NON-SURGICAL INTERVENTIONS FOR PELVIC ORGAN PROLAPSE IN WOMEN: A COMPONENT NETWORK-META ANALYSIS AND COST-EFFECTIVENESS ANALYSIS - PROTOCOL

SHORT STUDY TITLE / ACRONYM

Non-surgical interventions for pelvic organ prolapse in women

PROTOCOL VERSION 1.0

RESEARCH REFERENCE NUMBERS

IRAS Number:	Newcastle University Faculty of Medical Sciences Ethics Committee 2814/49493
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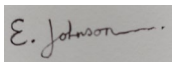
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigators agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor

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

Co-Chief Investigator:

Signature: 

Date: 29/10/2024

Name: (please print):

Miss Eugenie Evelynne Johnson

Co-Chief Investigator:

Signature:  .

Date: 29/10/2024

Name: (please print):

Prof Luke Vale

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STUDY SUMMARY

Study Title	Non-surgical interventions for pelvic organ prolapse in women: a component network meta-analysis and cost-effectiveness analysis
Internal ref. no. (or short title)	Non-surgical interventions for pelvic organ prolapse in women
Study Design	Evidence synthesis (component network meta-analysis and cost-effectiveness analysis)
Study Participants	N/A
Planned Size of Sample (if applicable)	N/A
Follow up duration (if applicable)	N/A
Planned Study Period	1 December 2024 to 31 January 2026

Research Question/Aim(s)	1. What are the most effective non-surgical interventions for managing POP in women? 2. What are women's preferences for these interventions? 3. Which of these interventions is the most cost-effective from an NHS perspective?

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
National Institute for Health and Care Research Health Technology Assessment Programme (NIHR HTA)	Research grant NIHR161575

ROLE OF STUDY SPONSOR AND FUNDER

Neither the funder nor the sponsor have any role in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. Neither the funder nor the sponsor will make and decisions with respect to these aspects.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

There is no study steering group for this project. The study involves a clinical advisory group and patient advisory group

Clinical Advisory Group

We have convened a clinical advisory group (CAG) of urogynaecologists and women's health physiotherapists to allow the clinical perspective on non-surgical treatment of POP to be embedded within our work, including interpretation of results and assistance in disseminating our findings. Members of the CAG will include our clinical co-applicants (Prof Bugge, Ms Thakar, Mrs Dwyer, Ms Igualada-Martinez and Ms Guerrero) as well as:

- Rohna Kearney, Consultant Urogynaecologist: Deputy Medical Director of Saint Mary's Managed Clinical Service, Saint Mary's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester. Will provide further expertise on urogynaecology and was clinical lead for POP for the 2019 NICE guidelines.
- Maria Oldfield: Clinical Specialist Physiotherapist/Team Lead in Pelvic Health; St Mary's Rehabilitation Unit, St Mary's Hospital, Manchester. Will provide further expertise regarding women's health physiotherapy.
- Annika Taithongchai: Urogynaecology Subspecialty Trainee; Department of Obstetrics and Gynaecology, King's College Hospital, London. Will provide further expertise regarding urogynaecology.

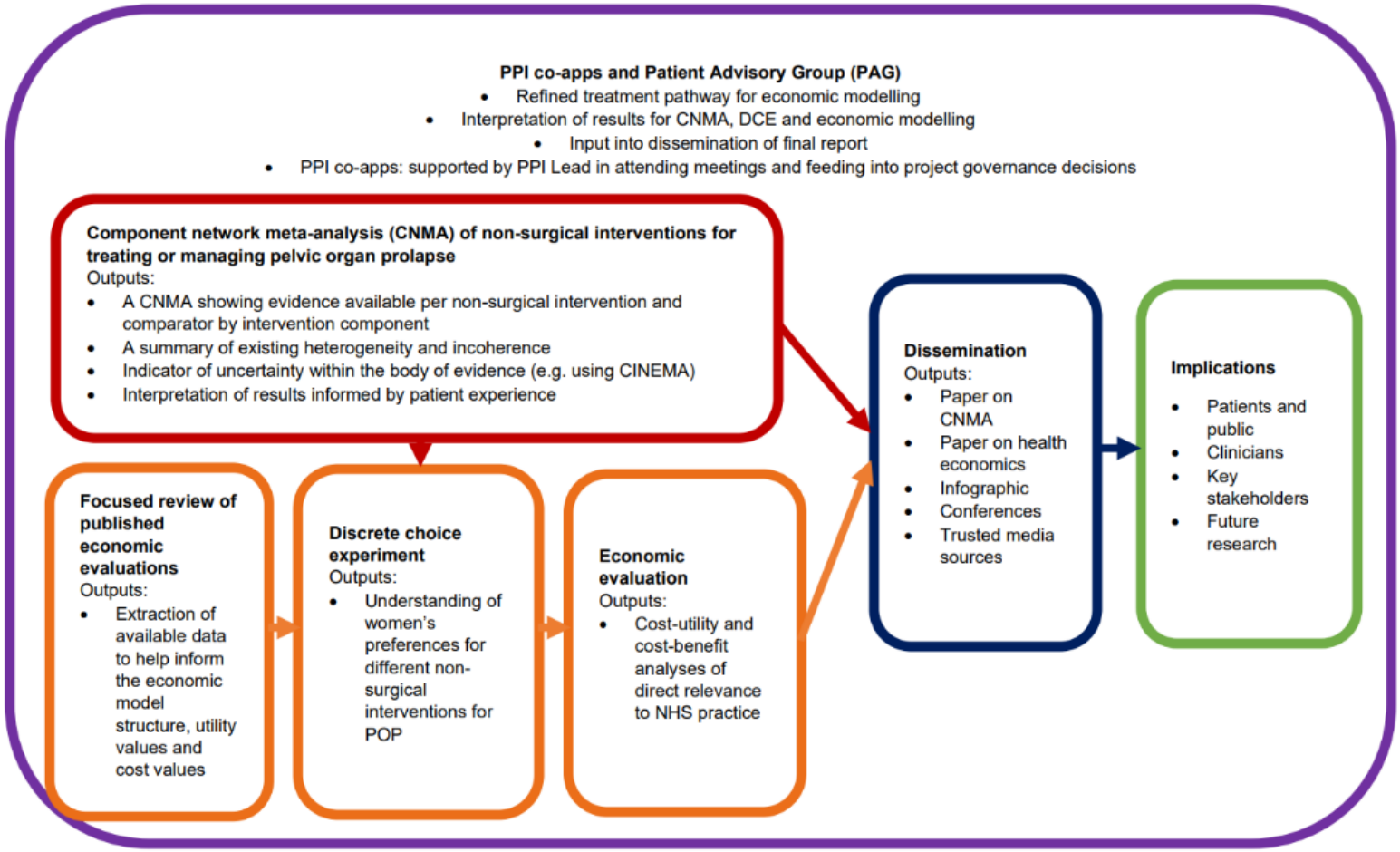
Patient and Public Advisory Group

See Section 8.2 for further details.

KEY WORDS:

Pelvic organ prolapse
Pelvic floor disorders
Meta-analysis
Cost-utility analysis
Health Technology Assessment
Discrete choice experiment

Non-surgical interventions for managing pelvic organ prolapse in women: flowchart



NON-SURGICAL INTERVENTIONS FOR PELVIC ORGAN PROLAPSE IN WOMEN: A COMPONENT NETWORK META-ANALYSIS AND COST-EFFECTIVENESS ANALYSIS - PROTOCOL

1 BACKGROUND

What is the problem being addressed?

Pelvic organ prolapse (POP) is the descent of the female pelvic organs (uterus, bladder, bowel or vaginal vault) into the vagina.(1) POP is common globally, with its prevalence based on a sensation of a mass bulging into the vagina ranging between 5% and 10%.(2) A UK survey found 8.4% of women reported a vaginal bulge or lump.(3) As the UK population is growing and prevalence of POP increases with age,(4) it is expected that POP will be an increasing issue for women and NHS services. In October 2021 women with lived experience of POP discussed our bid in a workshop, citing the high prevalence of POP as a key reason why research into POP and its treatments is needed.

The causes of POP are multifactorial, with greater parity, vaginal birth, advancing age, obesity, previous hysterectomy and family history of pelvic floor dysfunction being risk factors for pelvic floor disorders.(1) Women with POP experience bother that reduces their physical and mental health.(5) Women can experience the sensation of ‘something coming down’ into their vagina, a physical lump that can protrude out of the vagina, as well as co-existing symptoms attributable to pelvic floor dysfunction disorders such as urinary symptoms such as urinary incontinence (UI), bowel symptoms like obstructed defecation, difficulties with sexual intercourse and pain.(6) At a PPI workshop we facilitated, participants often discussed the stigmatising nature of POP, as well as the negative “life altering” impact it had on their self-esteem, well-being, mental health, day to day activities and quality of life.

Current guidelines from the National Institute of Health and Care Excellence (NICE) recommend non-surgical treatments as first-line treatment for POP.(7) Broadly, these can be defined as either lifestyle or physical interventions. Lifestyle interventions can include advice or help to achieve weight loss, while minimising heavy lifting and either preventing or treating constipation could relieve the symptoms of POP by decreasing intra-abdominal pressure.(7)

In terms of physical interventions, pelvic floor muscle training (PFMT) is the first option recommended by NICE for women with symptomatic POP.(7) PFMT is a series of voluntary contractions of the pelvic floor muscles. It is thought to work to treat POP through two mechanisms. Firstly, consciously contracting the pelvic floor muscles when intra-abdominal pressure is increased helps prevent descent of the pelvic floor organs during these times (e.g. when coughing or bending).(8) Secondly, improvement in pelvic floor muscle strength offers structural support.(8) These co-existing mechanisms elevate and stabilise the pelvic floor, thereby reversing some of the changes associated with POP.(8) Various adjuncts to PFMT have been tested, including biofeedback, electrical stimulation or cones. All of these aim to improve the quality of and/or adherence to the PFMT. Biofeedback uses apparatus that use either pressure measurements, such as surface electromyography (EMG) or ultrasound (USS), to assist with training.(9) Electrical stimulation can be provided by machines or battery-powered systems that deliver currents and frequencies at different intensities, thought to improve muscle function in weak pelvic floor muscles.(10)

Pessaries are also recommended by NICE for women with symptomatic POP.(7) A pessary is a mechanical device inserted in the vagina to support the pelvic organs.(10, 11) Support pessaries are inserted into the vagina and placed between the pubic bone and posterior vaginal fornix, supporting descending pelvic organs.(12) Space-filling pessaries fill the vaginal space, thereby creating a suction effect that increases the likelihood of retention and providing support.(12) First fittings of pessaries are usually undertaken in clinics (usually in secondary care); women can either then return to clinic for management or self-manage their pessary.(11)

A workshop we held with women with POP also identified yoga and pilates as potential physical interventions to treat POP. Yoga emphasises the integration of physical poses, controlled breathing, and concentration or meditation. It has been suggested that specific yoga practices can tone and strengthen the pelvic floor muscles,(13) which could function as an alternative or supplement to PFMT.(14) Similarly, it is theorised that specific Pilates exercises focusing on pelvic stability, mobility and body alignment can increase pelvic floor muscle function, since most exercises associated with Pilates are performed at the same time as contracting core abdominal muscles and the diaphragm.(15)

Current guidelines that support practice are based on systematic reviews restricted to pairwise comparisons, making the evidence base difficult to interpret due to the number of pairwise comparisons needed to assess the effects of the multiple forms of non-surgical treatment.(12, 16, 17) A component network meta-analysis (CNMA), which has not yet been performed in this area, would help ensure the evidence is more readily interpretable and usable within practice. Furthermore, it would provide a more rigorous evidence base for use in an economic evaluation.

There has been little consideration about which treatments make the best use of NHS resources, despite an NHS expenditure of £45 million on POP treatment between 2017 and 2018.(18) There is little relevant economic evidence, with only two economic evaluations comparing just two of the relevant treatments identified by the 7th International Consultation on Incontinence (ICI).(19, 20) The ICI consultation concluded that: “Due to the nature of reporting or the findings themselves the evidence … is far from compelling.”(21)

Members of a PPI workshop we held noted they would like to know what treatments work, comparing as many of them to one another as possible. Shaped throughout by our PPI process, we will conduct what we believe is the first CNMA surrounding non-surgical treatments for POP. We expect there will be trade-offs between the different outcomes of interest as well as between different processes of care. Therefore, we will also develop a discrete choice experiment (DCE) to estimate women’s preferences for different treatments. The results of the CNMA and DCE will be integrated into a model-based economic evaluation. Together, this will provide better information than currently available to help guide women with POP, healthcare practitioners and policy makers on treatment options.

2 RATIONALE

Why is this research important in terms of improving health and/or wellbeing of the public and/or to patients and health and care services?

The high prevalence of POP, its direct costs to the NHS and often hidden costs to those affected and their families, coupled with the controversy surrounding the use of mesh surgery, has brought the spotlight onto non-surgical interventions. There are various non-surgical management options for POP but also considerable uncertainty surrounding the best choice. There are no current comprehensive quantitative evidence syntheses of treatment effectiveness and efficiency across the spectrum of non-surgical POP treatments, as these have only previously been compared in a series of pairwise comparisons. The plethora of pairwise comparisons makes it difficult for patients and healthcare professionals to make informed choices about treatments. Similarly, the lack of cost-effectiveness data makes it difficult for healthcare commissioners and managers to judge what provision of care best meets needs given limited NHS resources.

Women want to be better informed about POP treatment choices,(22) a fact emphasised during our PPI workshops. Here, women with lived experience of POP wanted to know more about available non-surgical interventions and which worked best when compared against each other, particularly given concerns around the use of vaginal mesh. A CNMA would both directly and indirectly compare non-surgical interventions when used either alone or in combination and show their relative effectiveness. The DCE will estimate women's preferences for the different treatments, showing how these preferences may differ between individuals. Thus, it would help answer the majority of questions identified by the James Lind Alliance surrounding pessary use for POP.(23) By using these data, we

will also provide evidence on their relative cost-effectiveness. Thus, this research is important to women, healthcare professionals and services as it would:

- ensure women have access to the best comparative information about treatments;
- enable appropriately informed clinical conversations; and
- promote 'best evidence' treatments for women with a view to promoting the best treatment outcomes within the available NHS resources.

3 THEORETICAL FRAMEWORK

Although a network meta-analysis (NMA) has been completed on surgical procedures for treating POP,(24) a standard NMA would fail to address the complexity and heterogeneity between non-surgical interventions for POP. For the potentially heterogeneous and complex interventions used to treat POP, a CNMA is a methodologically robust approach that will provide the best available evidence for decision making.(25) There is currently no completed CNMA in this area.

To demonstrate the feasibility of CNMA, we conducted a scoping search using the Cochrane Incontinence Specialised Register, a highly specific database of RCTs and quasi-RCTs collated from sources such as MEDLINE, CINAHL, Embase, CENTRAL and clinical trials registers. It is the most comprehensive source of potentially eligible papers surrounding POP. From the Register, we screened records from inception to January 2023, identifying 33 eligible studies (median number of participants n = 91) based on our inclusion criteria (see methods below). Sixteen of these studies were published since 2017, the date of search for evidence underpinning the 2019 NICE guideline update,(7) showing the steep trajectory of research surrounding non-surgical treatments for POP. We completed high level data extraction of the 33 studies to assess comparability of outcomes and populations. This process identified 20 interventions, either alone or in combination, that could be combined within a CNMA.

Women want to be better informed of treatment options available to them,(22) but we are not aware of any work quantitatively exploring women's preferences for different non-surgical treatments for POP. As such, the DCE will be important to help guide individual treatment decisions and inform cost-effectiveness estimates. Few economic evaluations have been conducted and these have limited applicability to the NHS, do not consider all relevant comparators, and have substantial limitations in conduct and reporting. Therefore, incorporating the CNMA and DCE data into an economic model will provide evidence on costs and cost-effectiveness that the NHS is currently lacking.

4 RESEARCH QUESTION/AIM(S)

4.1 Objectives

This work will answer three research questions:

- What are the most effective non-surgical interventions for managing POP in women?
- What are women's preferences for these interventions?
- Which of these interventions is the most cost-effective from an NHS and personal social services perspective?

4.2 Outcome

The study will determine the relative effectiveness, safety, cost and cost-effectiveness of non-surgical managements for POP in women. For the CNMA the outcomes will include: quality of life; severity of POP; subjective cure and/or improvement of POP symptoms; and activities of daily living. We will

assess these outcomes at short (0-6 months), intermediate (6-12 months) and long term (>12 months) time points to reflect both initial treatment response and possible decay of effect.

For the economic evaluation the outcomes will be cost to the NHS and personal social services, quality adjusted life years (QALYs); incremental cost per QALY gained; monetary benefits derived from the results of the DCE and incremental net monetary benefits (INMB).

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

5.1 Component network meta-analysis

5.1.1 Protocol development

Prior to commencement of the CNMA, we will develop a full protocol and publish this on PROSPERO following the recommendations of the PRISMA-P guideline.(26)

5.1.2 Search for clinical effectiveness studies

We will build upon the search for the Cochrane Incontinence Specialised Register (which includes RCT and quasi-RCT records from databases such as MEDLINE, CINAHL, Embase, CENTRAL and clinical trials registries) covering from inception to 31 March 2023, when the register was last updated. For records from 1 April 2023 onwards, the search strategies used to maintain the Specialised Register will be used to bring the search up to date, updating each from the date of last search for each individual database. No restrictions will be applied to the searches (such as language or date of publication).

We will run searches for RCTs, quasi-RCTs and economic evaluations (needed for the economic evaluation, see Section 3.3) in months 2 and 7 to ensure the searches are as up to date as possible at the point of analysis.

5.1.3 Eligibility criteria

Study design: We will include RCTs, quasi-RCTs, cross-over RCTs and cluster-RCTs.

Setting: We will include studies located in any country or setting.

Population: We will include studies of women with symptomatic POP aged ≥ 18 (any stage), irrespective of comorbidities (e.g. UI), in these compartments: anterior vaginal wall prolapse; posterior vaginal wall prolapse (enterocoele, rectocoele); and uterine or vaginal vault prolapse. We will include RCTs comparing women with POP and UI compared to women with POP and no UI and studies assessing the effect of recurring POP on women after failed surgery undergoing non-surgical treatment.

Interventions: We will include studies assessing the effects of single or combined use of: lifestyle advice (e.g. advice or help to achieve weight reduction); individual or group PFMT (with or without biofeedback); electrical stimulation (alone or with PFMT); yoga or pilates; biofeedback devices; pessaries of any kind. Our PPIE workshop identified yoga, pilates and biofeedback devices as interventions of interest. High-level data extraction from our scoping exercise identified 20 different combinations of interventions that can be included within the CNMA.

Comparators: We will include studies where the comparators are either: no active intervention; usual care (as described by study authors); sham intervention; surgery or delayed surgery; or any non-surgical intervention listed as eligible for the review above.

Outcomes: A PPIE survey we conducted in June 2022 and subsequent workshop in December 2022 (see Patient and public involvement) identified the outcomes listed in section 4 as important outcomes to women.

5.1.4 Study selection

The results of the searches will be deduplicated in EndNote and exported to Rayyan for screening.(27) Two independent reviewers will assess titles and abstracts of each record, then full texts of selected papers according to the above eligibility criteria, with disagreements resolved by discussion or arbitration

to a third reviewer if required. Where studies are published in a language other than English, we will obtain translations to assess for eligibility. We will consider any papers where we are unable to obtain translations as 'Awaiting classification'.

We will perform forwards and backwards citation chaining on relevant systematic reviews and included studies to identify any studies that may have been missed by the search.

5.1.5 Data extraction

We will develop a data extraction form with the following items: study author and year; country; setting; number of participants; affected compartment; severity of POP; parity; prior hysterectomy; participants' age; participants' BMI; inclusion criteria; exclusion criteria; details on primary and secondary outcomes; length of follow-up; relevant outcome data; declarations of interest; and study funding sources. We will use the Template for Intervention Description and Replication (TIDieR) checklist to describe the components of the interventions and comparators used within each study.(28)

Two independent reviewers will then pilot the data extraction form on 10% of included studies. Where necessary, we will modify the data extraction form following piloting before the two independent reviewers extract data for the remaining studies, with any disagreements resolved through discussion or arbitration to a third review author. Where data are unclear or missing, we will contact study authors to obtain these missing data or clarify information.

5.1.6 Critical appraisal

Two reviewers will use Cochrane's 'Risk of Bias 2' tool to critically appraise included studies,(29) resolving disagreements through discussion or arbitration to a third review author. The reviewers will assess risk of bias according to the effect of assignment to the intervention (intention to treat). The reviewers will assess the following domains at the outcome level: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. For each domain, the reviewers will answer either 'yes', 'probably yes', probably no', 'no' or 'no information' before assigning a risk of bias judgement of either low risk, high risk or some concerns.

5.1.7 Data synthesis

We will describe important clinical and methodological variables for included studies.

We will perform all analyses in R using the netmeta package, which provides a frequentist approach to NMA.(30) An NMA enables the estimation of indirect and direct comparisons not addressed within primary trials.(21) Such analyses assume consistency in the evidence of the network between direct and indirect evidence. Where there are sufficient data, we will assess the consistency of direct and indirect evidence within each closed loop and the whole network using the design-by-treatment method.(30)

We will conduct an NMA using random-effects modelling. However, where there are sparse networks or insufficient data to reliably estimate the between-study heterogeneity we will compare goodness of fit of fixed effect and random effects models, with the better fitting model providing the results. If both models are equally suitable, we will utilise the simplest model available. If appropriate, we will consider the correlation between multi-arm trials. The geometry of the NMA network will be displayed using network diagrams.

We will estimate intervention effects along with 95% confidence intervals. We expect outcomes to be reported as mean differences (MDs). If there are variations in the measurement tools used, we will utilise a standardised mean difference (SMD) to analyse the data. For each outcome, we will use the most common comparator treatment. A relative ranking of treatments will be provided.

The CNMA, which uses weighted least squares regression, will firstly be conducted using the additive model. This model assumes that any combination of components is the additive sum of their components. We will also utilise interaction models (forward selection approach).(30) This method starts sparse and moves forwards to increase the richness of the model. It also allows for the interventions to

not be considered equal, as is the case with the additive model. Gradually, we will add interactions to the model until the stopping criterion is fulfilled. The selection process stops if all P values of the Akaike Information Criterion (AIC) for the remaining interactions are above 0.157.(31)

5.1.8 Subgroup and sensitivity analyses

Subgroup analyses will be performed on: those who have and have not undergone failed surgery; and exercise interventions (PFMT, pilates and yoga). We will undertake sensitivity analyses to explore the effect of study design, risk of bias, follow-up time and heterogeneity.

We will assess the impact of POP severity through sensitivity analysis; our completed scoping work identified that the majority of studies include women with either stage I and/or II POP. If data allows, we will model the individual stages of POP in separate analyses. Failing this, we will assess the impact of POP severity by creating multiple models removing subgroups (e.g. studies which include those with stage III POP) from the analysis. Our scoping work also highlighted that most of the literature reported on women with anterior POP. Where data allows, we will assess type of POP compartment (e.g. anterior, posterior) in varying models to understand the effectiveness of the interventions across different subgroups.

5.1.9 Assessment of certainty within the CNMA

We will evaluate the credibility of the standard NMA using Confidence in Network Meta-Analysis (CINeMA).(32) Two independent reviewers will assess the certainty of the evidence in each standard NMA, assessing the following six domains: within-study bias; reporting bias; indirectness; imprecision; heterogeneity; and incoherence.(32) The two reviewers will resolve any disagreements through discussion or arbitration to a third reviewer.

5.1.10 Reporting

We will report the CNMA according to the PRISMA-NMA checklist.(33)

5.2 Discrete choice experiment

Women may have preferences not just for the health outcomes of treatment but also in which care is delivered. Estimating effects in terms of quality-adjusted life years (QALYs), which focus on both quality and quantity of life, would not capture preferences for the ways care is delivered. An approach that can capture preferences for health effects and the way care can be delivered is a DCE. A DCE is a quantitative method increasingly used to elicit preferences from participants (e.g. patients, the public and policy-makers).(34) A DCE involves presenting individuals with a series of choices, usually pairwise, between hypothetical options and participants are asked to state which option they prefer. The options are described by a set of common attributes (which might relate to difference in the process of care, risks of complications, long-term outcomes, etc.) and levels, which describe the range over which the attribute may vary between options.

In this DCE, we will derive attributes and levels from the evidence synthesis (see Section 3.1), consultations with women as part of our PPI (see Section 4), and clinicians. We will speak to women to identify attributes of the intervention and their key effects. This, along with the evidence synthesis (which will provide estimates on relative effects for different outcomes), will form the basis of the DCE attributes and levels. By working further with our experts by experience, we will explore the appropriateness of attributes and levels and the choice task. One attribute will be a cost attribute, so that we can estimate the willingness to pay for a unit change in each attribute and estimate the benefits of any given intervention included in the economic modelling (see Section 5.3).(35, 36)

We will design the DCE in NGENE, choosing the design with the lowest D error so that the DCE elicits as much information from participants as possible.(37, 38) If necessary, we will block the design to ensure the number of choice tasks would be a reasonable amount for a participant to do whilst still covering all the necessary choices from the D-efficient design. To explore whether participants are engaging with the questions set out in the DCE, we will include a dominance question, whereby

participants will be presented with the very best outcomes for every attribute compared with the very worst. There should be no reason for the participant to select the choice set containing the worse outcomes over the choice set containing the better ones, thus the dominance question will evaluate overall engagement with the questions.

We will seek comments and advice from our experts by experience on a draft of a survey and make changes accordingly. We will use an online survey company to prepare the survey and perform a soft launch to check the DCE is behaving the way we are expecting. Following this, we will seek to recruit 1000 women from the public, identified by the survey company's online panel. As there are no formal sample size calculations to derive the sample size of a DCE, we will choose the largest pragmatic sample possible. We will analyse data in a random utility framework using appropriate logistic regression methods, such as conditional logit/multinomial logit models.

5.3 Economic model

We will conduct model-based cost utility (CUA) and cost-benefit (CBA) analyses, building a Markov decision model informed by the experience of our PPI group and the evidence synthesis (see Section 5.1). The model will compare the alternative treatment strategies at the level of a care provider, allowing strategies starting with a single intervention (e.g. PFMT) to be compared with strategies where women have a choice between interventions. We will consider sequences of treatments (i.e. an initial index treatment followed by further intervention, should it be required). The model will simulate individual patients receiving treatment for POP to estimate their costs and outcomes over their lifetime. The journey of patients through the model will depend upon the treatments they receive and their individual characteristics (e.g. age, comorbidities).

We will assign a set of parameters (transition probabilities and state rewards (cost and health utility scores)) for each patient in each follow-up pathway, modelled based on their characteristics. Transition probabilities and event rates will be derived from the evidence synthesis (see Section 5.1) and existing health technology assessments.(11, 39) With respect to costs, we will include costs from an NHS and personal social care services (PSS) perspective; these will include the costs of delivering the interventions and their consequences over the expected lifetime of the women involved. Intervention costs will be informed by the description of the intervention provided by the relevant included studies in the CNMA and advice from our clinical experts and experts by experience. Subsequent care will depend upon the events that occur but will also be informed by the patterns of care observed in previous health technology assessments. We will derive these costs from existing available sources,(40-42) supplemented by micro costing based on expert advice from our PPI and clinical experts. For the CUA, we will extract utilities events (e.g. recurrences, incontinence) that occur within the model from existing literature.(11, 39) For the CBA, we will use the results of the DCE to value profiles of outcomes generated by the model using methods developed for previous studies.(35, 36)

For the CUA, we will report incremental costs per QALY, while for the CBA we will report INMB. For the CBA, we will explore the impact of incorporating heterogeneity in women's preferences into the model. We will explore uncertainties in the model through deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA). The DSA will consider the impact of different discount rates, time horizons and parameter sets (e.g. those provided by the subgroup and sensitivity analysis described in Section 5.18). We will present further sensitivity analyses in the form of tornado diagrams to illustrate the impact of changes in model parameters on the estimated incremental cost per QALY. In the PSA, we will assign suitable distributions to each model parameter; the choice of these distributions will be guided by parameter type and standard statistical methods of their estimation (though, for example, gamma or log normal distributions for cost parameters, beta distribution for utility and transition probability parameters are commonly used). Additionally, we will perform Monte-Carlo simulation (which samples the parameters at random) to generate the estimates of costs and outcomes accounting for any parameter uncertainties. We will present data as costs and effects plots and, for the CUA, cost-effectiveness acceptability curves (CEAC), with probability INMB > 0 for the CBA.

8 ETHICAL AND REGULATORY CONSIDERATIONS

The Newcastle University Faculty of Medical Sciences Research Ethics Committee has reviewed this study and has provided a favourable opinion. As an evidence synthesis project, we will not be working with patients recruited from the NHS and there will be no confidential patient information obtained.

We will seek further ethical approval for our DCE (see Section 5.2), once the DCE survey has been designed.

The study will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines and any appropriate NHS R&D approval(s) will be obtained. Annual progress reports, end of study declaration, and a final report are submitted to the Sponsor, within the timelines defined in the regulations.

8.1 Assessment and management of risk

An independent risk assessment has been carried out by the sponsor.

This project aims to utilise complex evidence synthesis and health economic methodologies, alongside ensuring PPIE. Delivering all components of the project within 14 months is ambitious. However, core team members have been costed appropriately to ensure delivery of the project within this timeframe.

Success measure	Risks and mitigations
Successful completion of the project led by a junior PI	**Risk:** The Co-PI (Miss Johnson) is not experienced enough to manage the challenges that arise from a complex, multi-component project. **Mitigation**: Miss Johnson is being supported in her role by a highly experienced Co-PI, Prof Vale. He has seen numerous HTA projects of a similar nature, including in the urogynaecology field, to completion. He will provide regular and ongoing support to Miss Johnson. Other members of the research team, including Dr Meader, Ms Wallace and Prof Bugge, are all also highly experienced in managing and delivering NIHR-funded projects successfully.
Recruiting enough women for the PAG before commencing the study	**Risk:** Failure to recruit enough women for the PAG in time. **Mitigation:** Our prior work to support this application has already demonstrated a large amount of interest from women with POP in being involved in this project. We have close connections with RCOG, who can advertise through their Women's Voices group, while Miss Johnson has built strong relationships with community groups and the voluntary sector through their work with the NIHR IO.
Completion of the CNMA	**Risk**: Limited evidence on which to be able to conduct a CNMA. **Mitigation**: We have performed a feasibility assessment for the proposed CNMA by screening records from the Cochrane Incontinence Specialised Register. From this feasibility work, we identified 33 studies that meet our eligibility criteria for the CNMA. After completing high-level data extraction on these studies to assess the overall comparability of their outcomes and populations, we identified 20 interventions alone or in combination that could feasibly be combined within a CNMA. We are therefore confident that there is enough relevant evidence available to be able to conduct the CNMA.

Success measure	Risks and mitigations
Completion of the DCE	**Risk**: Inability to conduct the DCE. **Mitigation**: The DCE will be conducted using rigorous and well-rehearsed methods that have proved successful over a range of situations and clinical conditions. The use of a general population survey alleviates the main risk of failure to recruit, although adds the risk that participants may not understand the consequences of prolapse. To mitigate against this, we will use quota recruitment to recruit women with experience (either direct experience or via family/friends) along with a general population of women.
Completion of the economic evaluation	**Risk:** Limited evidence on which to be able to conduct an economic evaluation. **Mitigation:** This risk relates to the known risks of the CNMA and the mitigation that applied there (see above). Furthermore, should a definitive economic evaluation not be possible, we will still be able to conduct an early economic evaluation and highlight key areas for further primary research.
Adaptability to changes within the study team	**Risk**: Loss of key research team members (e.g. due to illness). **Mitigation**: Both the Evidence Synthesis Group at Newcastle University and Global Centre for Health Economics at LSHTM are large and have multiple people with expertise and experience in the proposed methods. As such, we will be able to draw on support from these groups to minimise delays in project completion. With respect to the clinical and PPI co-applicants, we have deliberately included multiple individuals to fulfil these roles so that, should one be absent, we can draw on the advice and support of others without undue delay.

8.2 Peer review

This protocol was reviewed by members of the NIHR Research Design Service prior to submission to funding. It was independently reviewed by 7 reviewers as part of the research funding process. Reviewers included relevant research methodologists, topic experts and experts by experience.

8.3 Patient & Public Involvement

8.3.1 Principles of PPI

Within our PPI, we will adhere to the core principles outlined in the UK Standards for Public Involvement.(43, 44)

8.3.2 Role of the PPI co-applicants

Further to helping shape the proposed project, our PPI co-applicants will continue to govern the project. They will attend meetings within the core research team of PIs and co-applicants to ensure the patient and public perspective is represented and heard in our decision-making processes. Supported by the PPI Lead, our PPI co-applicants will also be offered the opportunity to be involved in co-ordinating and delivering activities with the patient advisory group (PAG), should they wish to do so.

8.3.3 Recruitment of the patient advisory group (PAG)

During the funded project, we plan to convene a patient advisory group (PAG) to continue to govern the project and shape the methods used. Reflecting on the constructs of the ACTIVE framework for patient involvement in systematic reviews,(45) we will conduct an open call over a fixed time-frame for PAG members and aim to recruit up to 10 women with a lived experience of POP, either as a patient, carer or friend or family member of someone with POP.

We will recruit for members of the PAG by using links that the research team have established with organisations with an interest in women's health, such as the Royal College of Obstetricians and Gynaecologists' (RCOG) Women's Voices, the Pelvic Floor Society, the United Kingdom Continence Society (UKCS) British Society of Urogynaecologists (BSUG) research network, and the Pelvic, Obstetric & Gynaecological Physiotherapy (POGP) network. Additionally, we will advertise the opportunity to be involved via online platforms such as VOICE International and Mumsnet and ask our PPI co-applicants to distribute the opportunity within their networks. In recruiting and selecting members of the PAG, we will use guidance from the NIHR INCLUDE project to ensure a diverse range of voices and perspectives are included.(46)

8.3.4 Patient involvement in the project

The PAG and our PPI co-applicants will continue to be central to informing and shaping the funded project. As per the constructs of the ACTIVE framework, the approach to PPI will be continuous and involve direct interaction with both our PPI co-applicants and PAG members.(45) Our co-applicants will be given the opportunity to lead and shape the approach to PPI interactions with the PAG.

Throughout the project, we aim for our PPI co-applicants and PAG members to be controlling our work (i.e. working in partnership with the rest of the research team and making decisions under the guidance and support of the PPI Lead).(45) Having already had extensive PPI input into shaping the interventions and outcomes eligible for the CNMA (and, by extension, forming part of the economic evaluation model), our PPI co-applicants and the PAG will feed into the interpretation of the CNMA results. Furthermore, we will discuss the care pathway experiences of our PPI co-applicants and the PAG to inform and discuss the results of the economic model and the development of the DCE. As reported above, this will include the development and discussion of the appropriateness of attributes and levels for the DCE, and in developing the DCE survey tool (see Section 3.2). Members of the PAG will be asked to view and comments on the draft version of the DCE survey tool, which will be revised accordingly prior to distribution.

We will weave the perspectives of our PPI co-applicants and the PAG throughout the results to highlight how the experiences and perspectives of women with POP either complements or contrasts with our findings. We will ask our PPI co-applicants and the PAG to review and comment on protocols and the final report, particularly the plain language summary.

We will hold a workshop with our PPI co-applicants and members of the PAG to discuss dissemination in the final months of the project; this will allow us to identify the best outlets to share our work in and may also include co-creating dissemination materials.

8.3.5 Training and support

The PPI Lead will hold an induction to the project for the PAG, as well as training surrounding systematic review and basic health economic methods. These sessions will be supported by other members of the project team, as needed. All PPI contributors will be encouraged to contact the PPI Lead for additional support as required, ensuring that specific training can be delivered or so we can signpost to already-existing resources (e.g. Cochrane's Evidence Essentials).

To maintain communication, we will send monthly updates to our PPI co-applicants and the PAG to inform them of progress and invite any queries and comments, as well as hosting four formal progress meetings in months 1, 4, 7 and 12. These formal progress meetings will provide an additional forum for our PPI co-applicants and the PAG to raise any areas where they require additional support or training.

8.3.6 Impact and evaluation

Throughout the project, we will use the Public Involvement in Research Impact Toolkit (PIRIT) to track the contributions of our PPI co-applicants and the difference they have made to our work.(47) Using PIRIT, we will evaluate the impact of PPI on our project against our initial plans and highlight this impact appropriately in the final report and additional publications.

Furthermore, we will design and distribute surveys to the PAG at two time points (7 and 12 months) using the secure online platform Qualtrics,(48) which will be based on the principles outlined in the UK

Standards for Public Involvement.(43, 44) The survey at month 7 will allow us to evaluate and potentially amend our approaches (e.g. modes of communication or opportunities for further support). We will compare the evaluations at months 7 and 12 to reflect on and assess progress and satisfaction with our PPI approach throughout the project.

8.3.7 Reporting of PPI

We will report PPI in the final report and any publications using the GRIPP2 checklist.(49) This will further aid us in transparently highlighting the impact and role of our PPI co-applicants and PAG on our results.

8.3.8 PPI funding

We will reimburse all activities according to NIHR recommended rates;(50) we have adequately costed funds for all activities into this project.

8.4 Protocol compliance

The Investigators will conduct the study in compliance with the Protocol given favourable opinion by the Newcastle University Faculty of Medical Sciences Research Ethics Committee or the DCE from the LSHTM Ethics Committee. Any amendment to the Protocol or other approved documents will be reviewed by PMG before application to the relevant RECs. Any amendments will be documented in Appendix 2 – Amendment History.

8.6 Data protection and patient confidentiality

As an evidence synthesis project, the study will not make use of data that is not within the public domain. It will also not involve any data from patients.

For the DCE, data will be sought from the general public. No data will be collected that will the allow the identification of any DCE respondents. Data for the DCE will be supplied by the survey company and kept on a secure site on the LSHTM network. Only the analysts involved in the analysis of the data will have access to the data set. Only summary data will be shared with other co-investigators and study researchers and to sponsor. Data will be stored in compliance with LSHTM data storing rules. The data custodian is Professor Luke Vale.

8.7 Funding and Indemnity

The study is funded by a grant awarded by the NIHR Health Technology Assessment programme.
The necessary insurance is provided by Newcastle University.

8.8 Access to the final study dataset

The data used in the CNMA and economic evaluation model will be available to the co-investigators and study researchers. The individual-level data from the DCE will be restricted to the health economics team. Summary results will be shared for the PAG and CAG.

Requests for re-analysis of the DCE data set will need to be approved by the co-Chief Investigators. As the participants who complete the DCE are contracted to provide the data by the survey company, no formal consent will be sought for subsequent use of the dataset.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

We have planned the following outputs from this research:

- a detailed final report;
- at least three peer-reviewed academic journal articles (the systematic review and CNMA, the DCE, and the economic evaluation);
- conference presentations at relevant societal and methods-focused meetings;
- and summary articles and materials aimed at a broader audience, including patients, that will be distributed with help from PPI and relevant charitable and professional bodies with whom we have engaged.

9.1.2 Dissemination and impact for practitioners and policymakers

Completion of this project will provide the most comprehensive assessment of the effectiveness and cost-effectiveness of non-surgical interventions for POP to date. The major components of the results (the CNMA, DCE and economic evaluation) will all be published in relevant peer-reviewed journals (e.g. the International Urogynaecology Journal) and presented an international topic-specific conference (e.g. the International Continence Society Annual Conference).

We will involve stakeholders in research planning to ensure the evidence is grounded, relevant, accessible and useful and feed into NICE, European Association of Urology (EAU) and ICI guidelines. We will also leverage links to organisations such as RCOG and POGP from within the research team to ensure that results from the study are appropriately disseminated to practitioners. Furthermore, this work will help answer questions posed by the 2019 NICE guidelines on management of POP,(7) as well as priority questions posed by the JLA.(23)

Upon completion of the project, we will also highlight key primary research gaps in the area, allowing the NIHR to commission new trials to address outstanding questions surrounding non-surgical interventions for POP.

9.1.3 Dissemination and impact for patients and the public

Insights from PAG representatives and clinicians will, in part, help us identify our target audience, use appropriate language and focus on the possible impact of the research on practice or daily life. For example, attendees at one of our PPI workshops highlighted platforms such as the radio (e.g. BBC Radio 4) and podcasts as dissemination options targeted to the wider public. We will converse with Newcastle University's press office around their role in disseminating our findings, considering these suggestions.

We will engage with a creative agency to create an infographic summarising the results of our research through visuals and plain language. To do this, our PPI representatives and PAG, as well as members of the research team, will be invited to a meeting where we will share our findings, during which the infographic will be created live. We have allocated sufficient funding to engage with a creative agency to produce this infographic into our project proposal.

Our PPI representatives and PAG will be able to formally participate in the dissemination of the research, if they wish to do so, by snowballing the findings of the project and the infographic to their networks. Additionally, we will share the infographic and a plain language summary of the work with organisations, charities and networks that support women with POP (e.g. RCOG Women's Voices).

As highlighted by the Cumberledge Report,(22) and our PPI workshops foregrounding this research proposal, women wish to be better informed about non-surgical treatment options for POP and which of these options work best. Once completed, this research will provide women with POP answers to these questions, particularly through the dissemination of plain language versions of the results. In turn, this will empower women to be able to have open and informed discussions with clinicians about their options for treating POP, using the best available evidence.

9.2 Authorship eligibility guidelines and any intended use of professional writers

Please refer to the Appendix 1 (authorship policy) for full details on authorship.

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11. APPENDICIES

11.1 Appendix 1- Authorship policy

1. DEFINING AUTHORSHIP
   Authorship of published or presented papers is based on the following criteria.(51)

   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 (52, 53) and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE).(51)

   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.(51) Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.

   All contributors who the first criterion set out in section 1 above should be offered the opportunity to meet the other three criteria set out in section 1.

   Where possible, all studies 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 XXXXX study group” or “Jane Doe, John Doe, John Smith, Ann Other and the XXXX study 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 xxx Study Group').(53) Again, the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

   Tentative decisions on authorship should be made as early as possible.(52) These should be justified to, and agreed by, all co-applicants. Any difficulties or disagreements will be resolved by discussion and a simple majority vote, where required. In the case of a tie, one of the Co-Principal Investigators will have the casting vote.

a. 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, 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 study's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals.(51)

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

4. DISCLAIMERS
Authors should ensure they include the study funder's disclaimer: refer to the funders 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 study group. All reports of work arising from the study, including conference abstracts, outputs describing methodological aspects of the study, and any outputs describing results from the study, should be peer reviewed during monthly meetings attended by all co-applicants. The co-applicants 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.

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 study team with a concern about authorship should discuss it with the relevant Chief Investigator, or Line Manager.

13.2 Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
-	1.0	29.10.24	EEJ, LV	Full draft of protocol to NIHR