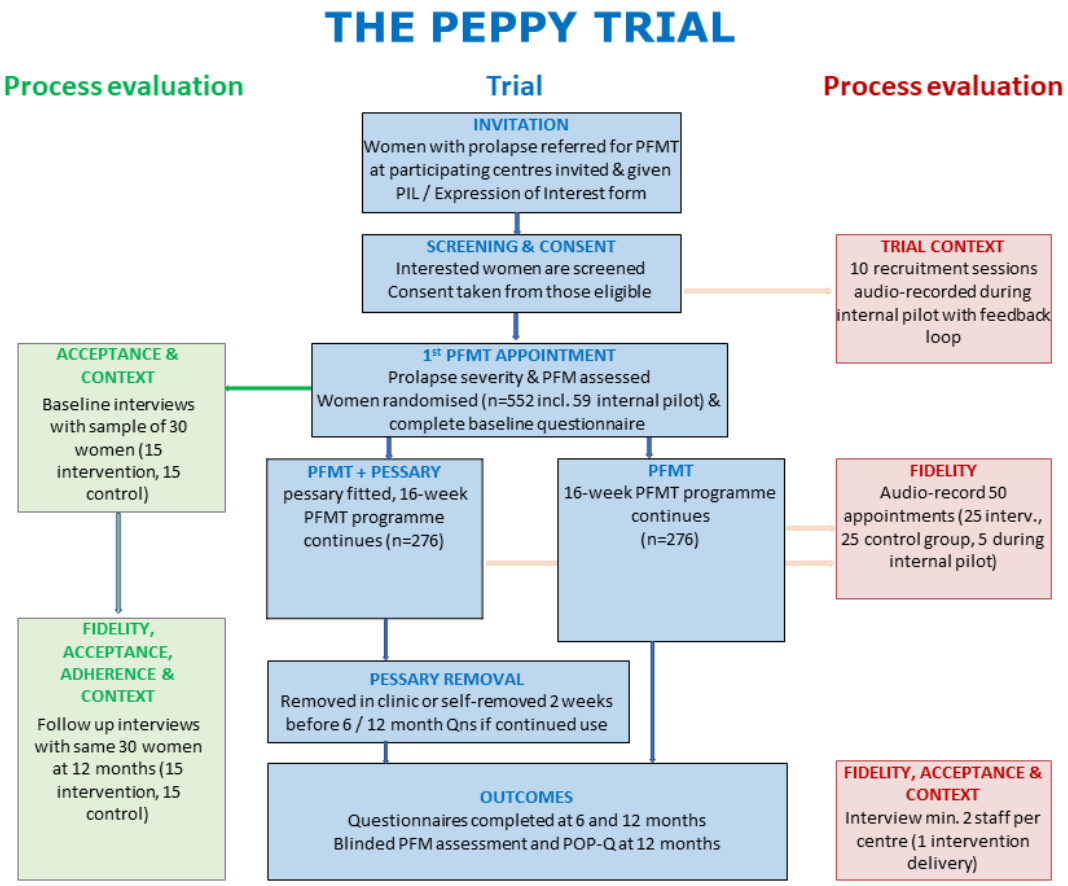
The objectives are:

1. To undertake a randomised controlled trial to establish if a supervised PFMT programme with the addition of a vaginal pessary, compared to supervised PFMT alone, is more effective in improving prolapse symptoms, sexual function, prolapse-specific and general quality of life,

adherence to treatment, perceived treatment self-efficacy, benefit and satisfaction, pelvic floor muscle function and prolapse severity at 12 months.
2. To undertake an internal pilot to ensure the trial can recruit, randomise and retain sufficient numbers of participants, and deliver the intervention as planned.
3. To undertake an economic evaluation to establish whether supervised PFMT plus vaginal pessary is cost-effective compared to supervised PFMT alone.
4. To undertake a process evaluation to inform trial recruitment methods and to explore and expand the proposed programme theory by understanding intervention context and implementation (fidelity, acceptability and adherence) within the trial.

3. TRIAL DESIGN

The study is a multicentre parallel group superiority randomised controlled trial that includes an internal pilot study, economic evaluation and a process evaluation (PE) with PPI embedded throughout. The randomised controlled trial will minimise on age (<52/≥52 years), prolapse severity (POP-Q System: stage 0/1, stage 2, stage 3/4) and centre. The trial has a pragmatic design, testing effectiveness and cost-effectiveness of a treatment policy within an NHS context. The trial reporting will follow CONSORT guidance [17].



3.1 Intervention to be evaluated

Supervised PFMT plus vaginal pessary

The intervention being evaluated is an evidence-based supervised PFMT programme: 16 weeks duration (5 appointments, with a minimum of 3 face-to-face), with the addition of a vaginal pessary being fitted. In most cases PFMT will be supervised by a physiotherapist specialising in pelvic floor rehabilitation, and the pessary fitted by a healthcare professional specialising in gynaecology and pessary care. This may occur at the first PFMT appointment or at a follow-up pessary-fitting appointment soon after.

Supervised PFMT
The control group will receive supervised PFMT, as described above. This is in line with the standard NHS patient care pathway recommended for women presenting with symptomatic prolapse which is a 16-week supervised programme of PFMT [18].

Further details about the intervention are provided in section 5.1.

4. TRIAL RECRUITMENT

4.1 Trial population
552 women ≥18 years who have been referred for PFMT for the treatment of prolapse of any stage will be randomised. NICE guidelines recommend that PFMT is considered for women with stage I and II prolapse [18], however in practice women with more severe prolapse at stage III are also referred for PFMT and are considered more likely to benefit from PFMT plus pessary (POGP survey) and therefore will be included.

4.2 Setting
Recruitment will take place in the context of hospital outpatient departments and community clinics where PFMT is delivered. Initial identification of potential participants will involve screening of clinic referrals and waiting lists for PFMT for prolapse.

4.3 Inclusion and exclusion criteria

Inclusion criteria:
We will include all women ≥18 years who have been referred for PFMT for prolapse of any severity, even if they have had previous prolapse treatment at any time (PFMT, pessary, surgery) as currently PFMT would be offered for all such women. If a woman has significant vaginal tissue atrophy, this will be treated according to the centre's usual practice, and will not be reason for exclusion or delay in randomisation.

Exclusion criteria:
We will exclude: women for whom prolapse is not the main presenting problem; women currently using a vaginal pessary (unless they discontinue for 1 month); women who are pregnant or less than 6 months' postnatal; women having active treatment for pelvic cancer; women with severe vulval disease; women who have cognitive impairment affecting capacity to give informed consent.

4.4 Identifying and approaching participants
Centre staff will identify women with prolapse referred for PFMT from referral letters and waiting lists and make contact with them prior to their first PFMT appointment to provide a Participant Information Leaflet, an invitation (Invitation 01) to consider taking part and an expression of interest form to return. Women who indicate they are interested will be screened for eligibility and have a participation discussion, prior to completing the consent form and baseline questionnaire.

All participants will have the option to complete the consent form and questionnaires electronically rather than completing a paper copy. A written record of the consent discussion, including discussion date, will be kept in the Eligibility CRF, and a copy filed in the medical records.

4.5 Non-recruited participants
The following anonymised information will be monitored and collected for all eligible women who choose not to take part:
- Year of birth
- Date of consultation when approached about the trial
- Reason for not participating if willing to give a reason

4.6 Informed consent

Dedicated staff members at each centre (appropriately trained and named on the delegation log) will make follow-up contact with women who indicated they would like to discuss the trial in full and carry out eligibility screening. They will obtain informed consent (written or e-consent) from those women who are eligible and willing (Main Trial, Consent Form 01). Paper consent forms will be checked, signed and dated. A copy of the consent/e-consent form will be held in the Site Investigator's File and the Trial Office's Trial Master File (TMF) and a copy will be given to the participant. Participants will complete a baseline questionnaire (postal or electronic as per the participant's preference).

Informed consent to participate in the trial will be sought and obtained according to Good Clinical Practice (GCP) guidelines. As part of the informed consent process, potential participants will be made aware of all aspects of the trial, including the potential risks and their responsibilities. There is no minimum time that potential participants should be given to decide whether to participate in the trial. Potential participants will be given enough time, and as long as they want, to accept or decline involvement and will be given opportunity to ask questions and to have these answered before giving consent.

It will be explained that entry into the trial is entirely voluntary, and that treatment and care will not be affected by their decision, and they can withdraw at any time. In the event of their withdrawal, it will be explained that their data collected to date cannot be erased and will be used in the final analyses.

Participants who cannot give informed consent (e.g. due to cognitive incapacity) will not be eligible for participation. Following informed consent, if a participant loses capacity, the consent given when capable remains legally valid. Identifiable data collected with consent will be retained and used in the study but no further data will be collected or research procedures carried out.

Participants who are not able to read or write (but who have capacity and can speak English sufficiently to understand the information being provided verbally) can agree to take part in the trial. In such cases, the trial team will provide them with written literature about the trial and read and discuss this information with the potential participant, if appropriate using interpreters provided by recruitment centres (where available). There should also be a discussion about the support networks that the participant has to facilitate their participation in the trial (for example help to complete questionnaires). If the potential participant is fully informed and wishes to take part in the trial, they will be asked to sign or make their mark on the consent form.

Within the consent form participants will be asked if they are willing to have an intervention appointment audio-recorded (yes/no) and if they are willing to hear more about being interviewed (yes/no) as part of the process evaluation. They will also be asked about being contacted in the future about this and (optionally) other relevant research.

Procedures to seek and gain informed consent from eligible potential participants are agreed and confirmed by Research Ethics Committees with responsibility for reviewing applications for research. The application for approval is made via the NHS Health Research Authority Research Ethics Service.

4.6.1 e-Consent

For participants who opt to consent using an e-consent form, they will do this via the secure web-based trial management system provided by CHaRT. If this option is preferred, participants will be asked to provide their email address which will be entered into the secure web-based trial management system. Participants will be sent a verification email with a link to verify their email. Once the email address is verified, participants will be automatically emailed the PIL (PIL 01) and a link to the participant e-consent form and baseline questionnaire for their unique study number. The e-consent form will be identical to the approved paper version of the consent form, with the approved PIL version number and date automatically populated. The participant will be

asked to provide their signature online via a signature box using a finger tracing via a touch screen or using a mouse.

Completed e-consent forms will be checked, and electronically counter-signed by someone listed on the delegation log with appropriate delegated responsibilities. The countersignature will only be recorded after discussion has taken place with the participant about the study and any questions have been answered. Only once both participant and person receiving consent signatures are present will informed consent be considered to have been obtained. Any e-consent obtained will be verbally confirmed by the centre and the Trial Office before intervention commences. Participants will be sent a copy of the e-consent form for their own records and a copy will be retained in the investigator site file and TMF.

Should participants choose not to take part in the study their email address will be deleted from the trial management system after 3 months.

The trial management system used to record e-consent has a clear audit trail with tracking of all inserts or updates made. Database interactions are logged against a user and date/time and the audit trail can be downloaded and analysed at any time by authorised users.

4.7 Randomisation and allocation

When eligible consented participants attend their first PFMT appointment they will be randomised to one of the two groups using a secure web-based database and randomisation system developed and hosted by the Clinical Trials Unit (The Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen). Allocation will be minimised on age (<52/≥52 years), prolapse severity (POP-Q System: stage 0/1, stage 2, stage 3/4) and centre, ensuring balance between randomised groups in these factors. If a potentially eligible woman is identified in clinic prior to triage for PFMT (e.g. in a consultant gynaecology clinic appointment which involves vaginal examination), screening, consenting, randomisation could be triggered earlier.

Centre staff will make arrangements for each participant's follow-up PFMT appointments, and in addition a pessary fitting appointment, within 2 weeks, for participants randomised to PFMT plus pessary. Pessary fitting may occur at the first PFMT appointment, for example if the physiotherapist is trained in fitting pessaries, or if it is current practice to provide both services together.

4.8 Blinding

It is not possible to blind women or treating clinical staff to group allocation, however assessment of pelvic floor muscle function and prolapse severity at 12-month follow-up will be conducted by an assessor blinded to the participant's trial group. Participants will be requested in correspondence relating to their appointment not to disclose their group allocation to the blinded assessor, and the assessor will remind them of this at the start of the examination appointment. The assessor will be asked to record whether or not they were aware of group allocation prior to the assessment.

4.9 Administration arrangements post recruitment (if applicable)

The centre research team should:

- File a copy of the consent form in the hospital/clinic notes along with information about the trial.
- Enter trial data regarding the participant into the bespoke trial website.
- Maintain trial documentation at the centre.
- Return a copy of any signed paper consent form to the Trial Office.

5. TRIAL INTERVENTION

The intervention being evaluated is a combination of treatments that are already provided (usually separately but more recently in combination) within the NHS. Development of the intervention protocol has been undertaken by our multidisciplinary team in consultation with PPI collaborators and professional bodies, mindful of Equality, Diversity and Inclusion (EDI) considerations. Centre staff involved in the research will receive training in delivery of the trial and the intervention protocols at a Site Initiation Visit (SIV).

5.1 Supervised PFMT plus vaginal pessary

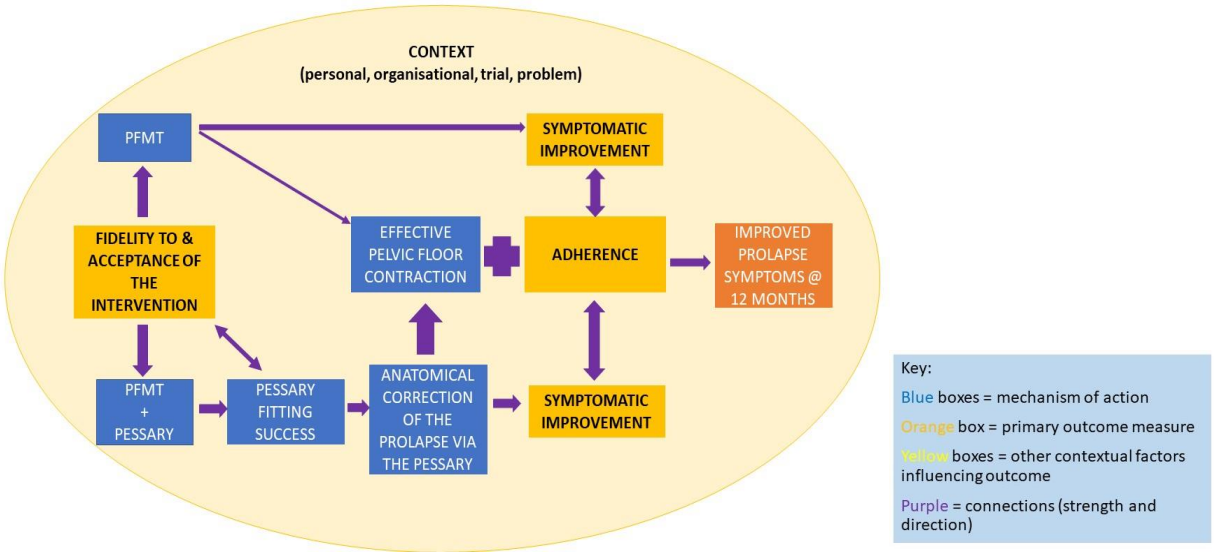
The intervention being evaluated is an evidence-based supervised PFMT programme [5]: 16 weeks duration (5 appointments, with a minimum of 3 face-to-face), with the addition of a vaginal pessary being fitted. Women will receive an individualised PFMT programme which will be progressed at each appointment. At the first appointment an explanation of types of prolapse, anatomy and function of pelvic floor muscles will be given using diagrams and a model pelvis. An internal assessment of the pelvic floor muscles will be carried out to confirm a correct exercise technique and assess pelvic floor muscle strength and function (using the PERFECT Scheme) [19] and prolapse severity (a minimisation variable) will be recorded (POP-Q System: stage 0/1, stage 2, stage 3/4 – this is a simple version of the POP-Q staging [20]). An individualised home exercise programme will be prescribed based on examination findings. Women will be encouraged to progress exercises, with the aim of achieving ten times 10-second maximum holds and up to 50 fast contractions three times per day. Exercises undertaken will be recorded by participants in a diary. Women will also be taught how to pre-contract the pelvic floor muscles against increases in intra-abdominal pressure (the Knack exercise) and be encouraged to use this technique daily. The home exercise programme will be modified at appointments on the basis of examination findings and diary recordings. Use of electromyography biofeedback, pressure biofeedback, and electrical stimulation as part of the PFMT programme will not be permitted. Such adjuncts may not be suitable for participants using a pessary in the PFMT and Pessary group, therefore will not be used in either trial group. Supervised PFMT will be delivered by a clinician (usually a specialist physiotherapist or nurse, depending on the service model at each centre) with formal training in pelvic floor rehabilitation.

A vaginal pessary will be fitted after the participant has completed the baseline questionnaire and been randomised (usually both will occur at the baseline/first PFMT appointment), in accordance with usual practice at the participating centre. There will be no restriction on pessary type, and women may be offered to self-manage their pessary if this option is available at their centre [21]. The type and size of pessary a woman uses will be recorded and reported. Pessary care will be delivered by a clinician (usually a gynaecologist, nurse or physiotherapist, depending on the service model at each centre) with specialist training in fitting and managing vaginal pessaries. Participants will be asked to use the pessary for at least 16 weeks (during the period of supervised PFMT) but can continue to use it if desired. Pessary review appointments will be offered to participants with the frequency dependent on whether they are self-managing or not. Participants who self-manage their pessary (who can remove the pessary themselves) will be asked to remove the pessary and those who do not self-manage will be asked to come to clinic to have the pessary removed 2 weeks before they receive their 6 and 12 month questionnaires. Participants will record details of their pessary use (insertion, removal, replacement, complications) in a diary (alongside their PFMT exercise recordings). Participants continuing pessary use after their time in the trial will receive care via their centre's usual pessary service.

An initial programme theory has been developed, proposing the pathway between intervention and outcome (Figure 1). The hypothesised mechanism of action is that successful pessary use will anatomically correct the prolapse. The anatomical correction will enable a more effective pelvic floor contraction which will lead to a greater improvement in prolapse symptoms than PFMT alone. Contextual factors suggested by previous evidence and theory to influence the pathway to outcome are included in the programme theory. Specifically, the outer circle signifies that intervention delivery, and outcomes are all influenced by context [22]. The nature of the

influence of contextual factors will be explored in the process evaluation. As an example, it is hypothesised that changes in symptoms due to the interventions may influence adherence differently, and the combination of the effectiveness of the contraction and the adherence to the prescribed regimen of PFMT will in turn influence outcome.

Figure 1. Proposed programme theory



5.2 Supervised PFMT

The control group will receive supervised PFMT, as described above (section 5.1), without addition of a pessary. This is in line with the standard NHS patient care pathway recommended for women presenting with symptomatic prolapse which is a 16-week supervised programme of PFMT [1].

6. OUTCOME MEASURES

6.1 Primary outcome measure

Our primary outcome measure is participant-reported symptoms of pelvic floor dysfunction measured using the Pelvic Floor Dysfunction Inventory-20 (PFDI-20) [29] at 12 months. PFDI-20 measures the severity of pelvic floor-related symptoms. It contains 20 questions about the presence of prolapse (6 items), bladder (6 items) and bowel (8 items) symptoms, and how bothersome these are, with three respective subscales (UDI-6, CRADI-8, POPDI-6). Each sub-score ranges from 0-100 and the total score from 0-300: higher scores reflecting more bothersome symptoms.

6.2 Secondary outcome measures

Secondary outcomes include participant-reported pelvic floor dysfunction-related quality of life (QoL) measured using the Pelvic Floor Impact Questionnaire-7 (PFIQ-7) [23]. The PFIQ-7 was developed and validated in parallel with the PFDI-20 and includes questions on the effect of bladder (7 items), bowel (7 items) and prolapse (7 items) symptoms on activities, relationships and feelings. There are three subscales (UIQ-7, CRAIQ-7, POPIQ-7), with each sub-score ranging from 0-100, and the total score ranging from 0-300: higher scores reflect more impact on quality of life.

Other participant-reported secondary outcomes are general health-related QoL (EQ-5D-5L) (two-part instrument: five items on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, plus the EQ-5D Visual Analogue Scale) [24]; Patient Global Impression of Improvement (PGI-I) (single-item participant rating of change in a condition since having treatment, validated for prolapse, with 7 responses from “very much better” to “very much

worse") [25]; the ICIQ Vaginal Symptoms (ICIQ-VS) Sexual Matters subscale, with 4 items and score from 0 to 58, higher scores indicating worse sexual function [26]; uptake of other prolapse treatment (including surgery); self-efficacy for PFMT (Pelvic Floor Muscle Exercise Self-Efficacy Scale) [27]; and adherence to trial interventions (exercise/pessary use and experience diary).

An economic outcome, Quality Adjusted Life Years (QALYs), will be calculated from EQ-5D-5L data using the recommended tariff values [28].

Two clinical secondary outcomes are pelvic floor muscle strength and function (Modified Oxford Scale (MOS), 0 "no contraction" to 5 "strong (with lift) contraction", assessed via digital palpation) [29]; and prolapse severity (Pelvic Organ Prolapse Quantification (POP-Q) method, Stage I-IV) [20]. From our experience, use of the POP-Q system is challenging to implement in trials across many centres and different health professional groupings, therefore an experienced gynaecologist will be identified to undertake the POP-Qs at each centre.

Outcomes will be measured at baseline, 6 months and 12 months (with the exception of pelvic floor muscle and prolapse severity assessments which take place at baseline and 12 months). Pessary use will be paused 2 weeks before the 6 and 12 month time-points for women in the PFMT plus pessary group, to allow the pelvic organs to reposition without the pessary support prior questionnaires being completed and (at 12 months) clinical assessment being carried out. We will record if women do not pause pessary use prior to assessment and use this information in a sensitivity analysis.

6.3 Long term outcomes

To facilitate the possibility of assessment of long term outcomes we will consent (Consent Form 01) women to long-term follow-up via routine health records and follow-up questionnaires.

7. DATA COLLECTION AND PROCESSING

7.1 Pilot study data collection on recruitment

The Trial Office will record the number of centres open to recruitment and number of participants recruited per centre per week. Screening logs completed by centres will be reviewed monthly during the internal pilot phase to assess the numbers of participants invited and recruited to the trial. Recruitment issues in centres will be identified early and solutions put in place to rapidly resolve them.

Audio-recordings will be made of a sample of recruitment discussions to support trial recruitment methods [30-32]. Potential participants will receive a letter (Letter 02), 'recruitment study PIL' (PIL 02) and consent form/link to e-consent form (Consent Form 02) either in clinic or, in most cases, by post after receipt of their expression of interest form. On that Expression of Interest form, potential participants can indicate if they are willing to hear more about the recording of the recruitment discussion, only those who tick 'yes' will be sent an information pack. Potential participants can return a paper copy of the consent in a stamped addressed envelope or complete e-consent. The link for e-consent is embedded within the invitation Letter 02 and within the PIL. The link will connect to a GCU secured REDCAP form. Once completed by the participant it will be checked by a member of the PEPPY research team who will countersign it and return a copy to the participant.

On receipt of consent and with consent from the recruiter (Consent 05), approximately 10 recruitment conversations will be audio-recorded using small, unobtrusive digital recorders. At least one recording will be from each of the 5 pilot centres. If more than one person is undertaking recruitment at a centre, recruitment will sample for diversity in professional background of recruiter. Sampling will also target variation in women's characteristics such as ethnicity.

Approximately 3-5 interviews with participants from each trial group will be undertaken as part of the pilot to explore women's views of recruitment and of the trial generally. Approximately 5

recruiters (1 per pilot centre) will be interviewed at the end of the pilot study to explore their views of recruitment and of the trial generally.

Audio-recordings of recruitment sessions and extracts of data from interviews in the pilot phase that are specific to recruitment will be transcribed verbatim (see Section 12). Analysis will follow a Framework Approach [33] that will focus on actions that can be taken to support recruitment. Analysis and data extracts will be presented to PPI and other research team members for discussion about guidance for centres to support ongoing recruitment. Pilot study audio-recordings of appointments between participants and treating clinicians will be transcribed verbatim. Data will be analysed using the developed analytic framework (see Section 12). For more detail on the processes of data collection and analysis of audio-recordings and interviews please see process evaluation Section 12.

7.2 Measuring outcomes

Table 2 summarises what measures are assessed at baseline, 6 and 12 month time-points. Further details about outcome measures are provided above in section 6.2. The Patient Global Impression of Severity (PGI-S) (single-item participant rating of condition severity, with 4 responses from "normal" to "severe") will be included in the baseline questionnaire in place of the PGI-I [34]. Data on intervention fidelity will be gathered at each PFMT appointment by the treating clinician who will review the participant's PFMT/pessary diary and record fidelity to PFMT and pessary use (where appropriate).

Outcome data will be collected from participants mainly using participant-completed questionnaires administered via post, e-mail and telephone as required. If a questionnaire is not returned after the first request, two further requests will be made by the Trial Office. The first reminder will be by email/letter based on the participant's preference. The second reminder will be by phone, and if the participant agrees the data will be collected over the phone. Gift vouchers to the value of £10 will be sent to participants with their 12 month questionnaire.

Table 2. Overview of trial outcome measure data collection

Data collected	**Time-point**		
Primary Outcome	**Baseline**	**6 months***	**12 months***
Pelvic floor symptoms (PFDI-20)	Q	Q	Q
Secondary Outcomes			
Condition-specific quality of life (PFIQ-7)	Q	Q	Q
Patient Global Impression of Improvement (PGI-I)	Q (PGI-S)	Q	Q
Sexual function (ICIQ-VS Sexual Matters subscale)	Q	Q	Q
Uptake of other prolapse treatment		Q	Q
Self-efficacy for treatment	Q	Q	Q
Intervention adherence (PFMT + pessary)	Diary at appointments 1-4 & 6M questionnaire		Q
Pelvic floor muscle strength / function (MOS)	C		C (blinded)
Prolapse severity (POP-Q)	C^s		C (blinded)
Economic outcomes			
General health-related quality of life (EQ-5D-5L)	Q	Q	Q
Healthcare utilisation questionnaire	Q	Q	Q

** women in the PFMT plus pessary group will have a pessary review appointment at 2 weeks before they receive their 6 and 12 month questionnaires at which the pessary will be removed (if they are still*

using a pessary). Q - Data gathered in self-report questionnaire C - Data gathered during vaginal examination in clinic [s] simple version of the POP-Q.

7.3 Baseline appointment

A Baseline CRF will be completed at the baseline appointment including relevant participant details and information required for randomisation (e.g. age, height, weight, medical history, assessment of vaginal tissues, prolapse severity, pelvic floor muscle strength and function). Participants will be randomised and complete the baseline questionnaire. PFMT treatment will then begin and the treating physiotherapist will record the prescribed PFMT and add it to the participant's exercise diary for their information.

7.4 Follow-up

6 month follow-up
The 6 month questionnaire will be posted or emailed to participants for completion. Women using a pessary will be asked to pause pessary use 2 weeks before completion of this questionnaire . An appointment for pessary removal will be arranged if required.

12 month follow-up
The 12 month questionnaire will be posted or emailed to participants for completion. Women using a pessary will be asked to pause pessary use 2 weeks before completion of this questionnaire . An appointment for pessary removal will be arranged if required. Participants will attend a 12 month appointment for blinded assessment of pelvic floor muscle strength/function and prolapse severity.

7.5 Change of Status/Withdrawal procedures

Participants remain in the trial unless they choose to withdraw consent. Participants are free to withdraw from the trial at any timepoint. All changes in status, with the exception of complete withdrawal of consent, mean the participant is still followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal is retained and used in the analysis.

Following informed consent, if a participant loses capacity, the consent given when capable remains legally valid. In such circumstances, identifiable data collected with consent will be retained and used in the study but no further data will be collected or research procedures carried out.

Participants who do not receive their allocated treatment or receive the other (non-allocated) intervention or discontinue their healthcare management are not considered withdrawals and will be followed-up for all trial outcomes unless they request otherwise. One of the outcomes is treatment received. This is a pragmatic study and will monitor accruing data on treatment initiated and continued during the study which will inform the proportion of participants continuing in the two randomised treatment pathways.

Participants who request that no further questionnaires are issued (i.e. completing questionnaires) will be followed up for other trial outcomes unless they are complete withdrawals.

Participants for whom any outcome data are available are included in an intention to treat analysis.

7.6 Data processing

The local research team staff will enter locally collected data in the centres. Staff in the Trial office will work closely with the local research team to ensure the data are as complete and accurate as possible. Postal questionnaires will be entered into the study website by trial office staff.

7.7 Long term follow-up

We plan to seek funding to follow-up participants in the longer-term using data from NHS and other government central registries, and GP and hospital notes. We seek informed consent for this at the outset of the trial.

8. SAFETY

8.1 Definitions

Term	Standard definition
Adverse Event (AE)	Any untoward medical event affecting a clinical trial participant.
Serious Adverse Event (SAE)	Where an AE: • results in death; • is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe); • requires hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability or incapacity; • is a congenital anomaly or birth defect, • is otherwise considered medically significant by the investigator

Adverse events are not:

- continuous and persistent disease or symptom, present before the trial, which fails to progress;
- signs or symptoms of the disease being studied.

Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will only be considered an AE or SAE if it is related to the trial interventions.

8.2 Trial specific considerations

In this trial, all related AEs will be recorded (see definition of “related” in section 8.3.2 below). All serious related AEs will be recorded as SAEs. All deaths (any cause) will also be recorded as SAEs.

Due to the reporting and collection of these events as primary and secondary outcome measures, the following do not need to be reported as AEs or SAEs:

- Pelvic floor symptoms including pelvic organ prolapse, urinary and colorectal-anal symptoms
- Sexual dysfunction

Furthermore, pre-existing conditions and any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration will not be classed as Serious Adverse Events.

PEPPY specific expected adverse events:

The PEPPY trial involves interventions to treat pelvic organ prolapse which are well established in clinical practice. Expected adverse events (although unlikely) arising from PFMT and pessary usage are:

- Pelvic floor muscle soreness
- Low back pain
- Vaginal irritation/discomfort
- Granulation of vaginal tissue
- Involuntary expulsion of pessary
- Vaginal smell
- Vaginal discharge
- Vaginal infection
- Vaginal bleeding
- Psychological distress due to vaginal assessment (e.g. as a result of previous abuse or distressing labour)
- Pessary entrapment in the vagina requiring removal in theatre
- Urinary retention requiring catheterisation
- Faecal impaction requiring hospital intervention
- Fistula: recto-vaginal or vesico-vaginal
- Vaginal cancer
- Ureteric obstruction

8.3 Procedures for detecting, evaluating, recording & reporting AEs and SAEs

8.3.1 Detecting AEs and SAEs

All AEs and SAEs meeting the criteria for recording within the PEPPY trial (see section 8.1) are recorded from the time a participant consents to join the trial until the last trial follow-up. The Trial Office and centre staff will ask about the occurrence of relevant AEs/SAEs (i.e. those that meet the criteria for recording within the PEPPY trial) at every appointment, within follow-up questionnaires, ad hoc phone calls and other contact with the participant.

8.3.2 Evaluating AEs and SAEs

When an AE or SAE occurs, it is the responsibility of the local Investigator (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event.

Assessment of Seriousness

The Investigator must make an assessment of seriousness as defined in Section 8.1.

Assessment of Relatedness (causality)

The local Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

- **Related:** resulted from administration of the research procedures.
- **Unrelated**: where an event is not considered to be related to the research procedures.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Expectedness

Expectedness will be assessed for all AEs and SAEs by the local Investigator.

8.3.3 Recording AEs and SAEs

Adverse events will be recorded in the case report forms (CRFs) or questionnaires. The local Investigator (or delegate) should then record all relevant SAEs on the SAE form.

In addition, death for any cause (related or otherwise) is recorded on the SAE form.

8.3.4 Reporting SAEs

Reporting responsibilities of centres

Once the local Investigator becomes aware that an SAE has occurred in a trial participant, they must report the information to the Trial Office/Chief Investigator within 24 hours of becoming aware of the event as per the Sponsor guidance.

The SAE form must be completed as thoroughly as possible with all available details of the event and signed by the local Investigator or designee. If all the required information is not available at the time of reporting, the Investigator must ensure that any missing or follow-up information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

To report an SAE to the Trial Office, centre staff can either complete a hard copy of the SAE form and email it to the Trial Office or upload the SAE onto the trial website. If the SAE form is uploaded onto the trial website, the Trial Manager will be automatically notified.

If, in the opinion of the local PI and/or the CI, the event is confirmed as being serious but not related, or serious, related and expected, expedited reporting to Sponsor is not required. Rather these will be summarised and reported to Sponsor, REC, Funder, TSC and DMEC in their regular progress reports. Only expedited if serious, related and not expected event.

Reporting responsibilities of the Trial Office

The Trial Office will notify the Sponsor within 24 hours of receiving the signed SAE notification if the event is serious, related and not expected.

The sponsor will provide an assessment of the SAE. A Sponsor cannot downgrade an assessment from the local PI or CI. Any disparity will be resolved by further discussion between these parties and documented in the TMF.

8.3.5 Regulatory reporting requirements

The CI or delegate reports any SAEs that are related to trial procedures and not expected to the REC within 15 days of the CI becoming aware of it using the HRA SAE form.

All SAEs are summarised and reported to the Ethics Committee, the Funder, the Trial Steering Committee and the Data Monitoring and Ethics Committee in their regular reports.

8.3.6 Follow up procedures

After initially recording and reporting an SAE, the local Investigator is required to follow each participant as indicated by clinical practice. Follow up information on an SAE should be reported to the Trial Office as described above in the Section on ‘Reporting responsibilities of centres’. The Trial Office will notify the Sponsor about any follow-up information.

8.3.7 Pregnancy

Pregnancy is not considered an AE or SAE, however if a participant becomes pregnant while participating in the trial, the details of the pregnancy should be reported to the treating clinician and research team as soon as the participant becomes aware and the participant will be

withdrawn from the trial and her care will be provided by the centre. Notification of pregnancy during the trial will be reported in the change of status form.

9. SAMPLE SIZE AND PROPOSED RECRUITMENT RATE

9.1 Trial sample size

Five hundred and fifty-two women (276 per group) will be randomised to provide 90% power to detect a difference of 12 points in the PFDI-20 score at 12 months. This allows for a 40% pessary fitting non-success rate, which would potentially reduce the group difference in PFDI-20 from 20 (the upper limit of the minimal clinically important difference [35]) to 12, which remains within the lower limit of 6.2. A standard deviation of 40 is assumed, two-sided alpha of 0.05, and 15% loss to follow-up.

A sample size of 552 also provides power for the analysis of secondary outcomes, e.g. we will have more than 90% power (2-sided test, 5% level of significance) to detect a 20% difference between groups in the proportion of women with a Modified Oxford Scale rating of 2 or less (assuming that at least 50% in the PFMT plus pessary group obtain a score of more than 2 at 12 months).

The number of potentially eligible women (those referred for PFMT for prolapse) reported by participating centres ranged from 7 to 40 per month, median 17. Assuming 70% of women will be eligible and 50% agree to participate, in 13 centres recruiting for an average of 12 months (maximum 18 months with centres starting in a staggered fashion), approximately 900 women could participate, allowing us to cover seasonal variations and other unexpected recruitment issues and still reach our target of 552 randomised participants.

9.2 Progression beyond the pilot

A number of criteria will be considered carefully when deciding upon the feasibility and appropriateness of continuing with the trial, relating to centre and participant recruitment and pessary fitting success (Table 1).

Table 1. Criteria to inform progression from pilot to full trial

Progression criterion	Red	Amber	Green
1. Recruitment rate is at least 4 women per centre per month (from 3rd month onwards)	1 centre	2-4 centres	5 centres
2. Number of centres opened during pilot	1 centre	2-4 centres	5 centres
3. Total number of participants recruited during pilot	<20	20 to 58	59
4. Pessary fitting success* rate is 60% or greater	1 centre	2-4 centres	5 centres

**centre confirms with participant 1 week after fitting that the pessary can be successfully and comfortably retained when in situ*

One or more criteria at amber would indicate action and review was needed to: improve recruitment methods e.g. based on findings from process evaluation interviews and audio-recordings; increase centre numbers using those centres we have in reserve; increase sample size to compensate for lower than anticipated fitting success rates. One or more criteria at red would reflect a position where the trial could only progress with a very strong recovery plan approved by the funder, and monitored closely to ensure it is effective once in place.

Qualitative data from the process evaluation collected during the internal pilot will be used to identify actions that can be taken to support recruitment (see Sections 7 and 12). A newsletter will be sent to all centres that offers feedback on strategies to increase recruitment and ways to enhance delivery of the intervention in line with trial protocol.

9.3 Recruitment rates

Individualised recruitment targets will be given to centres depending on their recruitment potential and progress, however for planning purposes we have estimated conservatively that centres will randomise 4 women per month from their 3rd month onwards (Figure 2). The Data Monitoring and Ethics Committee (DMEC) will be asked to monitor EDI characteristics within the recruited sample in comparison to norms from the latest census data.

Figure 2. Recruitment projection across 13 centres over 18 months
orange denotes number of centres recruiting

To mitigate against poor recruitment, we will:

1. Focus first on setting up those centres that have the shortest waiting lists for both PFMT and pessary appointments, those that already have combined PFMT/pessary fitting clinics, and those we know have recruited efficiently in previous trials.
2. Use methods which have been successful in our previous trials of conservative management of prolapse [5,6,21]. All trials recruited to target (or beyond) and had excellent retention. In particular, the TOPSY trial [21], involving women with a pessary, had a 97% retention rate at 4-year follow-up. Successful recruitment methods include giving the choice of paper or electronic consent and questionnaire completion, which helps to avoid issues of digital exclusion. For centres there will be monthly centre forums where the team can share recruitment advice with centres and centres can share good practice with their peers.
3. Monitor recruitment closely during the pilot phase by reviewing screening logs and asking centres for feedback on any barriers they identify in the recruitment process. We will discuss these findings at PMG meetings, which include our PPI team members, and also seek advice from the TSC as needed to identify additional strategies to overcome these barriers.

10. STATISTICAL ANALYSIS

Analyses will be conducted according to a pre-specified Statistical Analysis Plan. All participant characteristics (e.g. age, prolapse severity, parity, BMI, ethnicity) and outcome measure data will be summarised, by group, using the appropriate descriptive statistics: mean and standard deviation for continuous outcomes (or medians and interquartile range for skewed data), and counts and percentages for dichotomous and categorical outcomes.

The main effectiveness analysis will be based on the intention to treat principle. The analysis of the primary outcome measure will estimate the mean difference (with 95% confidence intervals) in the PFDI-20 score at 12 months between the PFMT plus pessary and PFMT alone groups

using a longitudinal ANCOVA model (which assumes incomplete outcome data to be missing at random). The model will incorporate PFDI-20 scores at 6- and 12-month time-points, with age group, baseline prolapse severity and baseline PFDI-20 score as fixed effects and recruitment centre as a random effect. The treatment effect will be estimated from the linear combination of treatment plus time-by-treatment interaction. Missing baseline data will be imputed. The longitudinal ANCOVA model will also estimate mean differences in PFDI-20 at 6 months. Statistical significance will be at the 5% level.

The missing at random assumption for primary outcome data will be assessed further in sensitivity analyses. Treatment effects will be estimated under varying assumptions of data being missing not at random using pattern- mixture models [36]. A complete case analysis will also be conducted.

Given the potential for discontinuation of PFMT and/or pessary use, we will conduct a secondary analysis of compliers to estimate the effect of receiving the intervention as randomised, using complier average causal effect (CACE) estimators [37]. The CACE analysis will take a maximum likelihood approach, which can assume incomplete data to be missing at random, and can be adjusted for covariates. This analysis will provide unbiased effect estimates of receiving PFMT plus pessary (efficacy), which will complement the unbiased intention to treat effect estimates of being offered PFMT plus pessary (effectiveness). An “as treated” analysis will analyse participants on the basis of treatment received (Y/N).

Subgroup analyses will be carried out within the following groups: age (<52/≥52 years) and prolapse severity (POP-Q System: stage 0/1, stage 2, stage 3/4)). Stricter levels of statistical significance (1%) will be sought, reflecting the exploratory nature of these analyses. Heterogeneity of treatment effects amongst subgroups will be tested in an analysis of the 12-month outcome only (i.e. not a longitudinal model), using the appropriate subgroup by treatment group interactions [38].

Secondary outcomes will be analysed using an appropriate generalised linear model (for example, binary logistic regression for dichotomous outcomes such as improvement in prolapse stage (Y/N), and ordinal logistic regression for ordered categorical outcomes such as perception of global improvement (PGI-I)). All models will be adjusted for minimisation covariates (age, prolapse severity and centre) and baseline score (where applicable).

All analyses will be described in the Statistical Analysis Plan, to be approved by the TSC and DMEC. A single main analysis will be performed at the end of the trial when 12-month follow-up has been completed. The independent DMEC will review confidential interim analyses of accumulating data at its discretion but at least annually.

11. ECONOMIC EVALUATION

A formal economic evaluation will be undertaken to assess the relative cost-effectiveness of the PFMT + pessary compared to PFMT only.

11.1 Collection of resources use and data

Resource use data collected will include both primary and secondary care NHS services used by participants. A resource use questionnaire will be designed for self-completion by participants at baseline, 6 and 12 months to record resource use over the trial period.

Healthcare resources required for the delivery of the PFMT and pessary care will be recorded at each centre. Details of the PFMT and pessary care delivered for each participant will be recorded by centre staff.

11.2 Participant level costs

The Participant Resource Use Questionnaire will be used to collect data on use of primary and secondary care services this will include; GP, Nurse, Physiotherapy, Outpatient, Inpatient Stay, Emergency or Unplanned service use (A&E, NHS 24/111)) and medication related to prolapse

symptoms. Data will be self-report with participants asked to state if they have used the service in the time since the proceeding questionnaire (1 month pre baseline questionnaire) and if yes how many times.

11.3 Quality of Life

Participant health-related quality of life data will be collected using the EQ-5D 5L as described in Section 6.2 on Outcomes.

11.4 Cost effectiveness

The economic evaluation will be conducted from an NHS perspective. All resource use will be valued in monetary terms using appropriate unit costs. Unit costs for primary and secondary care resources will be taken from the PSSRU Unit Costs of Health and Social Care publication [39]. Any medications used by participants will be valued using the British National Formulary [40]. Total and mean cost per participant will be calculated for each group using methods to account for uncertainty around the mean estimates of costs [41].

Quality Adjusted Life Years (QALYs) will be calculated from EQ-5D-5L data using the recommended tariff values [28].

The primary economic evaluation will be a within trial cost utility analysis. Analysis will be completed as intention to treat, based on randomised group. Costs and QALYs will be combined to calculate the incremental cost per QALY gained along with the incremental net benefit [42].

In addition, a Markov decision model with a monthly cycle will be employed to evaluate effects of the intervention on costs, QALYs and cost-effectiveness over a 5-year horizon. Trial data will be supplemented with data from our existing studies of PFMT and pessary for prolapse [5,6,21] to develop the health states and identify suitable transition probabilities. All costs and outcomes beyond 1 year will be discounted at 3.5% [43].

12 EMBEDDED PROCESS EVALUATION

12.1 Overview

A mixed-methods process evaluation will address the three key process evaluation functions: context, implementation and mechanisms of action [44]. Context, a core element of the MRC complex intervention framework [14], will be explored in terms of the personal, organisational, trial and problem contexts [22]. Implementation will be considered '*in the light of NPT'* (Normalisation Process Theory) [45] (May et al, 2018 p18), with specific focus on fidelity to the intervention; acceptability of the intervention; adherence to the intervention within care delivery and by the participant. These components can be cross referenced to cognitive participation, coherence and collective action with the NPT. Mechanisms of Action, or the initial Programme Theory as expanded within the new MRC framework, is outlined in Figure 1. Table 3 below links the data collection methods to the process evaluation functions.

Table 3. Process evaluation data collection and links to process evaluation function

Functions	Types of data collection				
	Audio-recorded appointments (25 intervention, 25 control)	Interviews with trial participants (n=15 intervention, 15 control)	Interviews with staff who recruit or deliver the intervention (n=26)	Open question in 6 & 12 month questionnaires (n=552 each time-point)	Completion of NoMAD tool (n=39 approx.)
Context	X			X	X
Implementation – fidelity		X	X	X	
Implementation – acceptance	X				
Implementation – adherence	X			X	
Programme Theory					

Shaded box indicates that the method is a main source of data for the process evaluation function; the unshaded boxes (marked with x) indicate a subsidiary source of data for the process evaluation function.

12.2 Sample, recruitment, consent and data collection

The sample, their recruitment and consent and data collection for each of the five components is described below.

12.2.1 Audio-recordings of PFMT plus pessary and PFMT alone participant appointments to assess intervention implementation and fidelity

We will aim to record 50 participant/clinician intervention appointments (25 in the PFMT plus pessary group and 25 in the PFMT alone group). Approximately 3-5 of these appointments in each group will be recorded within the pilot study. Variance within the sample of recordings will be aimed for, based on: centre (at least one recording per centre); appointment number (ensuring representation across appointments 1-5); women's age (to maximise range); and treating clinician (variation in individual clinicians).

Treating clinicians will be asked to agree to appointment recording as part of the SIV, and will be asked to sign consent (Consent Form 06). Information about recording of some appointments is contained within the main trial PIL for women (PIL 01). Participants will indicate if they consent to appointment recording on their main trial consent form (by initialling box). The Process Evaluation researcher will check if a woman has consented to recording before asking the treating clinician to record the appointment. The treating clinician will verbally reconfirm consent with the woman prior to the recording.

With consent in place, small digital recorders will be placed in the consulting room or phone call recorded to gather all instruction given.

12.2.2 Qualitative semi-structured interviews with trial participants to explore context, fidelity, acceptance, adherence and programme theory

In order to achieve information power [46], 30 trial participants will be interviewed (15 PFMT plus pessary group, 15 PFMT alone group). Approximately 3-5 of these interviews in each group will be undertaken as part of the pilot study. Sampling will be maximum variation with variance on: woman's age (as wide a range as possible); ethnicity (ensuring representation from varied ethnic groups); prolapse severity (all levels of severity recruited); centre (district general hospital, university hospital, community clinic).

The main trial PIL (PIL 01) introduces the interview study, women are then asked to consent to receiving further information about the interview study. The PE team will review participants who indicate 'yes' on the trial consent form and invite a sample of participants, aiming to

achieve the maximum variation outlined above. Those invited will receive a letter of invitation (Letter 03), a PIL (PIL 03) and a consent form/e-consent form (Consent Form 03). The PE researcher will contact the woman a few days later to ask if she is willing to be interviewed. If yes, she will be asked to verify her preferred method of providing consent (paper or electronic), and then sign and return the consent form in the stamped addressed envelope provided or complete an e-consent. If the participant prefers e-consent, they will be sent an email with a link to a GCU secured REDCAP consent form. On receipt of the form, a PEPPY researcher will check it and if it is complete they will counter sign the consent form and return a copy to the participant. Only when consent has been received and counter signed will the first interview be arranged.

Interviews will take place with the same woman at baseline and at 12 months. Interviews will be undertaken in the medium preferred by the participant: face-to-face, MS Teams/Zoom or phone and each interview will last approximately 1 hour. With consent, all interviews will be audio-recorded. Interview schedules have been developed with PPI input, ensuring EDI principles and mindful of the components of NPT. Topics for discussion include: views on recruitment; the problem (prolapse) and personal context; fidelity to, acceptance of and adherence to the allocated intervention.

12.2.3 Interviews with staff who recruit to the trial or deliver the PFMT plus pessary and the PFMT alone interventions to explore context, fidelity, acceptance, adherence and programme theory

In order to achieve information power, at least two staff members from each centre (at least one of whom is responsible for delivering the intervention, both PFMT and pessary fitting) will be interviewed (approximate target n=26). Approximately 5 recruiters (one from each pilot centre) will be interviewed as part of the internal pilot. Sampling will aim for diversity in centre and staff professional group.

The PE researcher will identify recruiters and treating clinicians from the delegation logs at centres. Potential participants will be sent an invitation email (Letter 04), PIL (PIL 04) and e-consent link to the consent form that is hosted on a GCU secured REDCAP platform (Consent Form 04). On receipt of the fully completed e-consent the PE researcher will check the form, countersign it and return a copy of the completed consent to the participant. The PEPPY researcher will then contact the participant to arrange the interview.

Interviews will be undertaken by MS Teams/Zoom or by phone, will be audio-recorded and will last approximately 30 minutes. For recruiters, interviews will focus on factors that influence recruitment, including organisational context. For those who have been involved in delivering PFMT, with or without pessary, and fitting pessaries, interviews will focus on: problems, organisational and trial context; fidelity to, acceptance of and adherence to delivery of the interventions; and views about the programme theory.

All audio files will be deleted from the secure server once data analysis is complete.

12.2.4 Open question in the questionnaire booklet (acceptance, programme theory)

A single open question will be included in the 6 and 12 month follow-up questionnaires sent to all women in the sample to ask about their views on the intervention they have received. These data will be used to refine the programme theory.

12.2.5 Completion of the NoMAD instrument (NPT, programme theory)

Staff at each centre who manage services and deliver the PFMT plus pessary intervention (identified through delegation logs and at SIVs) would be asked to complete the NoMAD (Normalisation Measure Development) questionnaire prior to the intervention being delivered in their area of practice [47]. The introductory information on the questionnaire explains that questionnaire completion is taken as consent. At the end of intervention delivery for all participants within a centre, those who have been involved in delivering and managing

intervention delivery (based on the delegation log) will be asked to complete the NoMAD questionnaire. NoMAD is a validated 20-item tool, that maps onto NPT constructs, and aims to assess activity related to how staff, individually and collectively, work to normalise a new intervention within their working practices [47]. The tool has questions that cover the four NPT constructs and their sub-constructs. The instrument will be adapted, as advised, to focus on the PFMT plus pessary intervention.

12.3 Data analysis

Initially each dataset will be analysed individually to reach separate conclusions. Findings will then be synthesised across datasets. Qualitative data will be transcribed (or extracted for the questionnaire data) verbatim and NVivo used for data management. Transcription will be undertaken by a GCU-approved transcribing company. GCU approval contains a confidentiality agreement and the necessary GDPR regulations. The analysis will be led by MD, with CBu also coding a purposive sample of transcripts. The process evaluation sub-group of the research team (including PPI members) will have oversight of the analysis. MD and CBu, along with the sub-group as a whole, will interpret the data through discussion. The main analysis findings will not be shared with the full research team until the trial findings are revealed. Findings from the recruitment interviews will be fed back to the research team to inform any changes to the recruitment approach.

Interviews and qualitative data from the open question within the questionnaires will be analysed using Braun and Clarke's six stages of thematic analysis [48]: (1) Familiarisation of data, (2) Generation of codes, (3) Combining codes into themes, (4) Reviewing themes, (5) Determining the significance of themes and (6) Reporting of findings. The first 3 steps will be completed independently of NPT. Following iterative analysis, the process evaluation sub-group, will examine the synthesised findings 'in the light of' NPT [45] as part of step four. The team will map the emergent iterative findings onto the NPT constructs. This is followed by step five where the analysis will move from merely mapping the themes onto NPT constructs to discussions on their significance for implementation. In this way the analysis will complete with a sense of how the intervention was implemented within the context of the trial.

Audio-recordings of appointments between participants and treating clinicians will be transcribed verbatim. An analytic framework will be developed, based on the intervention protocol, to identify the core components of the intervention. Content analysis of the transcript will be applied based on the framework, with clear guidance to identify what code within the framework should be applied in what circumstances. Coded data will then be subject to quantitative descriptive analysis.

Descriptive statistics will be used to present findings on individual items of the NoMAD questionnaire. Where individuals have completed the survey prior to intervention delivery and then again at the end of the intervention period, change in paired responses will also be described. We will compare responses across centres and between those who deliver and those who manage delivery of the intervention.

13. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 Trial office in Glasgow

The Trial Office is in the Research Centre for Health (ReaCH) based within the School of Health and Life Sciences, Glasgow Caledonian University and provides day-to-day support for the recruiting centres and the running of the trial generally. The Trial Manager will take responsibility for the day-to-day transaction of trial activities, for example approvals, centre set-up and training, oversight of recruitment and follow-up rates etc. The Data Coordinator will provide administrative support to the trial, including organising all aspects of the questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal). The Process Evaluation Researcher in also based in the Trial Office facilitating coordinated working across the trial and the PE.

The Trial Office Team will meet formally at least fortnightly during the course of the trial to ensure smooth running and troubleshooting.

13.2 Local organisation at centres

At each centre the local PI and research nurse(s) are responsible for all aspects of local organisation including identifying potential recruits, consenting, completing and maintaining appropriate documentation. The centre agreement documents the full list of responsibilities for centres. Appropriate members of the local team are knowledgeable about the Protocol and will have appropriate Good Clinical Practice (GCP) training if applicable. A trial-specific delegation log is prepared for each centre, detailing the responsibilities of each member of staff working on the trial. The local team is also responsible for notifying SAEs to the Trial Office (see section 8).

13.3 Project Management Group (PMG)

The trial is supervised by its Project Management Group (PMG). This consists of the grant holders and Trial Office staff. Observers may be invited to attend at the discretion of the PMG. The PMG will aim to meet/teleconference every month initially, then every 2 months.

The research team has the expertise to provide the pelvic floor dysfunction knowledge and trial/process evaluation/health economics methodology aspects of the research.

The process evaluation sub-group of the research team (including PPI members) will have oversight of the process evaluation analysis.

13.4 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), with independent members, oversees the conduct and progress of the trial. The TSC Charter documents the terms of reference of the TSC, the template for reporting and the names and contact details of members of the TSC. This Charter is filed in the TMF.

13.5 Data Monitoring and Ethics Committee (DMEC)

An independent Data Monitoring and Ethics Committee (DMEC) oversees the safety of participants in the trial. The DMEC Charter documents the terms of reference of the DMEC and the names and contact details of members of the DMEC. This Charter is filed in the TMF.

13.6 Patient and Public Involvement (PPI)

Throughout the research we will adhere to the UK standards for Public Involvement [49], use the 2023 Public Involvement in Research Impact Toolkit and provide appropriate PPI training if required.

There are two PPI co-investigators. These co-applicants are long-standing members of the research team. They have guided the proposal via their lived experiences and insights.

Additional input into development of this application has come from The Nursing, Midwifery and Allied Health Professions Research Unit, Research Partnership Group (RPG). This diverse PPI group was established in 2018. The RPG indicated that the proposed research focussed on an important topic, and they provided input into the planning of the research design. A survey of POGP members, as key professional stakeholders, also informed this application.

Both PPI co-investigators, along with another PPI representative will sit on the PMG which steers the research and they will be invited to all the PMG meetings. We will have an additional two PPI representatives who will sit on the independent TSC. Our previous work with PPI on TSCs has shown that two (rather than one) PPI member provides mutual support and mentorship. This will mean that the research has input from five PPI representatives.

To support the PPI representatives, a successful PPI model that was incorporated into the TOPSY trial (NIHR 16/82/01) will be used. “The PPI Social” is a virtual setting where all PPI members (PMG and TSC) come together in a social space to connect, discuss the research in

their own space and raise any issues that they would like to be discussed. The PPI social will be facilitated by the Trial Coordinator.

One PPI co-investigator sits on the qualitative sub-group of the PMG and will be involved in analysis and interpretation of the process evaluation data.

With our PPI team members, we will develop a strategy to inform and engage our stakeholders. Our audiences are: women with prolapse; women's support organisations in our centres (e.g., VOCAL and BAME Research Group in Manchester) and nationally (e.g. RCOG Women's Voices); multidisciplinary healthcare professionals who support women with prolapse (e.g. urogynaecologists, women's health physiotherapists, nurses) and the organisations who support them (e.g. Pelvic Obstetric and Gynaecology Physiotherapy (POGP), RCOG, Royal College of Nursing (RCN)); policy influencing organisations (such as NICE); and policy makers such as the All-Party Parliamentary Groups on Older People and Women's Health, and Department of Health and Social Care. In particular, our PPI representatives will advise on the best ways to share information with women who have prolapse.

14. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

14.1 Research Governance

The trial office team at GCU will be supported by staff in CHaRT, a fully registered Clinical Trials Unit at the University of Aberdeen with particular expertise in running multicentre RCTs (Trials Unit (CHaRT) | Health Services Research Unit | The University of Aberdeen (abdn.ac.uk)). This aids compliance with Research Governance and the principles of GCP, and provides centralised trial administration, standard operating processes and database support.

The CI and Sponsor ensure that adequate systems are in place for monitoring the quality of the trial and that reports are prepared to a level appropriate to the risk assessment of the trial.

14.2 Data protection

Data collected during the course of the research is kept strictly confidential and accessed only by members of the research team. Data may be looked at by individuals from the Sponsor organisation or NHS centres where it is relevant to the participant taking part in this trial.

The CI and research staff involved with this project will comply with the requirements of the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. The HRA recommended wording to fulfil transparency requirements under the GDPR for health and care research has been included in the PIL.

The CI and research staff based in Scotland will also adhere to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality (revised-code-of-confidentiality-final.pdf (scot.nhs.uk)). Access to collated participant data will be restricted to the CI and appropriate trial staff.

Computers used to collate the data will have limited access measures via usernames, passwords and multifactor authentication.

Remote access to the network will be subject to robust authentication, and VPN (Virtual Private Network) connections to the network are only permitted for authorised users, ensuring that use is authenticated, and data is encrypted during transit across the network. No personal data will be downloaded or stored on local hard drives. All data input/access will be via the VPN and/or secure website.

Published results will not contain any personal data that could allow identification of individual participants.

The CHaRT senior IT development manager (in collaboration with the CI) manages access rights to the data set. Participants are allocated an individual trial number which is used to identify questionnaires and case report forms.

We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses and will implement the CHaRT data sharing agreement and guidance which are currently being finalised.

14.3 Sponsorship

Glasgow Caledonian University is the sponsor for the research.

15. ETHICS AND REGULATORY APPROVALS

Research Ethics and any appropriate NHS R&D approvals will be obtained prior to the commencement of recruitment. The trial will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. End of Trial declaration, and a final report are submitted to the Sponsor and the REC within the timelines defined in the regulations.

15.1 Protocol compliance and amendment

The Investigators will conduct the trial in compliance with the Protocol given favourable opinion by the West of Scotland Research Ethics Committee 4. Any amendment to the Protocol or other approved documents will be reviewed by Sponsor (and funder where appropriate) before application to REC and R&D unless in the case of urgent safety measures when the Sponsor is notified as soon as possible. Sponsor will advise if an amendment is substantial / non-substantial and which review bodies need to receive it. Any deviations from the Protocol will be fully documented.

16. MONITORING AND AUDIT

The trial is monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of GCP, and all other appropriate regulations. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate to the risk assessment of the trial. Investigators and their host institutions are required to permit trial related monitoring and audits to take place by the Sponsor and/ or regulatory representatives, providing direct access to source data and documents as requested.

17.1 Risk assessment

Independent risk assessment will be undertaken as required by the sponsor.

17. FINANCE AND INSURANCE

This trial is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR160810). The Sponsor holds appropriate insurance for the design and management of the research. NHS indemnity schemes or professional indemnity will apply to participants in the conduct of the research.

18. END OF TRIAL

The end of follow-up for each participant is defined as the final data capture on that individual. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the Sponsor and REC within 90 days, or 15 days if the trial is terminated prematurely. If terminated prematurely, the Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved, if appropriate.

A summary report of the trial will be provided to the Sponsor and REC within one year of the end of the trial. An end of trial report will be provided to the funders.

19. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Clinical data will be entered into the database by the designated team members working in each recruiting centre, together with data from questionnaires completed at clinic. Questionnaires returned by post to the Trial Office will be entered there. Staff in the Trial Office will work closely with local team members to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

Responsibilities for archiving are documented in the << site agreement>>. All essential data and documents (electronic and hard copy) are retained for a period of at least five years after close of trial according to the funder requirements and relevant Sponsor and CHaRT archiving SOPs. Electronic data will be archived by GCU.

20. SATELLITE STUDIES

It is recognised, that the value of the research may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advanced with the PMG and, if appropriate, with the TSC. Depending on the nature of the satellite trial, this may be considered a non-substantial or a substantial amendment to the REC approval for the PEPPY trial, or to require REC approval as a project in its own right. R&D management approval may also be required.

21. AUTHORSHIP AND PUBLICATION

Please refer to the Appendix A (authorship policy) for full details on authorship.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the PMG and TSC.

21.1 Other Dissemination

Once the main trial findings have been published, a lay summary of the findings will be sent to participants.

Trial findings will also be disseminated to healthcare professionals involved in the trial, , centre PIs and staff members.

More detailed plans for this dissemination will be considered and developed with input from PPI partners throughout the duration of the trial and will be finalised as part of the close-out plans.

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APPENDICES

Appendix A: Authorship Policy

AUTHORSHIP POLICY FOR PEPPY TRIAL

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria.[1]

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

ii. Drafting the work or revising it critically for important intellectual content; AND

iii. Final approval of the version to be published; AND

iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-author.

2. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals[2,3] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE)[1].

All contributors must fulfil the criteria detailed in section 1: DEFINING AUTHORSHIP in order to qualify for authorship.

Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or technical editing, language editing or proofreading the article is insufficient by itself to justify authorship[1]. Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.

a. Preferred CHaRT authorship

Where possible, all CHaRT trials should publish using all the named contributors who qualify for authorship in the byline i.e. Jane Doe, John Doe, John Smith and Ann Other.

However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstance, group authorship may be appropriate using bylines similar to “The PEPPY trial group” or “Jane Doe, John Doe, John Smith, Ann Other and the PEPPY trial group”. The article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. For some journals the journal will provide instructions on how to ensure the names of the collaborators appear on PubMed or equivalent.

Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group') [2]. Again, the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

b. Determining authorship

These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion numbers (ii) or (iii). Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript[1].

Tentative decisions on authorship should be made as early as possible[3]. These should be justified to, and agreed by, the Project Management Group (PMG). Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

c. Ordering of authors

The following rules may help with the ordering of authors, particularly for publications with individual authorship:

i. The person who has taken the lead in writing may be the first author.
ii. The senior author may wish to be the last named author.
iii. Those who have made a major contribution to analysis or writing (i.e. have done more than commenting in detail on successive drafts) may follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.
iv. All others who fulfil the four authorship criteria described in Section 1: DEFINING AUTHORSHIP may complete the list in alphabetical order of their surnames.

3. ACKNOWLEDGEMENTS

All those who make a contribution to a publication, but who do not fulfil the criteria for authorship, such as interviewers, data processors, staff at the recruiting sites, secretaries and funding bodies, should be acknowledged by name, usually in an 'Acknowledgements' section specifying their contributions. Because acknowledgment may imply endorsement by acknowledged individuals of a trial's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals[1].

The acknowledgements should also reflect any agreed acknowledgements (for example with suppliers) that were documented in supply agreements (or equivalent).

4. DISCLAIMERS

All papers arising from the trial should include any appropriate disclaimers.

Authors should also ensure they include the trial funder's disclaimer: refer to the funder's website for details. Be aware that other disclaimers may also be required.

5. QUALITY ASSURANCE

Ensuring quality assurance is essential to the good name of the trial group. All reports of work arising from the PEPPY trial, including conference abstracts, outputs describing methodological aspects of the trial, and any outputs describing results from the trial, should be peer reviewed by the PMG. The PMG will be responsible for decisions about submission following internal peer review. Submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

It is hoped that the adoption and dissemination of this policy will prevent disputes that cannot be resolved by informal discussion. However, any member of the trial team with a concern about authorship should discuss it with the relevant Chief Investigator, TSC, Line Manager or Research Lead as appropriate.

REFERENCES

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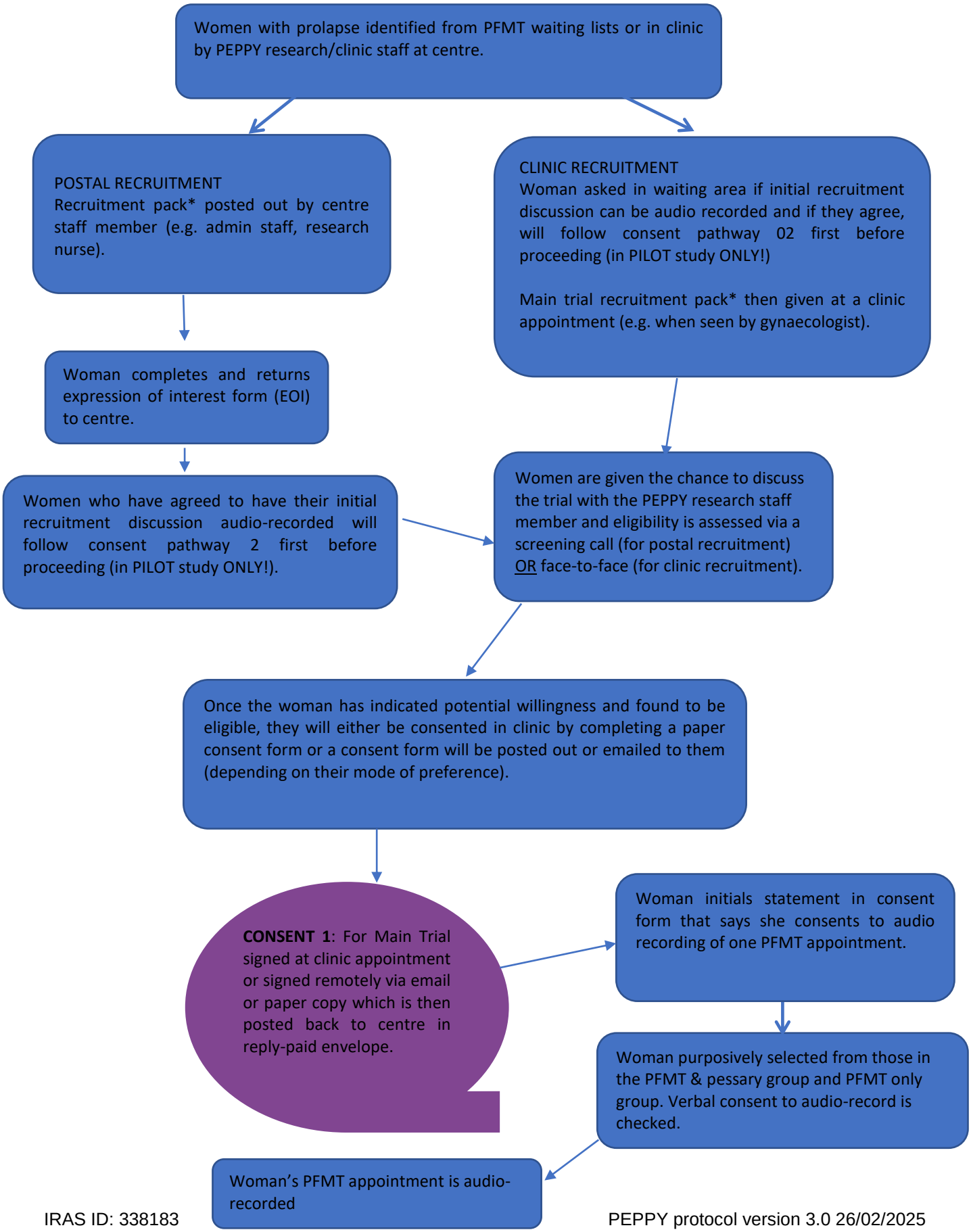
Appendix B: The PEPPY trial and process evaluation consent pathways

The following six flow charts diagrammatically outline the individual recruitment and consent pathways. The pathways are arranged chronologically. The Participant Information Leaflets (PILs) and consent forms used are summarised below and are referenced in the relevant flow chart.

1. **PIL and Consent 01**: for the main PEPPY trial (n=552 women), including an individual item on the consent form that asks for consent relating to the process evaluation for audio-recording of one PFMT appointment (n=50 women, 25 intervention group and 25 in control group) (see Consent 01 pathway) and willingness to be approached for an interview study (see Consent 03 pathway).
2. **PIL and Consent 02**: for the process evaluation, audio-recording of recruitment session between potential trial participants and the local recruiter (n=10 women in pilot study only)
3. **PIL and Consent 03**: for the process evaluation, interviewing women who are randomised and have initialled the statement on the main trial consent form indicating that they are willing to be approached for interview study at baseline (n=30 women; 2 interviews each): PFMT & pessary group (n=15 women) and PFMT only group (n=15 women) and a follow-up interview at 12 months.
4. **PIL and Consent 04**: for the process evaluation, interviewing health care professionals from PEPPY centres (aiming for a minimum n= 2 staff per centre, one staff member who delivers the intervention: PFMT & pessary).
5. **Consent 05**: for the process evaluation, audio-recording of recruitment session between potential trial participants and the local recruiter (for relevant healthcare professionals in pilot study only).
6. **Consent 06**: for the process evaluation, audio-recording of clinical PEPPY appointments (for relevant healthcare professionals).

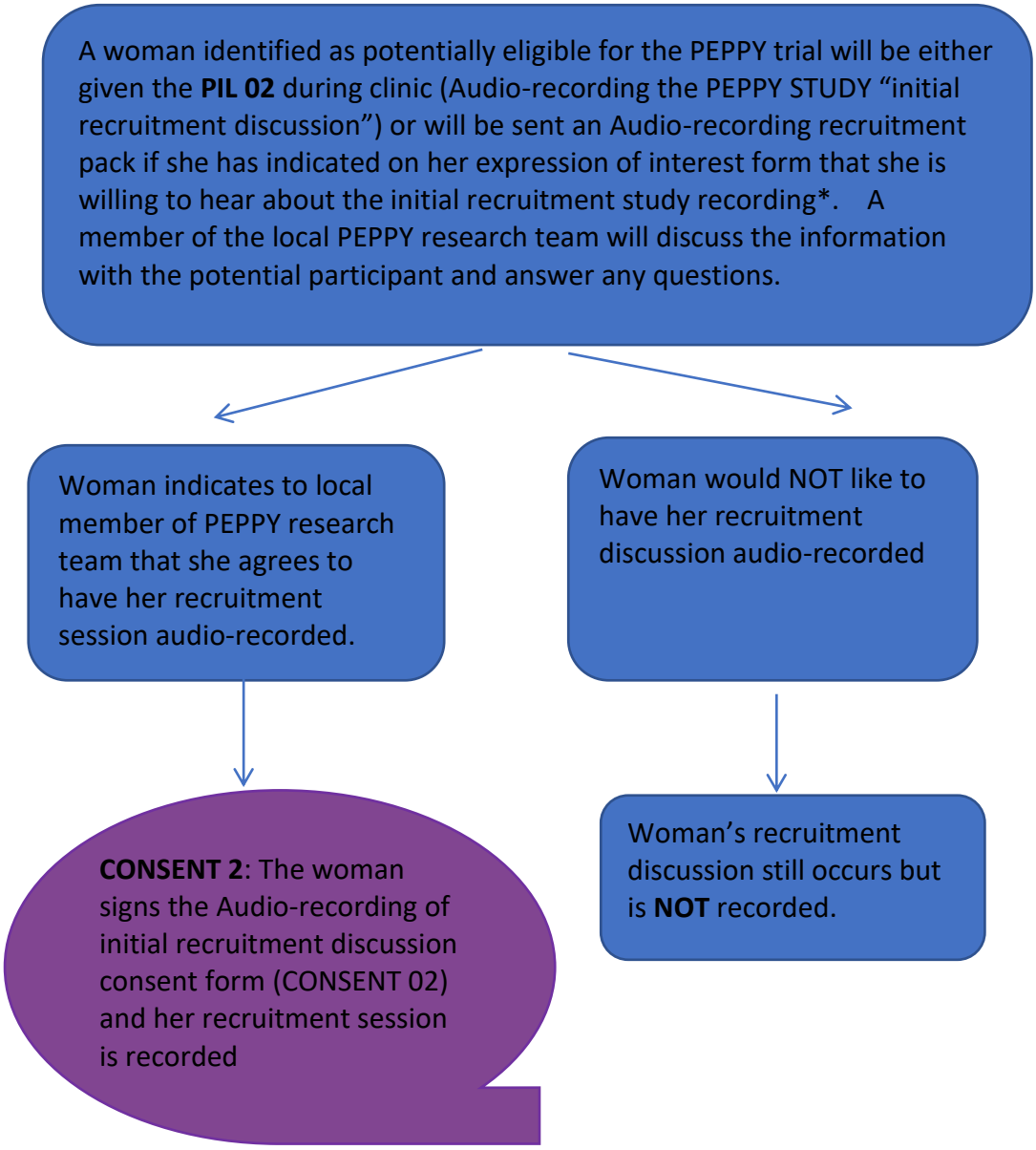
APPENDIX B, Section 1:
PEPPY CONSENT pathway 01: Consent to the main trial (n=552 women)
*Note: Recruitment packs consist of: Main Trial PIL 01, invitation Letter 01, expression of interest form and reply-paid envelope.



APPENDIX B, Section 2:
PEPPY CONSENT pathway 02: Audio-recording of recruitment discussion
n=10 Audio-recordings

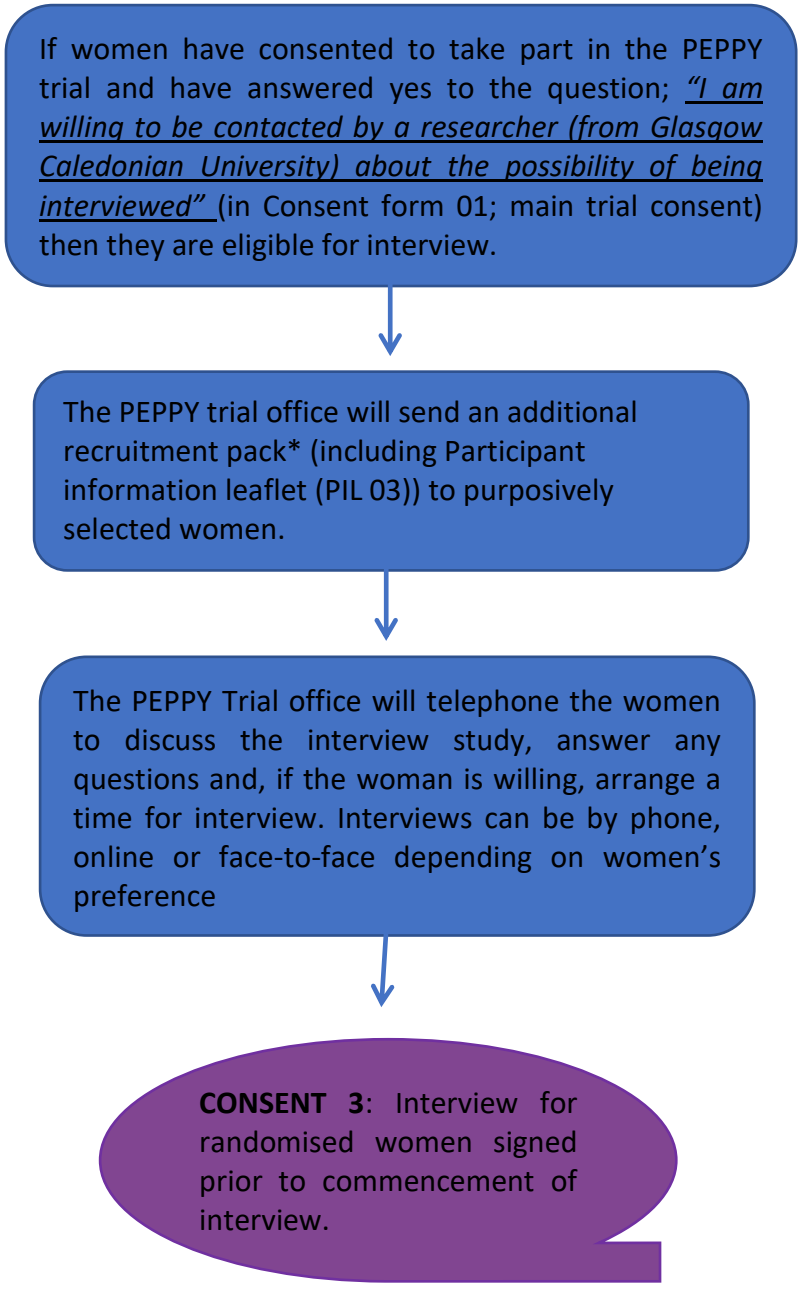
*** Recruitment pack contains invitation Letter 02, PIL 02 and a consent form 02 / link to an e-consent form**

Part of the process evaluation in the pilot study only (2 per centre).



APPENDIX B, Section 3:
PEPPY CONSENT pathway 03: Consent for woman to be interviewed
(n=30 women): PFMT & pessary group (n=15 women) and PFMT only group (n=15 women)

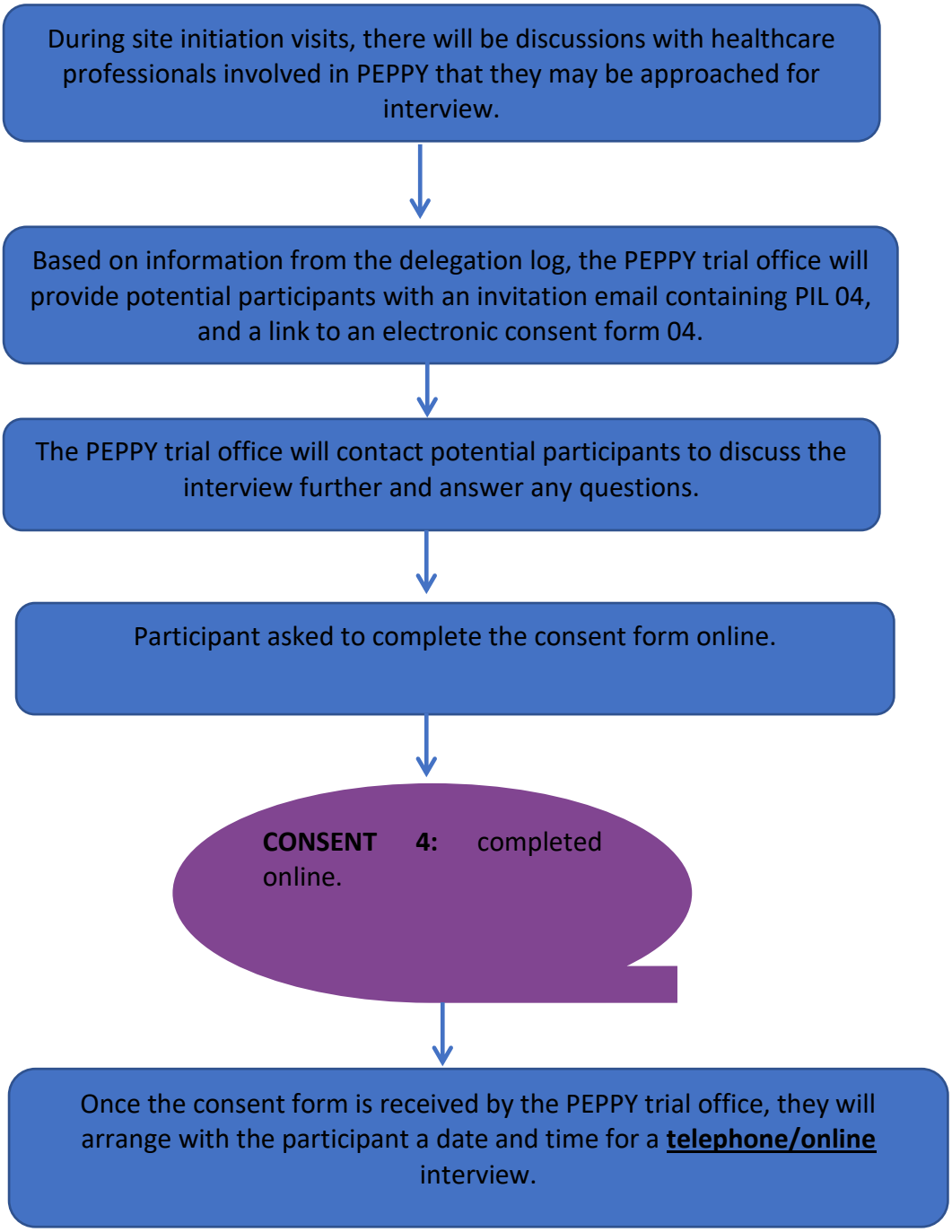
***Recruitment pack contains invitation Letter 03, PIL 03 and consent form 03**



Note: Prior to 12-month interview, participants will be contacted and consent to continue with 12-month interview will be checked verbally and a suitable time arranged to complete this follow-up interview.

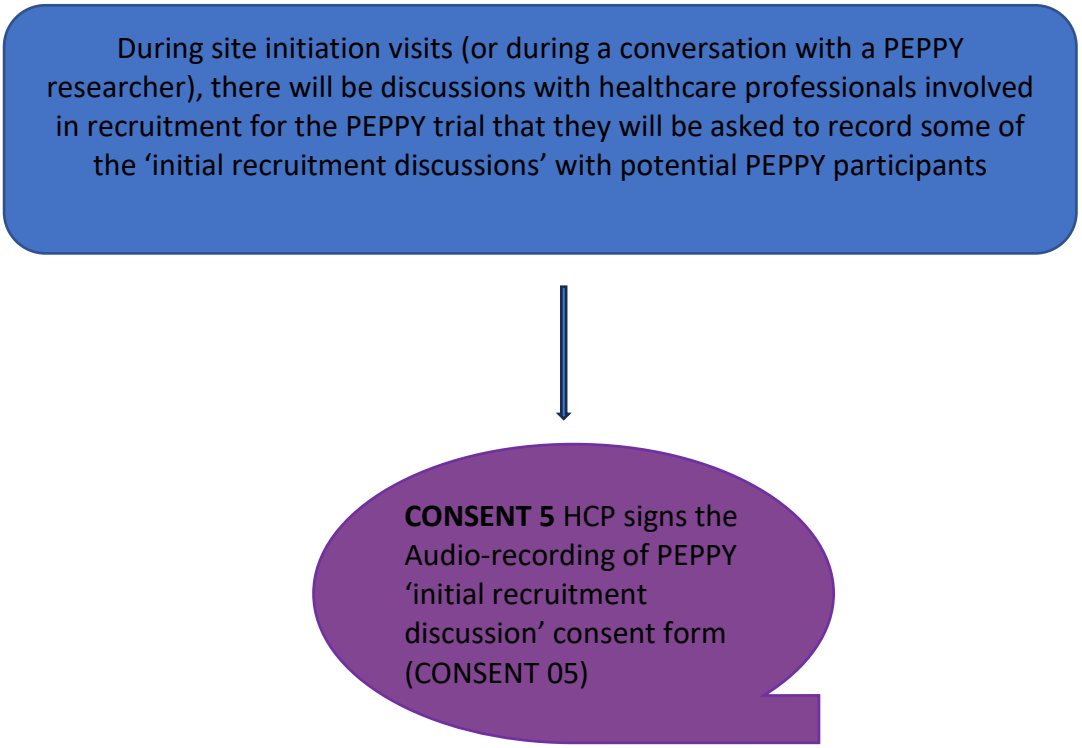
APPENDIX B, Section 4

PEPPY CONSENT pathway 04: Consent for interviewing health care professionals from PEPPY centres



APPENDIX B, Section 5:
PEPPY CONSENT pathway 05: Audio-recording of recruitment discussion for relevant HCPs

Part of the process evaluation in the pilot study only.



APPENDIX B, Section 6:
PEPPY CONSENT pathway 06: Audio-recording of PEPPY clinical appointments for relevant HCPs