UNIVERSITY OF BIRMINGHAM

PELVIC ORGAN PROLAPSE AND OESTROGEN:

A FEASIBILITY STUDY

By

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ABSTRACT

This thesis presents a feasibility study to assess the effect of local oestrogen in postmenopausal women undergoing pelvic organ prolapse (POP) surgery (LOTUS study). It stemmed from a Cochrane systematic review by Ismail et al (2010) which identified the dearth of a well organised randomised controlled trial with adequate sample size, validated outcome measures and long term follow up to assess the value of oestrogen in the prevention as well as management of pelvic organ prolapse. This thesis aimed to answer this question. Firstly, a systematic review was performed to ascertain the global prevalence of POP in women in order to understand the burden of disease using epimaps. The review found that the prevalence of symptomatic POP increased with age up to 65-75 years (mean of 35%); thereafter it plateaued. Secondly, another systematic review utilising the COSMIN checklist was carried out in order to determine which validated questionnaire or patient reported outcome measure best captured the subjective outcomes from women with POP. Strong evidence supported internal consistency and construct validity for Pelvic floor distress inventory short form 20 (PFDI sf 20), Pelvic organ prolapse symptom score (POP-SS) and electronic Personal Assessment Questionnaire pelvic floor (ePAQ-PF). Subsequently a feasibility study to assess the effect of local oestrogen in postmenopausal women undergoing pelvic organ prolapse (POP) surgery (LOTUS study) was set up as the first step in a phased approach to performing a large-scale study. The feasibility study concluded that a large multicentre RCT was feasible. In addition, a qualitative study was conducted to understand the factors that motivate these women for, and barriers to recruitment in clinical trials. From the findings of the two systematic reviews, the qualitative study and the feasibility study, a proposal for a robust multi-centric randomised controlled definitive study was designed.

DEDICATION

I dedicate my thesis to my parents Mr. Mohan Verghese and Mrs. Elizabeth Verghese for their selfless love and unwavering support during all my endeavours and for teaching me the art of resilience to face any challenge in life.

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Although pursuing a PhD has been a daunting task, the accomplishments were an extremely rewarding experience. My journey over the last 5 years has been influenced by the support of many people, for which I am truly indebted.

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LIST OF ABBREVIATIONS

ADePT	A process for Decision -making after Pilot and feasibility Trials
BCTU	Birmingham Clinical Trials Unit
BSUG	British Society of Urogynaecology
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COSMIN	Consensus-based Standards for the selection of health Measurement INstruments
DNA	Did not attend
EQ-5D	EuroQOL five Dimensions questionnaire
GP	General practitioner
HES	Hospital episode statistics
HRT	Hormone replacement therapy
ICS	International Continence Society
IIQ	Incontinence Impact Questionnaire
IMP	Investigational Medicinal Product
IUGA	International Urogynecological Association
LOTUS	Local Oestrogen Treatment in postmenopausal women Undergoing pelvic organ prolapse Surgery
MDT	Multidisciplinary meeting
NIHR	The National Institute of Health Research (NIHR)
PFDI SF-20	Pelvic Floor Distress Inventory Short Form 20
PFIQ-7	Pelvic Floor Impact Questionnaire-7
PGII	Patient Global Impression of Improvement
PISQ-12	Pelvic organ prolapse urinary incontinence sexual questionnaire-12
POPDI-6	Pelvic Organ Prolapse Distress Inventory -6

POP-Q	Pelvic Organ Prolapse Quantification system
PROM	Patient Reported Outcome Measures
PROSPECT	PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials
QALY	Quality Adjusted Life Years
QoL	Quality of life
R&D	Research and development
RCT	Randomised controlled trial
RFPB	Research for Patient Benefit
ROCRF	Recruitment Officer Case Report Form
RR	Relative risk
SAE	Serious adverse events
SD	Standard deviation
UDI	Urinary Distress Inventory
UI	Urinary incontinence
UTI	Urinary tract infection
VAS	Visual Analogue Scale
VUE	Vault or Uterine prolapse surgery Evaluation

PUBLICATIONS FROM THIS THESIS

Verghese TS, Middleton L, Cheed V, Leighton L, Daniels J, Latthe P. Randomised controlled trial to investigate the effectiveness of local oestrogen treatment in postmenopausal women undergoing pelvic organ prolapse surgery (LOTUS): a pilot study to assess feasibility of a large multicentre trial. *BMJ Open* 2020; 0:e025141. doi:10.1136/ bmjopen-2018-02514

Verghese TS, Merriel A, Leighton L, Latthe P. Willingness of postmenopausal women to participate in a study involving local vaginal oestrogen treatment as an adjunct to pelvic organ prolapse surgery: a qualitative study. *International urogynecology journal*, DOI: 10.1007/s00192-020-04480-5

Bulchandani S, Toozs-Hobson P, **Verghese T**, Latthe P. Does vaginal estrogen treatment with support pessaries in vaginal prolapse reduce complications? Post Reprod Health. 2015 Dec;21(4):141-5. doi: 10.1177/2053369115614704.

Chapter Publication

Menopause : Obstetrics & Gynaecology: An evidence- based Textbook for MRCOG; Third edition 2016 . **Verghese T**, Jenny Williamson and Lynne Robinson

ORAL PRESENTATIONS FROM THIS THESIS

Systematic review of patient-reported outcome measures (PROM) for pelvic organ prolapse in women. **2020 International urogynaecology association (IUGA) 45th Annual Meeting, Netherlands.**

Local Oestrogen Treatment in Postmenopausal Women Undergoing Pelvic Organ Prolapse Surgery (LOTUS) - feasibility study. **Yorkshire Modular Training Programme YMTP 2018** (awarded 1st Prize)

Preliminary results of Local Oestrogen Treatment in Postmenopausal Women Undergoing Pelvic Organ Prolapse Surgery (LOTUS) - feasibility study **British Society of Urogynaecology BSUG 2017** (awarded 3RD Prize)

Willingness of postmenopausal women to participate in a study involving local vaginal oestrogen treatment as an adjunct to pelvic organ prolapse surgery. **International Continence Society Annual Meeting, Florence, 2017.**

POSTER PRESENTATIONS FROM THIS THESIS

Prevalence and trends in risk factors of pelvic organ prolapse in women: a systematic review. **British Society of Urogynaecology BSUG 2019**

Articles submitted for publication:

1. Global prevalence of pelvic organ prolapse in women: a systematic review

2. Comprehensive overview of patient report outcome measures used in women with pelvic organ prolapse: a systematic review

CHAPTER ONE: INTRODUCTION

Pelvic organ prolapse (POP)

The International Continence Society (ICS) and International Urogynecological Association (IUGA) define pelvic organ prolapse (POP) as the downward descent of the pelvic organs, which results in a protrusion of the vagina and/or uterine cervix (1). The symptoms of POP were defined by the ICS as departure from normal sensation, structure, or function, experienced by the woman in reference to the position of her pelvic organs. Women usually experience symptoms of POP as vaginal bulge, pelvic pressure, lower backache and/or needing digitation to assist defecation (2). Women have a lifetime risk of between 6 and 20% of undergoing surgery for prolapse (3-6).

Urogynaecological complaints are the second most common reason for referral from primary care, accounting for 18.4% of gynaecological referrals in the United Kingdom (7). Of these referrals 38% were for urinary incontinence (UI), 36% were for symptomatic POP and 25% were referred with combined complaints of POP and UI (7).Women in the 20-29 years age group underwent prolapse surgery at the rate of 0.4/10,000 with the incidence rising to 34.3/10,000 in the 70-79 years age group (3).

In the Women's Health Initiative Study, 41% of women aged 50–79 years showed some degree of POP, including cystocele in 34%, rectocele in 19% and uterine prolapse in 14% (8). In a multicentre study of 1006 women aged 18–83 years, 24% had normal support and 38% had stage I, 35% stage II, and 2% stage III POP (8). Recurrence following POP surgery requiring reoperation was reported to occur in 10-30% of the women in various studies (9).

Oestrogen and its physiological effect on the vagina

The ovaries produce a large proportion of circulating oestrogen in women of reproductive age. Oestrogen encourages growth and development of the cells, so the vaginal epithelium remains thick, moist and in turn the vagina is supple and elastic. However, a dramatic reduction in circulating oestrogen occurs following the loss of ovarian function at the menopause. This oestrogen deficiency induces metabolic and trophic changes. Low oestrogen levels result in genital areas becoming dry, itchy and more easily irritated. A decrease in blood flow leads to fewer secretions and intercourse can become uncomfortable or painful.

The vagina expresses oestrogen receptors that are sensitive to changes in circulating levels of oestrogen. Low oestradiol levels following menopause led to reduced vascularity of the tissues, alongside decrease in the glycogen content of epithelial cells. This in turn leads to a fall in lactobacilli content and an increase in pH, encouraging the growth of certain bacteria, including coliforms (10). This may lead to over colonisation of the vagina, irritation and discharge. Low oestrogen levels result in atrophy of the vaginal epithelium, with more parabasal cells and fewer superficial cells seen on cytology. Associated symptoms include vaginal dryness, soreness, dyspareunia, dysuria or urinary urgency (11). Prolapse may be associated with weakening or atrophy of the genital tract tissues. Oestrogen deficiency secondary to menopause results in weakening of the supporting ligaments of the pelvic organs and the pelvic floor muscles, exacerbating symptoms of prolapse. Use of vaginal oestrogen improves the vaginal maturation index at the time of surgery (high-quality evidence) and increased vaginal epithelial thickness. Collagen types 1 & 2, mRNA increased 6.0 and 1.8-fold in the vaginal muscularis, collagen type I a protein

increased 9-fold in the muscularis whereas collagen III was not changed significantly. However more high-powered studies are required (10).

Pre-operative use of oestrogen and POP

There are four reported trials on the use of pre-operative oestrogen are which are described as follows: In 1992, Felding et al conducted a double blind RCT comprising of 48 postmenopausal women scheduled for pelvic floor surgery. The treatment group received 25 mcg oestradiol of vaginal pessary for 3 weeks pre-operatively. The hormonal status of vagina mucosa was evaluated cytologically as well as histologically before and after procedure. In addition, the incidence of cystitis postoperatively and within the first month afterwards was noted. Three patients in the treatment group and eight in the placebo group suffered from immediate postoperative cystitis (P = 0.19), whereas two patients in the treatment group and ten patients in the placebo group had another cystitis episode during the next month (P= 0.02).Statistical analysis for trend revealed that the oestrogen index and maturation index increased significantly in treatment group (P = 0.00014 and P = 0.0015 respectively). No such significance could be demonstrated in the placebo group (P = 0.1236) (12).

Similarly, Mikkelson conducted a double blind RCT (43 women) where the treatment group received 25 mcg oestradiol was administered 3 weeks prior to vaginal repair surgery. Therapeutic effect assessed 4 weeks after surgery. Post operatively significant reduction in the rate of bacteriuria (more than 100,000CFU/ml) were noted in the treatment group. At 3 years follow up (93% follow up rate) 19% in treatment group and 11% in placebo group developed recurrent cystitis, which was not statistically significant (13). The authors found that pre-operative vaginal oestrogen may reduce the incidence of bacteriuria in immediate post-operative period but no

long-lasting effects on recurrent cystitis or relapse. In a single-blind randomized controlled trial which recruited women with clinical atrophic vaginitis and post hysterectomy POP planning pelvic floor surgery. The women were randomized to 3 arms using a 1:1:1 ratio to receive vaginal cream (0.5 or 1.0 g) or control (no intervention) (14). Twenty women were enrolled to each arm. Vaginal cytology sample was obtained from the most dominant compartment preoperatively and on the day of surgery. It was found that the vaginal maturity index increased by 15.5% in treatment groups (14). Rahn et al conducted a randomized trial of postmenopausal women with a uterus and symptomatic anterior and/or apical prolapse at stage 2 or greater participated in the study. Preoperative oestrogen or placebo cream for 6 weeks was the intervention. Full-thickness anterior apical vaginal wall biopsies were obtained at the time of hysterectomy and analysed for mucosa and muscularis thickness, connective tissue synthesis, and degradation. Vaginal oestrogen application for 6 weeks preoperatively increased synthesis of mature collagen, decreased degradative enzyme activity, and increased thickness of the vaginal wall, suggesting this intervention improves both the substrate for suture placement at the time of surgical repair and maintenance of connective tissue integrity of the pelvic floor (15). Overall quality of evidence was poor, largely because of the sparseness of evidence and outcomes such as epithelial and subepithelial thickness serving as surrogate outcomes for tissue quality, postoperative wound healing, and long-term integrity of surgical repair. The interventions were provided for 2 to 12 weeks preoperatively with patient surveillance continuing from the time of surgery until 4 weeks to 3 years postoperatively (12-15). Ismail and colleagues in a Cochrane systematic review found limited evidence from RCTs regarding the use of oestrogens for the prevention and management of pelvic organ prolapse. The systematic review was unable to perform a

meta- analysis due to the poor quality, evidence and heterogeneity in the studies. They concluded that further studies are needed with long-term follow-up to assess oestrogen preparations, particularly for women using pessaries and before and after prolapse surgery (16).

Post-operative use of oestrogen and POP

No study providing vaginal oestrogen preoperatively has attempted to objectively track prolapse recurrence for a meaningful postoperative duration. Mikkelsen et al., who described the 3-year postoperative outcomes after preoperative treatment with vaginal oestradiol or placebo tablets before POP repair and included a questionnaire of patient satisfaction, but no standardized or validated metric of prolapse symptoms was used (13) .

If vaginal oestrogen does, in fact, improve the substrate for suture placement at the time of surgery, the therapy may need to be continued postoperatively until the time of complete scar maturation (12). Finally, as noted above, studies of vaginal oestrogen application need more consistent assessment of discontinuation rates and the reasons for discontinuation.

Vaginal oestrogen and its effect on POP

A Cochrane review by Ismail et al. about the effects of oestrogen on the prevention or management of POP concluded that the evidence was extremely limited to support a guideline for the preoperative use of vaginal oestrogen before POP repair (16).

Nonetheless, the increase in vaginal epithelial thickness observed in those participants complying with vaginal oestrogen may provide a benefit for wound healing (14). This hypothesis gains some support from Karp et al., where participants receiving the postoperative vaginal estradiol ring demonstrated less granulation tissue compared with those using a placebo vaginal ring (11).

The Cochrane review highlighted that the current guidance is primarily based on poor to moderate overall quality of evidence (16). Patient blinding to intervention was not possible for many of these studies that allowed no treatment as the comparator (12, 13). Three studies investigated local administration of oestrogen versus placebo or no treatment (12, 14, 15). Vaccaro and co-workers described a statistically significant difference in vaginal symptoms on a visual analogue scale (VAS) and Vaginal Health Composite Score between the treatment group and no treatment group in favour of the treatment group (14). Felding et al reported that thickness of the vaginal wall (assessed histologically) was statistically significantly increased in the treatment group compared to the placebo group (12) .The description about the randomisation, blinding process and predefined outcomes was unclear in all 3 studies (12-14).

With these findings and the lack of studies investigating the effect of vaginal oestrogen treatment on POP symptoms, the potential for local oestrogens in the prevention as well as treatment of POP needs to be further established.

There is a need for robustly conducted, adequately powered randomised controlled trial (RCT) comparing topical oestrogen to placebo evaluating quality of life related to pelvic floor symptoms.

Patient and public engagement

Patient and public engagement has been integral to the development of this project from inception. It has had a positive impact on the research design and delivery. In the initial phase of the development of the grant, I approached the local bladder support forum, which supports women with prolapse and incontinence. They provided valuable feedback from their members on the feasibility study protocol and patient information leaflets. The consensus from the women was they considered oestrogen creams acceptable however would prefer vaginal oestrogen pessaries due to the ease of insertion.

We conducted a survey on members of BSUG to understand the clinical perspective. It showed that 87% of the clinicians believed that postmenopausal women undergoing prolapse surgery would benefit from the use of low dose oestrogens. Of those surveyed, 44% were advising their patients to use oestrogens pre-operatively. The feedback from both the patient groups and clinicians provided a platform to design the study processes and documentation, which would facilitate the delivery of the research.Overall, my experience of integrating PPI as members of a research team had been very positive. It led to sustained momentum of engagement. Two ambassadors had been involved in the feasibility study and were enthusiastic to advise and develop the research project.

Feasibility study

Feasibility studies play a vital role in health research. These studies provide important information for the designing and development of large-scale RCT. This detailed preparatory stage maximizes the success of a definitive study by identifying problems with the screening, randomisation and recruitment processes. This process allows the

research team to

1) Identify and evaluate problems with study

2) Develop solutions and refine the definitive study protocol

It is essential we understand the difference between a feasibility and pilot study. In simple terms, a feasibility study evaluates if the study can be performed in real world context whereas a pilot studies is a miniature version of the definitive study aiming to test the hypothesis.

Methodological issues that feasibility studies assess:

What proportions of participants screened were eligible for the study?

Was the study intervention acceptable to the participants?

Was recruitment successful?

Did the consent and randomisation process work?

Were the choice of patient reported outcome measures appropriate for the study?

Were there high retention and follow up rates?

Can the feasibility study allow sample size calculation?

Feasibility studies ensure that a definitive trial is robust in terms of both internal validity (scientifically valid) and external validity (generalizable to real world). Though feasibility studies are valuable, more often we find that researchers conducting the feasibility study tend to report the outcomes of the intervention rather than focusing on the methodological issues. They can fail to identify flaws in the design and conduct to devise modifications for constructing a robust definitive trial.

There is limited guidance with regards to reporting feasibility studies as well to making of amendments, rationale of final decision and its consequences. The objective of such guidance must be to attain a trial design that will be fit for purpose.

The ADePT (a process for decision-making after pilot and feasibility trial) is process designed to systematically report and aid decision-making (17). It is a 3-step process (Fig 1):

1) Evaluation of the type of problem

2) Identification of potential solutions

3) Assessment of the best options

Step 1: Evaluate the type of problem:

The problem can be confined either to the trial alone, real world contexts or both. Issues in the trial maybe pertaining to recruitment, acceptability of an intervention, blinding or follow up. Acceptability is a problem that can affect the trial as well as real world context.

Step 2: Identifying solutions:

Discussing with entire research team to identify solutions, encouraging patient and public involvement, surveying the clinicians and participants to provide valuable feedback on their views and how they thought the trial could be modified. Another method of finding a solution is by systematically searching the existent literature and guidelines to identify similar patterns/challenges in other studies and how they addressed the issues.

Step 3: Assessment of solutions:

Solutions identified should try to reduce the tensions between the issues identified in the trial and real-world contexts. There will be solutions that work efficiently in the trial design however these solutions may not easily translate in real world setting or vice versa. The research team must brainstorm ideas and should be able to justify why they chose a particular pathway. It is important to document and transparently exhibit the problems faced as well as the assessment of solutions.

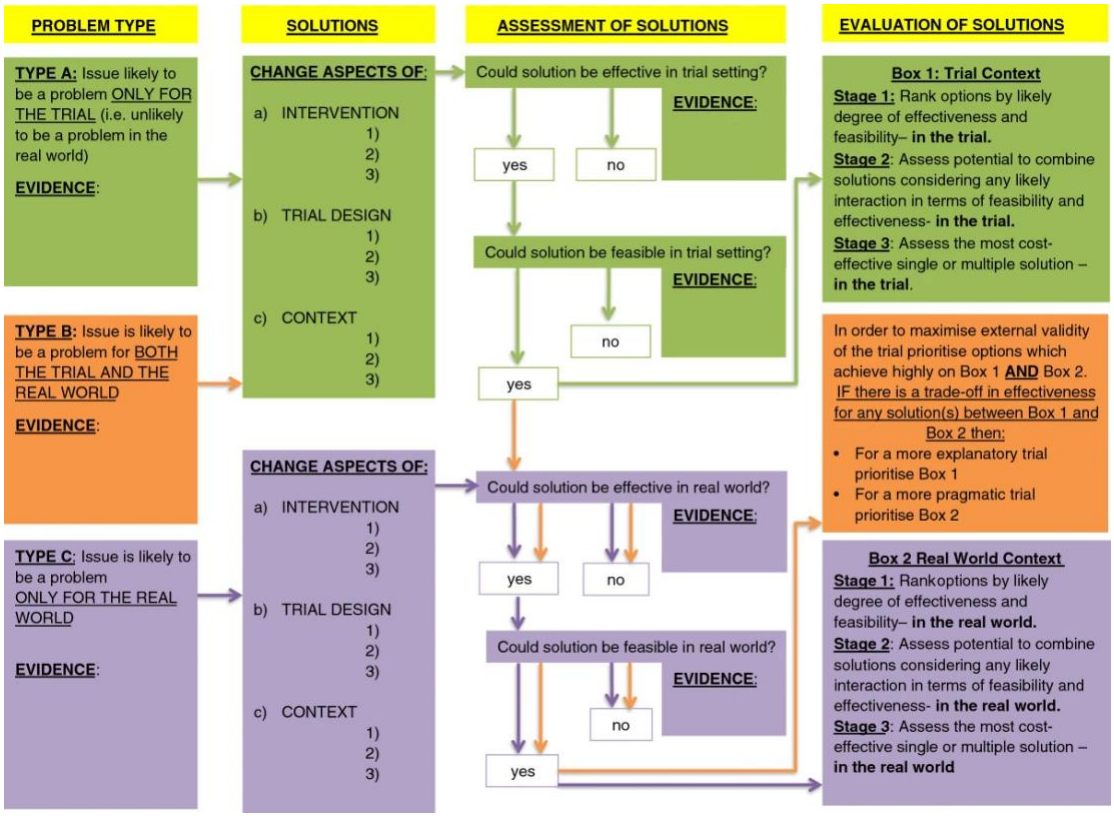

Figure 1: An algorithm for decision-making after Pilot and feasibility Trials (ADePT): adapted from Bugge et al Trials 14(Suppl 1)

Choosing the appropriate patient reported outcome measure (PROM)

Several disease–specific questionnaires have been developed to measure health related outcomes in women with POP. These include Pelvic floor distress inventory short form 20 (PFDI SF-20) (18), Pelvic floor impact questionnaire (PFIQ-7) (18), Pelvic organ prolapse urinary incontinence sexual questionnaire-12 short form (PISQ-12) (19).

The PFDI SF-20 and PFIQ-7 are complementary instruments utilized to assess the health-related quality of life (QoL) in women with pelvic floor disorders. Each

measure has three scales: urinary, colorectal anal and prolapse. The PFDI and PFIQ are responsive to change in women undergoing surgical and nonsurgical treatment for pelvic organ prolapse. The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) is a validated condition-specific QoL questionnaire to assess sexual function in those with urinary symptoms. This outcome measure is recommended by the International continence society (ICS). The PISQ-12 is the shortened measure of the PISQ 31 (20) addressing three domains: behavioural-emotive, physical and partner-related.

In order for a researcher or clinician to make a rational decision for utilizing these or other instruments in research studies or in clinical practice, it is essential to assess and compare their measurement properties in terms of reliability, validity and responsiveness (21). The Consensus based standards for the selection of health status measurement instruments (COSMIN) check list is a critical appraisal tool that can be utilised to assess the methodological quality of the measurement properties of health-related questionnaires, providing a consensus framework for taxonomy (22). Three key domains exist which are used to measure various measurement properties of health-related questionnaires. Reliability assesses the degree to which the questionnaire is free from measurement error. The second domain is responsiveness, which measures the ability of the questionnaire to detect change over time. Validity is the degree to which the questionnaire provides a measure of the construct it proposes to analyse. The domains themselves can be subdivided into various categories to assess selected properties of the questionnaire.

Validation studies of health measurement instruments need to be of high methodological quality to reach a conclusion about their measurement properties. The COSMIN checklist is a tool to evaluate and critically appraise the design

requirements and statistical methods of measurement properties of health assessments. In depth assessment of existing health related questionnaires for assessing POP is necessary to ascertain their validity, responsiveness and reliability. Studies pertaining to application of health related questionnaires have not fully addressed these features (21). In this thesis, a systematic review of existing patient report outcomes pertaining to POP was done in order to select the most suitable PROM.

Clinical assessments

Pelvic Organ Prolapse Quantification system (POP–Q) refers to an objective, site–specific system for describing, quantifying, and staging pelvic support in women. It provides a standardized tool for documenting, comparing, and communicating clinical findings with proven inter-observer and interobserver reliability (23).

There are six defined points for measurement in the POPQ system – Aa, Ba, C, D, Ap, Bp and three other landmarks: GH, TVL, PB. Each is measured in centimetres above or proximal to the hymen (negative number) or centimetres below or distal to the hymen (positive number) with the plane of the hymen being defined as zero (0).

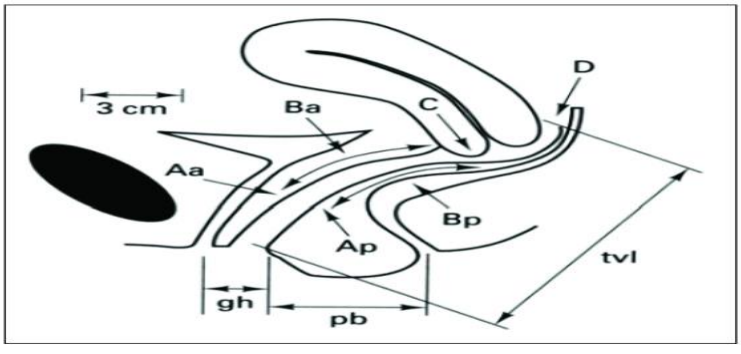

Figure 2: Points and landmarks for POP-Q system examination

Stage I is defined as the most distal portion of the prolapse is more than 1cm above the level of the hymen. Stage II is defined as the most distal portion is 1 cm or less proximal or distal to the hymenal plane. In Stage III the most distal portion of the prolapse protrudes more than 1 cm below the hymen but no farther than 2 cm less than the total vaginal length and Stage IV is complete eversion.

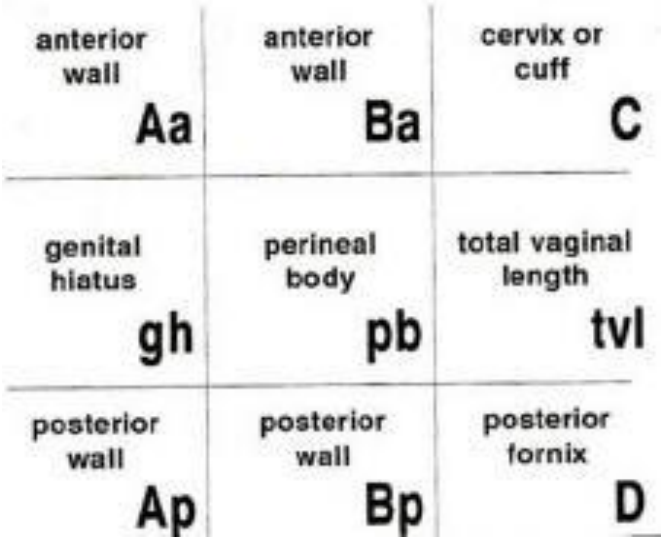

Figure 3: POP-Q grid

Aims of the thesis

In this thesis I have undertaken and conducted a feasibility study to assess the effect of local oestrogen in postmenopausal women undergoing POP surgery. In addition, I conducted a qualitative study to understand the needs of women participating in this study. I performed a systematic review to ascertain the global prevalence of pelvic organ prolapse in women and another systematic review on outcome measures used in studies relating to pelvic organ prolapse. All of the above components have assisted me in formulating a proposal for a robust multi-centric randomised control definitive study.

The key objectives of this thesis are:

1) To ascertain the global prevalence of pelvic organ prolapse in women by means of a systematic review.

2). To provide an overview of all evidence of important quality aspects of outcome measurement instruments utilised in POP study thereby to assist clinicians and researchers in selecting the most suitable outcome measurement instrument for their patient or in a study.

3) Evaluate the feasibility study to specifically assess the effectiveness of the patient identification and screening process, including reasons for failure to randomise eligible patients; evaluated the compliance with the treatment schedule.

4) To explore the factors that motivate women for and identify barriers to recruitment and participation in clinical trial among postmenopausal women with pelvic organ prolapse intending to have surgical management

CHAPTER TWO: GLOBAL PREVALENCE OF PELVIC ORGAN PROLAPSE IN WOMEN: A SYSTEMATIC REVIEW

Introduction

Women have a lifetime risk of POP surgery estimated between 12-19% (24). The prevalence of POP across the globe in numerous studies has been variably quoted. This may be attributed to the heterogeneity in the definition or classification of POP. In addition, the group of women studied may vary depending on objective finding of prolapse or symptomatic prolapse or only women who undergo surgical intervention for prolapse. The epidemiological features of POP have been generously reported worldwide; however, they are limited by sample size and heterogeneity. Our aim was to perform a systematic review of the literature to ascertain the geographical distribution of POP, its prevalence according to defined criteria for POP, and its variation within subgroups defined by age whilst taking into account the quality of the studies.

The reason for performing this systematic review is to establish the true extent of disease burden and thereby assist policy makers to target resources, improve treatments and health care planning in primary care.

Methods

This systematic review was performed in accordance with widely recommended methods. (PRISMA) (25). Ethics approval was not needed for this review.

Data Source

The following bibliographic databases were searched from the time of inception to February 2020: NICE evidence, Cochrane, EMBASE, Medline and Ovid. Our search consisted of MeSH subheadings, text words and word variations for prolapse; “pelvic organ prolapse”, “cystocele”, “rectocele”, “uterine descent” were combined with terms like “prevalence”, “community survey” and “incidence”. These were combined with terms representing relevant study designs e.g. cross-section, survey etc. The search was restricted to ‘human’ and ‘female’. We also hand searched the bibliographies of all relevant reviews and primary studies to identify cited articles not captured by electronic searches.

Study selection

Studies were selected based on pre-defined criteria:

Population: Women with pelvic organ prolapse (POP)

Condition: POP was defined either by the symptoms and/or POP-Q grading system or stage of prolapse. We endeavoured to collect information on both objective and subjective assessments of POP in order to capture maximum relevant data to ascertain prevalence globally.

We included studies that defined symptomatic POP based on patient reported outcome measures (PROM) like POPDI questions including “Do you experience bulging or something falling out you can see or feel in the vaginal area?” on the Pelvic Floor Distress Inventory/ Pelvic floor distress inventory short form (PFDI/PFDI sf 20) (18).

Outcome: Incidence and/ or prevalence of prolapse were recorded based on age groups 45-65, 66-75, 76-85 and more than 85 years

Design: Cross- sectional studies and surveys

Data extraction and quality assessment

Two reviewers (TSV and AS) extracted relevant data from the included studies. We retrieved information on the characteristics of the study including its quality and the prevalence rates of POP. In some studies, the existence of multiple symptoms of pelvic floor disorders amongst individuals could not be evaluated separately due to the structure of their questionnaires used and their manner of reporting. Hence, these studies were excluded.

The methodological quality of all selected papers were assessed as per the Newcastle Ottawa Scale adapted for cross sectional studies (26). The quality of the study was assessed under three domains: selection, comparability and outcomes. The cross-sectional studies were scored as Very Good Studies: 9-10 points, Good Studies: 7-8 points, Satisfactory Studies: 5-6 points and Unsatisfactory Studies: 0 to 4 points.

Numerators and denominators were extracted or estimated from each study for computing rates. In our review, prevalence measured how many women have POP at a single point in time, i.e., point prevalence.

Results

Twenty-one studies were included in the systematic review. Due to the heterogeneity in the reporting of prevalence and different populations (primary and secondary care), cumulative synthesis and meta-analysis could not be performed. The process of study

Figure 1

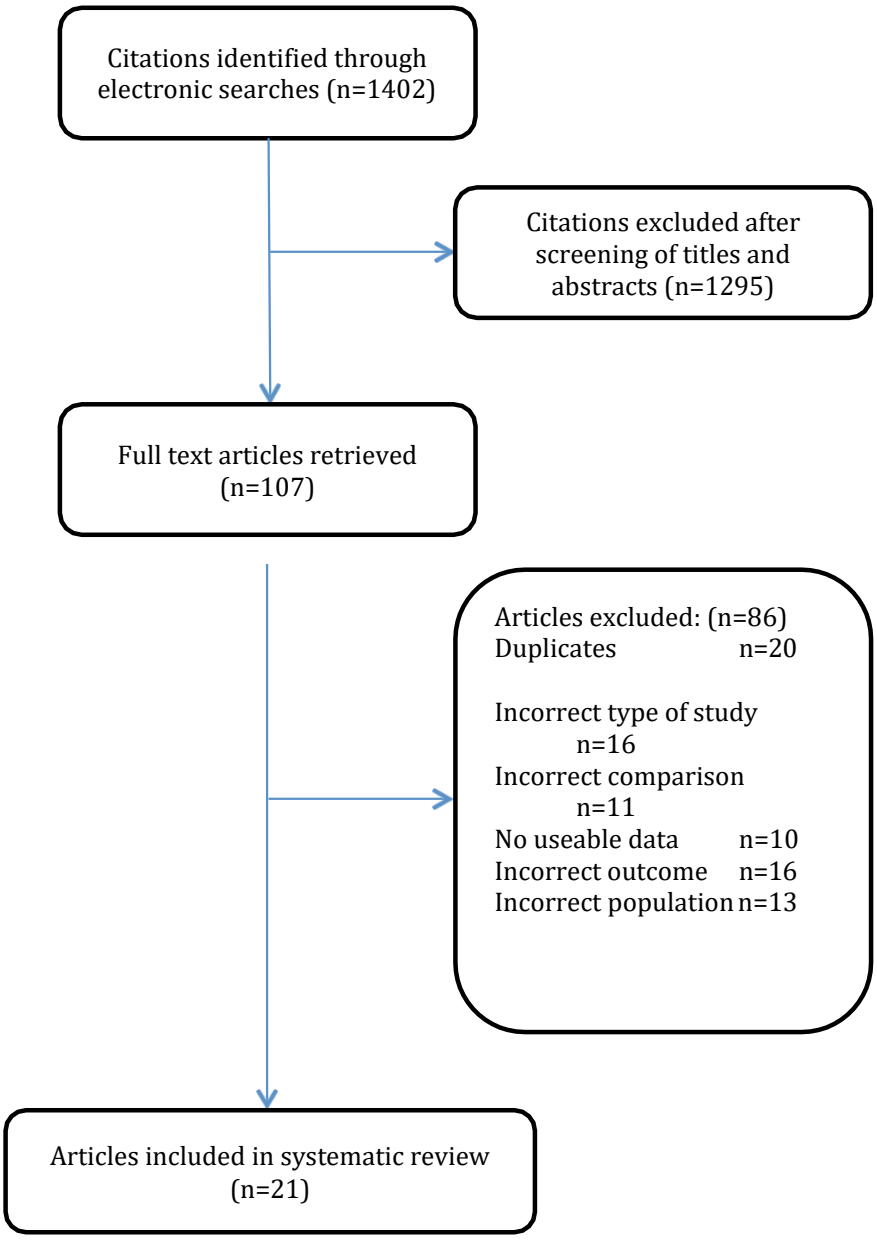

Figure 4: Study selection for the systematic review of POP

We analysed the characteristics of included cross sectional studies and national database studies (Table 1). In majority of the included studies the women were aged between 45- 85 years. The women completed validated symptom questionnaires or sections of questionnaires such as the pelvic floor distress inventory (PFDI) or pelvic floor impact questionnaire (PFIQ). Majority of studies objectively assessed women based on the POP-Q examination technique.

Utilising the adapted version of the Newcastle Ottawa scale for cross sectional and observational studies, the methodological quality of all included studies was assessed. The scale analysed the following attributes of each study: design, sample size, proportion of non-respondents, ascertainment of risk factors, assessment of outcome and statistical tests. The included studies scored between a scale of 9-6 i.e., very good to satisfactory quality (Table 2). Additionally, we noted prevalence in developed and developing countries depicted in terms of various age group criteria (Table 3). The data on prevalence of POP in included studies is summarised in figures 5-8. Epimaps in Figure 5-8 display the available data by countries, on worldwide prevalence of POP by percentage and subdivided by age. In developed countries the highest prevalence of POP was 59.4% and this was within the age group 45-75 years. This rate is higher in developing countries within the same age criteria of 45-75 years, which is reported at 70-75%. In developed countries, the reporting trend decreases to 10-22% beyond the age of 76 years.

Table 1: Study characteristics of cross-sectional studies included in the systematic review

No.	*Author, year, country*	*Year of data collection*	*Sample size*	*Description of cross-sectional study*
	Kumari (27) 2000 India	1996	225	Women were screened based on the WHO self-reported questionnaire. Participants were married women from a village in Chandigarh India. A house-to-house screening was performed by the district nurses.
	Nygaard (28) 2004 USA	2002	270	Women participating in the Women's Health Initiative (WHI) Hormone Replacement Therapy. POP Q was performed to assess stage of prolapse. Mean age 68.3 years (SD 5.6, range 57-84years), Mean BMI 30.4 Kg/m^2. POP Q stages (95%confidence intervals _CIs): Stage 0, 2.3% (95% CI0.8–4.8%); Stage I, 33.0% (95% CI 27.4 –39.0%); stage II, 62.9% (95% CI 56.8–68.7%); and stage III, 1.9% (95% CI 0.6–4.3%)
	Scherf (29) 2002 Gambia	1999	1067	Mean age of women 32.6 and mean parity was 4. POP was detected through symptoms and examination. 488/1067 women in this rural community were found to have POP.
	Chuenchompoonut, (30) 2005 Thailand	2005	215	Women attending the menopause clinic at King Chulalongkorn Memorial Hospital Thailand. The severity of any prolapse was classified using International Continence Society classification. 29.3% women had an anterior wall vaginal prolapse.

Tegerstedt, (31) 2005 Sweden	2004	5489	Women aged 30–79-year-old of Stockholm city were randomly selected from the computerized Swedish population register. Women completed a validated 5-item questionnaire about symptomatic prolapse. Total score above 30 indicated presence of POP. The sensitivity and specificity of the questionnaire was 66.5% and 94.5%. The sensitivity in detecting stage II disease or higher was 84.5%.
Lawrence (32) 2008 USA	2004	4103	Population based survey performed in California. Data were collected from April 2004 through January 2005. Mean age 56.5 years. Validated questionnaire EPIC utilized for gathering information.
Araujo (33) 2009 Brazil	2008	377	Women were screened and examined using POP-q system. Age and parity were the factors that increased the odds of development of POP.
Wusu-Ansah (34) 2008, Ghana	2008	174	Study was carried out in a rural community of Ghana. The PFDI and PFIQ questionnaires were used to capture information. Mean age was 45+/- 18.5 years. Increasing age was observed as statistically significant trend towards the development of POP.
DeBoer (35) 2011,Netherlands	2010	1380	Women who were aged 45–85 years and registered in eight general practices were invited to participate in a region in Netherlands. Participants completed validated self-reported questionnaires. Women rated the bother of various symptoms on a 5-point Likert scale.
Lien (36) 2012, Nepal	2010	174	Cross sectional studied that evaluated the prevalence of POP among women seeking healthcare services in rural areas in Nepal. The women completed validated questionnaires and examination was based on POP-Q. Mean age was 40.4 years (range16–80 years). Pelvic examination revealed 39.1%women had stage I 60.9% had stage II POP or above. Cystocele was the most frequent

			form of POP observed in this study.
Awwad (37) 2012, Lebanon	2011	557	557 eligible women were interviewed and examined in a rural community in Lebanon. 33.7% had stage II prolapse, 14.5% had stage III prolapse, and 1.6% had stage IV prolapse.
Islam (38) 2016 Bangladesh	2014	1590	The mean age of the women 42.3 (±8.1) years. Of the 1590 women screened using validated questionnaire, 258 were found to have symptoms of POP.
Cooper, 2014, UK (39)	2012	1830	To determine the prevalence of POP in community dwelling population in United Kingdom. The cross sectional study utilized the ICIQ -VS to assess the POP symptoms. Mean age of the population was 56.5 years (range 18–98) Symptoms were found to be strongly associated with prolapse; vaginal bulge/lump and bulge or lump outside of the vagina had a prevalence of 8.4 % and 4.9 % respectively.
Wu, 2014, USA (40)	2005-2010	7071	Study estimated the prevalence of POP from the National Health and Nutritional Examination Survey 2005– 2006 utilising symptom-based questionnaire.
Lonnee-Hoffman(41) 2014, Denmark	2006-2008	20285	The aim of this study was to assess prevalence self-reported POP in a Nordic county. Cross-sectional data collection from participants in the Nord-Trøndelag Health Study in 2006–2008. Constipation, above-normal BMI, or COPD were moderately associated with a history of POP while the associations with asthma or occupation involving lifting were weaker.

Akter (42) 2016 Bangladesh	2013	787	A cross-sectional survey of 787 women was conducted in four villages in one district in rural Bangladesh. Mean age of participants was 40.1 (±9.0) years. The presence of symptomatic POP was ascertained using validated WHO questionnaire. The symptom based questionnaire was found to identify 80–90 % of moderate and severe prolapses.
Horst(43) 2017 Brazil	2014-2015	226	Quantitative survey methodology was implemented to investigate POP in a population of Brazilian women from January 2014 to July 2015. The adapted validated Portuguese language PFDI- 20 was used to retrieve information. Slightly more than half of the women surveyed (52.3%) showed some degree of prolapse. Stage 1 prolapse was the most prevalent, with 72.2% of these involving the anterior compartment. Among the symptoms covered in the questionnaire, the most common in women with POP-Q stages 1 and 2 was a sensation of heaviness in the lower abdomen (18.5% and 32%)
Henok (44) 2017, Ethopia	2016	70	Study was conducted in Southwest Ethiopia, from January to March 2016. Mean age of 34.84+12.75. Interviewer-administered questionnaire was used to collect data. Binary logistic regression was used to determine factors associated with pelvic organ prolapse**.**
Masenga (45) 2018, Tanzania	2015	1047	Cross sectional community based study conducted in Kilimanjaro Region, Tanzania. Women aged 18±90 were recruited from January to May 2015. Women completed symptom based questionnaires POPDI-6, PFIQ7 and subsequently examined based on POP-Q. The median age of the participants was 46 years (range 18±90) and the median BMI was 25.5kg/m2 (range 15.2±49.3) 64.6% had an anatomical POP stage II±IV and 6.7% had a severe POP that descended 1 cm or more below the hymen.

Li (46) 2019 China	2014-2016	24848	A cross-sectional study of POP was conducted in rural China from February 2014 to March 2016. Symptomatic POP was assessed using POP-Q staging and validation questionnaires PFDI-20. Mean age of the women 45.40 ± 15.77. Mean BMI was 23.02 ± 3.12 kg/m2. POP stage I, II, III and IV were demonstrated according to the POP-Q classification system 28.8%, 63.6%, 0.6% and 0.4% women, respectively.
Jokhio(47) 2020 Pakistan	2007	512	5064 were interviewed, 551 attended for clinical examination. Baden-Walker system for the evaluation of POP findings.

Table 2: Quality assessment of the cross-sectional studies using the Newcastle-Ottawa scale

Quality assessment of the cross-sectional studies using the Newcastle-Ottawa scale

	Study	Selection				Comparability		Outcome		Score
No.		Representativeness	Sample size	Non-respondents	Ascertainment of exposure	Adjusted for confounders	Not Adjusted for confounders	Assessment of outcome	Statistical test	Out of 10
1	Kumari et al	*	*	*	*	-	x	*	*	6
2	Nygaard et al	*	*	*	*	**	x	**	*	9
3	Chuenchompoonut et al	*	*	*	*	-	x	*	*	6

4	Tegerstedt et al	*	*	*	*	**	x	**	*	9
5	De-Boer et al	*	*	*	*	**	x	**	*	9
6	Lien et al	*	x	*	*	**	x	**	*	8
7	Cooper et al	*	*	*	*	**	x	**	*	9
8	Wu et al	*	x	*	*	*	x	*	*	6
9	Lonnee-Hoffman et al	*	*	*	*	*	x	*	*	7
10	Awwad et al	*	*	*	*	*	x	*	*	7
11	Masenga et al	*	*	*	*	**	x	**	*	9
12	Henok et al	*	*	*	*	*	x	*	*	7

13	Li et al	*	*	*	*	*	x	**	*	8
14	Horst et al	*	x	*	*	**	x	**	*	8
15	Akter et al	*	*	*	*	*	x	*	*	7
16	Wusu- Ansah et al	*	*	*	*	*	x	*	*	7
17	Lawrence et al	*	*	*	*	*	x	*	*	7
18	Islam et al	*	*	*	*	**	x	**	*	9
19	Araujo et al	*	*	*	*	-	x	*	*	6

20	Scherf et al	*	*	*	*	-	x	*	*	6
21	Jokhio et al	*	*	*	*	*	x	*	*	7

- Indicates that a feature is present; x, that a feature is absent. But for comparability by design this checklist awards a maximum of two stars (**), one (*) or none if the feature is completely absent

Table 3: The table depicts the prevalence of POP globally based on the included cross-sectional studies

No	Author, year, country	Study	Definition	Total (N)	45-65yrs (%)	66-75yrs (%)	76-85yrs (%)	>85yrs (%)
1	Kumari (27) 2000, India	cross sectional	Symptom based	225	14.8	3.8		
2	Scherf (29) 2002, Gambia	cross sectional	Symptom based	1067	46			
3	Nygaard, (28) 2004, USA	cross sectional	POP Q	270	25	50	22	
4	Chuenchompoonut (30) 2005, Thailand	cross sectional	POP Q	215	43.3			
5	Tegerstedt (31) 2005, Sweden	cross sectional	Symptom based	5489	22.1	12.2	11	
6	Lawrence (32) 2008, USA	Survey	Symptom based	4103	11.4	6		

								7.9
7	Araujo (36) 2009,Brazil	cross sectional	POP Q	377	63			
8	Wusu-Ansah (34) 2008,Ghana	cross sectional	Symptom based	174	12			
9	DeBoer (35) 2011, Netherlands	Cross sectional	Symptom based	1380	3.7	6.4		19.7

							15.6
10	Awwad, 2012, Lebanon (37)	Survey	POP Q	557	74.6		
11	Lien(36) 2012, Nepal	Cross sectional	POP Q	174	60.9		
12	Cooper (39) 2014,UK	Cross sectional	Symptom based	1832	4.9-8		
13	Wu(40) 2014,USA	Cross sectional	Symptom based	7924	35	15	16
14	Lonnee-Hoffman (41) 2014, Denmark	Cross sectional	Symptom based	20285	59.4	30	

							4
15	Islam (38) 2016, Bangladesh	Cross sectional	Symptom based	1590	15.4	18.8	
16	Masenga, (45) 2018, Tanzania	Cross sectional	POP Q	1047	71.9	70.1	
17	Henok (44) 2017, Ethopia	Cross sectional	Symptom based	70	45	25	
18	Horst (43) 2017, Brazil	Survey	POP Q	226	52.3		
19	Akter (42) 2016,Bangladesh	Cross sectional	Symptom based	787	31.7		
20	Li (46) 2019,China	Cross sectional	POP Q	24,848	37.9	10.4	10.1

21	Jokhio (47) 2020,Pakistan	Cross sectional	Symptoms and examination	512	16.8	18	

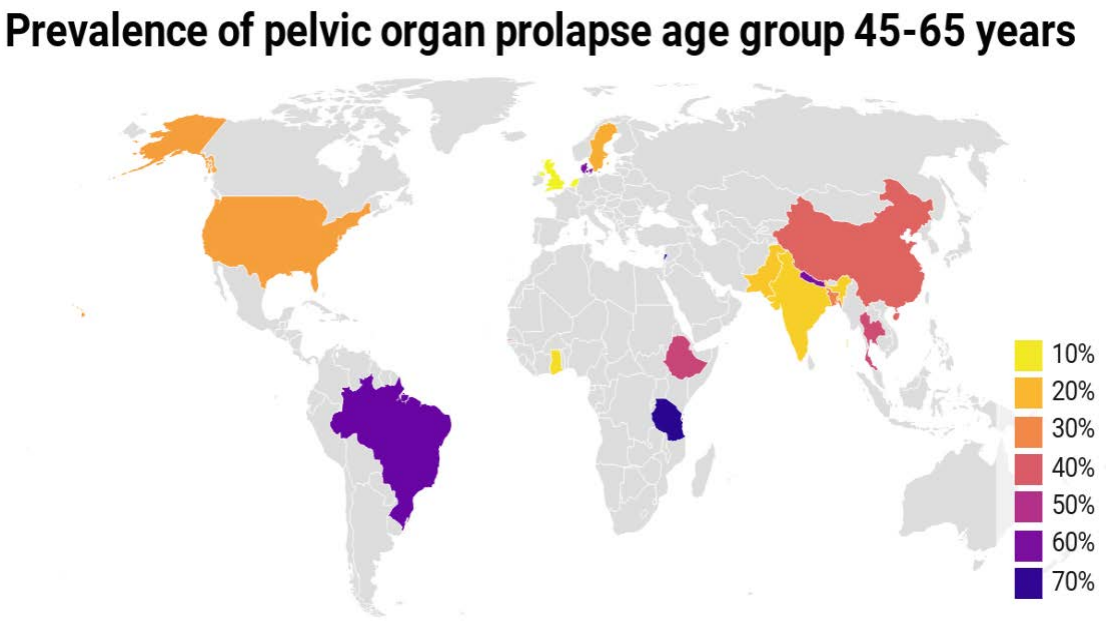

Figure 5: Prevalence of pelvic organ prolapse age group 45-65 years

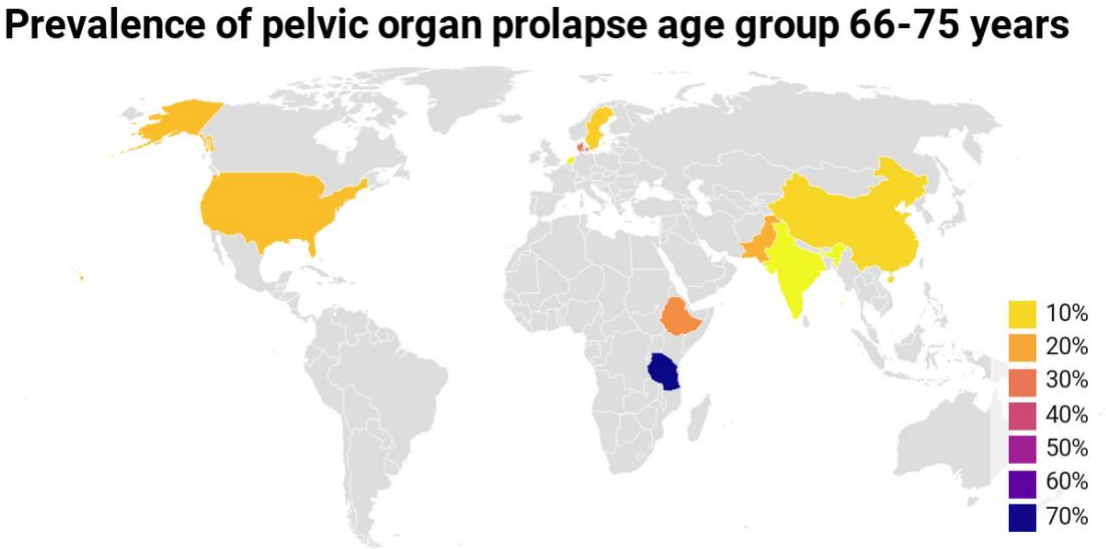

Figure 6: Prevalence of pelvic organ prolapse age group 66-75 years

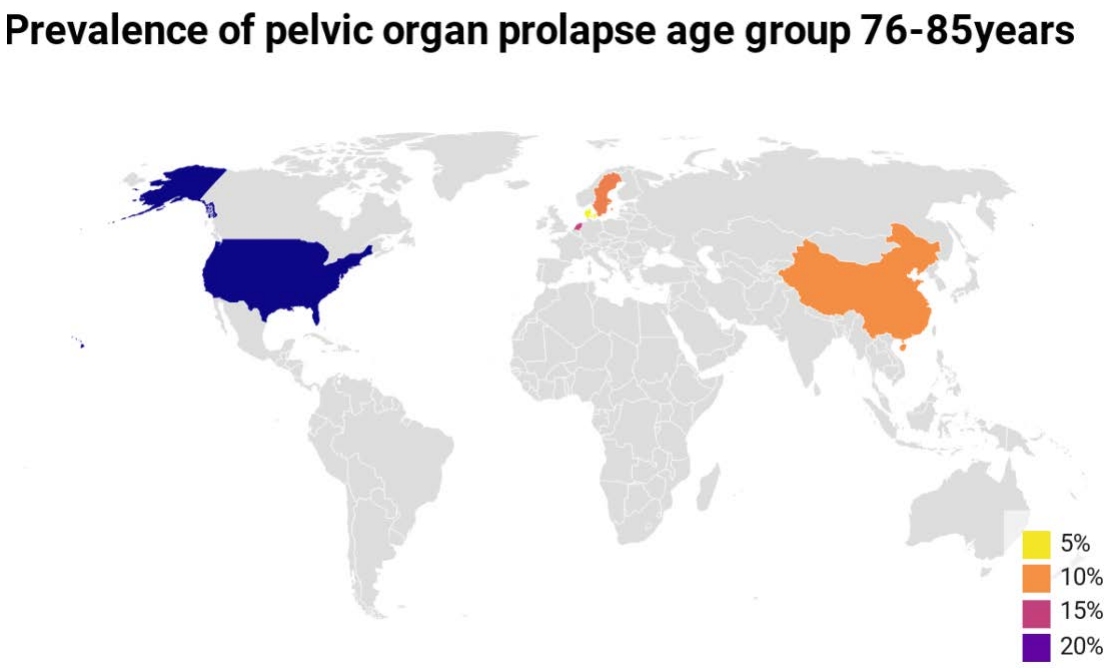

Figure 7: Prevalence of pelvic organ prolapse age group 76-85 years

Figure 8: Prevalence of pelvic organ prolapse age group >85 years

Discussion

In this systematic review we found that the highest prevalence of POP was noted in the 5th to the 7th decade of a women's life. Determining the global prevalence of prolapse has been challenging. This stems from the variety of methods of determining POP, which could be based either on symptoms or examination. We found that the type of method used highly influenced the prevalence rate reported in the studies. In this systematic review, we noted that the symptoms were assessed using validated tools such as PFDI SF 20 (mainly POPDI questions) or VSQ (visual symptom questionnaire) or WHO patient reported outcome measures. Barber et al screened for POP using validated questionnaires without physical examination and found 96% sensitivity and 79% specificity based on symptoms (48).

In our analysis of one national database studies and 6 cross sectional studies of POP, a newly published register-based study from Denmark had the largest sample size of 20285 to date (41). It estimated a lifetime risk of 18.7 % based on symptoms. This is consistent with a small, population based study from the Netherlands, which reported 20.3 % prevalence among octogenarians (35, 49).

The Scandinavian studies focused on any symptoms of POP. In contrast, symptom-based studies from USA reported prevalence limited to degree of 'bother'. The American studies quoted rates varying from 11 to 60% in the age group 45-65 years and it tapered to 4-8% between the ages of 76-85 years. Lawrence et al suggested that although pelvic floor disorders may be more common with increasing age, they might not be an inevitable part of the ageing process. Women should focus on modifiable risk factors for prevention such as constipation, weight loss, weight maintenance and seek treatment for all the conditions related to pelvic floor disorder when they occur

(32). A smaller UK study of 1832 women found the prevalence rate to be in the range of 5-8% in the age group 45-65 years (39).

On the other hand, objective assessment aids the clinician in planning and offering modes of intervention. Majority of the POP reported by POP-Q are based on data from medical records of surgical correction of stage 2 or 3 prolapse. Li et al conducted the largest cross-sectional study with sample size of nearly 25,000 women in China based on POP -Q assessment. It was found that most symptomatic women had stage II prolapse (46). They observed a prevalence of approximately 38% in 45-65years-age group followed by 10% in age group beyond 65 years. Interestingly this study also highlighted an increase in reporting of prolapse in urban population in contrast to rural China (46). The authors attributed this finding to women in urban population paying more attention to their quality of life and increased sensitivity to illness than rural population. Rural women had a tendency to ignore their symptoms or illness due to their lower socio-economic status.

In developing countries like Brazil, the incidence of hospital admission with diagnosis of POP is quoted as 2 per 1000 women per year (43). Age, body mass index and parity were found to associated with increasing prevalence of POP (50).

In countries like Bangladesh, there was under reporting from rural population due to embarrassment, stigma, low socio-economic living and lack of education. Self-reporting questionnaires limit the reporting of POP exclusively to women who are literate. 1 in 6 women (15.6%) in rural Bangladesh experience POP based on symptoms, which is higher than the previously reported prevalence of POP in this

setting (9.1 %)(42, 51) In this group of women, constipation was also reported as major risk factor besides parity for developing POP in later life.

Of note, the prevalence based on POP-Q ranged from 25 to 75% in the age group 45-65 years as compared to 11 - 59% claimed by the studies based on symptoms. This shows that not all prolapse cases will necessarily have symptoms and therefore the prevalence is underreported if we only focus on self-reporting questionnaires. Therefore, we recommend using a dual combination of validated questionnaires along with gynaecological examination (POP-Q) for determination of true prevalence of prolapse. The data should be adjusted for socio demographic and lifestyle factors. Age and parity were directly related to the prevalence of prolapse in women in all studies. The other factors mentioned in the studies included constipation, high BMI and chronic obstructive pulmonary disease. Smoking was a variable factor. A systematic review of risk factors for prolapse concluded that parity, vaginal delivery, age, and BMI are risk factors for POP and preoperative stage is a risk factor for POP recurrence (52). Despite studies stating lack of oestrogen or postmenopausal status enhances POP symptoms, the Nygaard et al study showed that there was no association between the presence of POP and the WHI Hormone Replacement Therapy clinical trial randomization assignment (oestrogen plus progesterone versus placebo), with prolapse occurring in almost exactly the same percentage of women in each group (28).

Wu et al described POP as an emerging health problem. They suggested that in the next 30 years the number of women with POP would double due to the increase in life expectancy (40, 53). From the review, we found that the prevalence of symptomatic POP increased with age up to 60-70 years, thereafter the prevalence became constant or plateaued. Tegersrdl et al observed that the odds of POP with age doubled when

adjusting for parity and the odds increased by eight times with parity when adjusting for age. The odds for having POP surgery significantly increased with age ($p<0.001$) and diminished with advancing age ($p<0.001$); compared with 40-year-old women (41). Swift et al, observed a definite trend toward increased POPQ system stage with advancing age, such that 21% of women were more than 70 years old (54). A large epidemiological study, established that the lifetime risk for parous women in a UK population of undergoing a single pelvic floor surgery was 12.2% by the age of 80 years (55). This could be attributed to women attending to their bothersome symptoms as at this age as they may be more inclined for surgical intervention, less family commitments and/ or exhausted all conservative therapies. The plateauing trend beyond the age of 80-85 years may be associated due to pre-existence of comorbidities in the women, which differs or prevents them from getting anaesthetic clearance or lack of reporting or short life expectancy of women in certain developing countries such as Nepal (36).

Strengths and Limitations

This systematic review focusses on the global prevalence of pelvic organ prolapse in both developed and developing countries. The data has been collated from large cross-sectional studies and national databases from individual countries. The studies selected presented the data either based on validated symptom-based questionnaires or objective assessment using the POP-Q quantification to assess the stage of prolapse. The authors were able to visually depict the distribution of POP with aid of epimaps and thereby portraying the burden of disease. This study was able to highlight the confounding factors in developing and developed countries that increase the risk of POP. In addition, this review highlights the countries that need

improvement on their reporting systems in epidemiology. This would assist their health systems in the respective countries to direct finances to improvement of medical care provided to women with chronic conditions such as POP.

As the diagnosis of POP was based on symptom-based questionnaires and/ or gynaecological examination, it is not possible to do a meta-analysis due to high heterogeneity in the data.

Implications for clinician and research

The information on the prevalence rates of POP have implication for provision of services to policymakers in terms of provision of improved access for these women to health care resources as well as the development of appropriate treatment protocols.

Future epidemiological studies should ideally be prospective, with explicit definitions of the outcome and representative of the general population. Close attention must be paid to study design as described in this paper.

Conclusion

We found that the prevalence of symptomatic POP increased with age up to 65-75 years (mean of 35%), thereafter the prevalence became constant or plateaued. Individual countries had their own systems in identifying and defining clinically significant prolapse, which led to varied prevalence rates. This study assists us to understand the burden of disease and thereby help target resources, improve treatment and highlight potential modifiable risk factors in primary healthcare. We recommend using a dual combination of validated questionnaires along with gynaecological examination (POP-Q) for determination of true prevalence of prolapse.

CHAPTER THREE: COMPREHENSIVE OVERVIEW OF PATIENT REPORTED OUTCOME MEASURES USED IN WOMEN WITH PELVIC ORGAN PROLAPSE: A SYSTEMATIC REVIEW

Introduction

Several patient reported outcome measures (PROMs) are widely used in urogynaecology in order to assess women's symptoms in clinical and research situations. Women with pelvic organ prolapse (POP) present with a variety of symptoms ranging from pressure symptoms, dragging sensation, feeling a bulge down below etc. These symptoms do not necessarily correlate to the severity of the degree or stage of the condition. In addition, POP can affect other domains such urinary, bowel, sexual and body image.

Comprehensive systematic reviews analysing the various PROMs are essential in order to provide clinicians evidence-based recommendations in the selection of the most suitable PROM for a particular condition. Tunis et al identified five major limitations in current PROMs: failure to obtain meaningful outcomes from patients, high degree variability in the outcomes reported across trials, poor information regarding the measurement properties of instruments, variation in outcome measurement instruments and reporting bias (56).

The COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) initiative aims to improve the selection of outcome measurement instruments in research and clinical practice by developing tools for selecting the most suitable instrument for the condition (22). The COSMIN methodology evaluates the PROM in a total of nine different aspects relating to the reliability, validity and responsiveness of the measurement tool (57). COSMIN provides a framework by

which the quality of the PROM development and validation studies can be assessed for rigor and quality. With increasing focus on patient centered care, PROMS play a vital role in understanding the impact of the condition on the patient's quality of life. Therefore, it is important that the PROMs are able to capture information reliably, along with being cost and time efficient. In order to understand how we can make good use of PROMs in daily practice, the first step needed is to have an overview of instruments suited to this task. Second, the level of evidence for the various measurement properties of each PROM has to be determined in order to make recommendations for clinical use.

This systematic review performs a comprehensive analysis and summarises the various PROMs available to use for women with POP. This review assists clinicians in identifying the best quality PROM for use in clinical and research situation by assessing the quality of PROM development studies. In addition, it identifies the gaps in knowledge on the measurement properties of PROMs, which can be used to design new studies on measurement properties.

Methodology of COSMIN

Consensus-based Standards for the selection of health Measurement Instruments (COSMIN http://www.cosmin.nl) were applied in this systematic review.

Identification of studies

The first step in the methodology recommended by COSMIN is the development of a search strategy.

A systematic search strategy was applied to the OVID versions of MEDLINE (1946–February 2019), EMBASE (1974–February 2019), and CINAHL (1806–February

2019) to identify articles reporting the development and measurement properties of PROMs developed for and/or validated in women with POP. The search was limited to human studies published in English from database inception up to December 2019. Abstracts and conference reports were excluded due to difficulties evaluating incomplete information. Reference lists of included articles were hand searched for further relevant publications. The search was limited to English language psychometric measures and articles reporting cross-cultural and translation validation of PROMs were excluded. Duplicate records were excluded.

The search terminology used combined terminology related to women AND specific terminology relating to pelvic organ prolapse AND this was combined with two existing search filters developed by Oxford PROM filter(58) and Terwee et al (59). The full search strategy is described in Appendix 1.

Selection criteria

Studies were selected based on the following criteria:

i PROMs focusing on women with pelvic organ prolapse/POP symptoms (construct of interest) and reported on the development of one or more psychometric properties of a PROM.

Exclusion criteria

i PROMs reported in clinical trials, reviews, conference abstracts and editorials.
ii PROMs focusing only on urinary incontinence, faecal incontinence and/ or body image
iii Women below the age of 18 years

Two researchers (TSV and JPD) selected papers independently based on the inclusion

and exclusion criteria as stated above. In cases of uncertainty, full papers were extracted and resolved by discussion.

Data extraction

The data that were extracted included the following:

1. Characteristics of the included PROM instruments and measurement properties evaluated

2. Summary of findings per measurement property

3. Quality of evidence for measurement properties of PROMs that have sufficient evidence for content validity.

Data analysis

Based on COSMIN evaluation, there are 9 measurement properties that appraise a PROM. These include content, structural, cross-cultural and criterion validity, hypothesis testing for construct validity, internal consistency, reliability, measurement error, and responsiveness (57). These properties are defined in Table 4.

Table 4: Definitions of measurement properties of instruments assessed by COSMIN guidelines

Measurement property	Definition
Content validity	The degree to which an instrument measures the construct(s) it purports to measure; the degree to which the content of an instrument is an adequate reflection of

	the construct to be measured
Internal consistency	The degree of the interrelatedness among the items; the extent to which scores for patients who have not changed are the same using different sets of items from same instrument
Reliability	The proportion of the total variance in the measurements which is due to ‘‘true’’ differences between patients
Measurement error	The systematic and random error of a patient’s score that is not attributed to true changes in the construct to be measured
Structural validity	The degree to which the scores of an instrument are an adequate reflection of the dimensionality of the construct to be measured
Hypothesis testing for construct validity	The degree to which the scores of an instrument are consistent with hypotheses based on the assumption that the instrument validly measures the construct to be measured
Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted instrument are an adequate reflection of the performance of the items of the original version of the instrument

Criterion validity	The degree to which the scores of an instrument are an adequate reflection of a ‘‘gold standard’’
Responsiveness	The ability of an instrument to detect change over time in the construct to be measured; item responsiveness

Definitions as described in COSMIN guidelines manual V1.0, 2018(60)

The most important measurement property for any PROM is Content validity. This property refers to the content of an instrument to adequately describe the property being measured. Therefore, this property has to be clear and easily identifiable by patients as the construct of interest. Table 5 defines the updated criteria for good measurement property. Only those PROMs that have comprehensible content validity qualified for full evaluation as depicted in Figure 9.

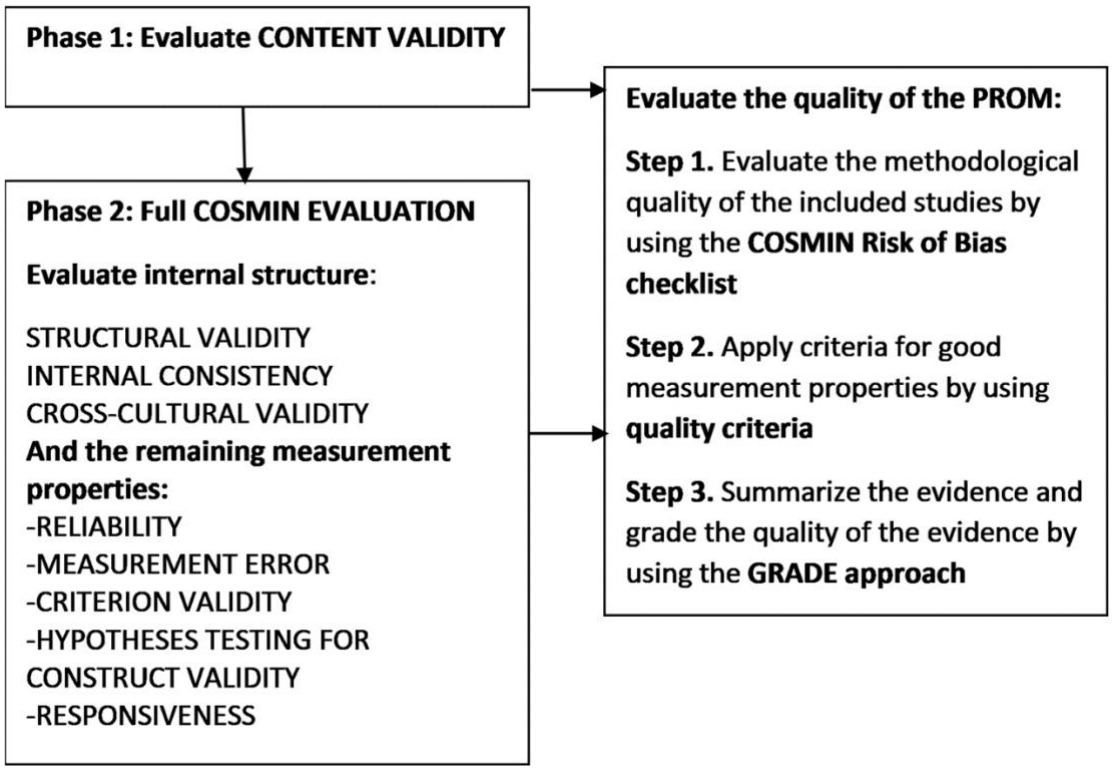

Figure 9: Selecting PROMs for full evaluation adapted from Mokkink et al COSMIN evaluation logarithm

Table 5: Quality criteria for measurement properties of heath questionnaires

Property Rating	Rating	Quality Criteria
Validity		
Content validity	+	All items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of the measurement AND the questionnaire is considered to be comprehensive
	?	Not enough information available
	-	Not all items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of the measurement OR the questionnaire is considered not to be comprehensive
Structural validity	+	Factors should explain at least 50% of the variance
	?	Explained variance not mentioned

	-	Factors explain < 50% of the variance
Hypothesis testing	+	Correlations with instruments measuring the same construct >/=0.50 OR at least 75% of the results are in accordance with the hypotheses AND correlations with related constructs are higher than with unrelated constructs
	?	Solely correlations determined with unrelated constructs
	-	Correlations with instruments measuring the same construct < 0.50 OR < 75% of the results are in accordance with the hypotheses OR correlations with related constructs are lower than with unrelated constructs
Cross-cultural validity	+	No differences in factor structure OR no important DIF between language versions
	?	Multiple group factor analysis not applied AND DIF not assessed
	-	Differences in factor structure OR important DIF between language versions

Criterion validity	+	Convincing arguments that gold standard is “gold” AND correlation with gold standard 0.70
	?	No convincing arguments that gold standard is “gold”
	-	Correlation with gold standard < 0.70
Reliability		
Internal consistency	+	Cronbach's alpha(s) > 0.70
	?	Cronbach's alpha not determined or dimensionality unknown
	-	Cronbach's alpha(s) < 0.70
Reliability	+	ICC / weighted Kappa >/= 0.70 OR Pearson's r >/= 0.80

	?	Neither ICC / weighted Kappa, nor Pearson's r determined
	-	ICC / weighted Kappa < 0.70 OR Pearson's r < 0.80
Measurement error	+	MIC > SDC OR MIC outside the LOA
	?	MIC not defined
	-	MIC < / = SDC OR MIC equals or inside LOA
Responsiveness		
Responsiveness	+	Correlation with changes on instruments measuring the same construct >/= 0.50 OR at least 75% of the results are in accordance with the hypotheses OR AUC >/= 0.70 AND correlations with changes in related

		constructs are higher than with unrelated constructs
	?	Solely correlations determined with unrelated constructs
	-	Correlations with changes on instruments measuring the same construct < 0.50 OR < 75% of the results are in accordance with the hypotheses OR AUC < 0.70 OR correlations with changes in related constructs are lower than with unrelated constructs

MIC = minimal important change, SDC = smallest detectable change, LoA = limits of agreement

ICC = intraclass correlation coef®cient, DIF = differential item functioning, AUC = area under the curve

+ = positive rating? = indeterminate rating

- = negative rating

(Reproduced with permission from Caroline Terwee, COSMIN(21))

Evaluation of each PROM

PROMS were assessed in a three-step process as depicted in Figure 10. Each reviewer (TSV and JPD) individually scored the PROM and disagreements were resolved after discussion.

Step 1: The methodological quality of each PROM was assessed based on the COSMIN Risk Bias Checklist (22, 57). A four-point scale ranging from very good, adequate, doubtful or inadequate was used to rate each study. The overall risk of bias was determined by taking the lowest rating of any item within each measurement property.

Step 2: **Applying the quality criteria**

2a: The reviewer assessed the content validity and development of each PROM. The reviewer assessed the comprehensiveness and relevance of the measurement property. The evidence was then classified as sufficient (+), insufficient (-) or indeterminate(?). Studies with insufficient evidence to support content validity were excluded from further assessment in the systematic review. These studies should not be recommended for use in capturing information regarding the condition.

2b: Remaining measurement properties: Those instruments with sufficient content validity were further assessed against the quality criteria for good measurement

properties.

Step 3: Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

The overall results of all the measurement properties of each PROM were assessed. Pooled results were compared against the criteria for good measurement. Finally, the quality of the evidence is graded (high, moderate, low, very low evidence), using a modified GRADE approach.

Results

Systematic literature search was performed. The search strategy is depicted in Figure 10. After removal of the duplicates, 1318 abstracts were screened. For complete text review based on the title and/or abstract, 75 articles were reviewed in detail and 45 were excluded. The selection strategy is depicted in Figure 10. The reasons for this were: not assessing POP symptoms (10), manuscript not relating to development or validation of psychometric measurement (18). The review team made a decision to exclude assessment of cross-cultural validity articles in order to focus on the validity of primary development of psychometric measurement properties for POP.

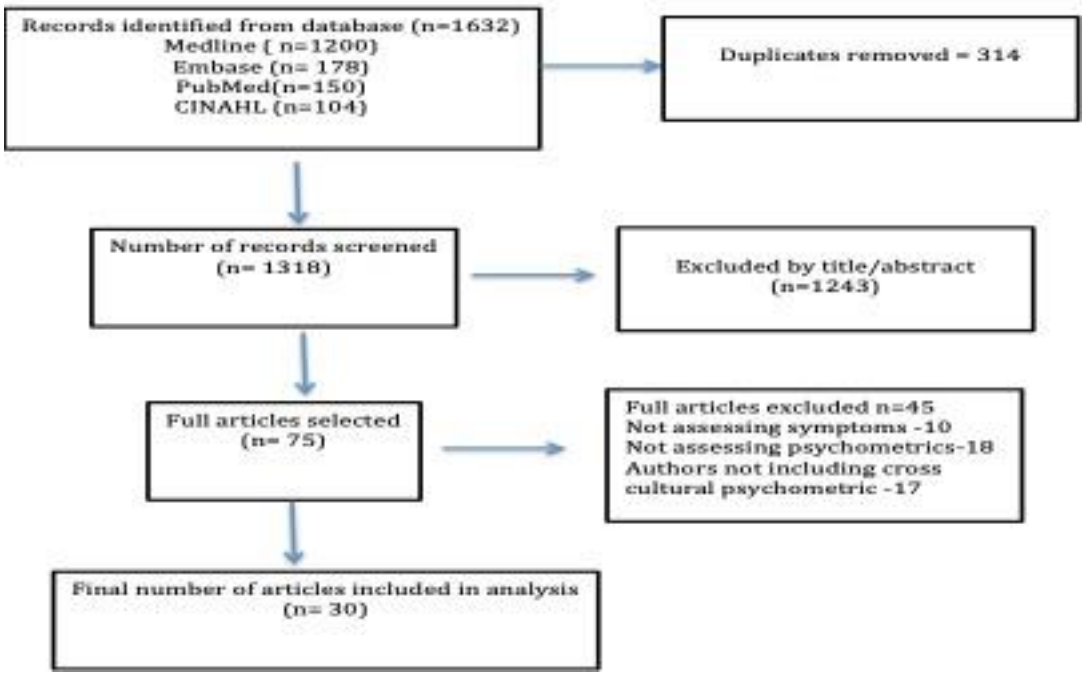

Figure 10: PRISMA flow diagram of included studies in the systematic review

Characteristics of included PROMs

A brief description of 12 PROMs along with their measurement properties evaluated in this review is depicted in Table 6. The table summarises the description of each PROM and the domains that PROM address. Individual PROMs evaluated various measurement properties. Development and validation studies were mainly performed in English speaking countries. The sample sizes ranged from 100-1000 women between the age groups of 18-85 years. We identified that not all measurement properties were assessed in detail for all PROMs. We performed full evaluation of PROM with sufficient content validity by using the COSMIN checklist tools.

Assessment of quality

Each individual PROM was assessed for its methodological quality. This information and evidence were obtained from the developmental and validation studies of each PROM. Using the quality criteria checklist as described by COSMIN tool(22) each

PROM was assessed in detail (Table 6).

PROM instruments for full evaluation

From the 12 PROMs that were evaluated, there were 3 PROMs that qualified for full evaluation. PFDI-SF 20, POP SS and ePAQ-PF are three instruments that were considered to have adequate or sufficient content validity. The content validity of the above mentioned three PROMs demonstrated high evidence in terms of relevance, comprehensiveness and comprehensibility. During the development of PFDI SF 20, 1006 women recruited from 4 prospective POP surgery trials conducted by Pelvic Floor Disorder Network (61). There was excellent correlation coefficient (Pearson correlation 0.88 $p<0.0001$) between the long and short forms of the PFDI. In addition there was good response rates at 3 and 12 months (standard response measure 0.71-0.85). The two measurement instruments have also shown to have good to excellent test-retest reliability of 0.7 and 0.91. The content and structural validity for the PFDI SF 20 demonstrated moderate or sufficient evidence of validity. There was an overall very low rate of missing data. In 2005, Barber et al attempted to determine the Minimal clinical important difference or change for the PFDI-SF 20 and PFIQ. They defined this change as the women who expressed symptoms being “little better” after surgery. A change of 15% (or 45 points) and 12% (or 36 points) in PFDI SF20 and PFIQ 7 respectively is described as minimal change (Table 7).

Similarly, ePAQ PF has gone through a robust validation process. Research has shown that patients have better response rates on electronic questionnaires as they become more efficient, user friendly and now become part of day-to-day life. The

validation process comprised of 228 women from secondary sector (mean age of 52) and 204 women from the primary sector. In depth qualitative studies were performed and acceptability of the ePAQ PF questionnaire was analysed. Most participants found the PROM acceptable. There was a 79% variance accounting for the structural validity of the PROM. Ascertaining the Cronbach's alpha assesses internal consistency which in turn is an indicator of reliability. A Cronbach's alpha score greater than 0.70 is preferable to state that the outcome measure has good reliability. This is noted as >0.70 in the ePAQ PF (Table 7). The validation studies provided evidence that supported hypothesis testing.

In 2008, Hagen et al developed the POP SS questionnaire. This is a 7-item questionnaire combined with a 5-point Likert scale. In the initial developmental studies, qualitative interview were performed on 10 women. They found the questionnaire acceptable and easily comprehensible. The PROM displayed sufficient content and structural validity. The POP SS also demonstrates a good internal consistency and reliability. The minimal change was calculated to be a decrease on POP SS score by 1.5 or more. Responsiveness test for the POP SS found the AUC 0.7, which is favourable. (Table 7 & Table 8)

Table 6: Detailed description of POP PROM studies and enumerating measurement properties the study evaluates

No.	Measure	Domains	Identified categories	Description	COSMIN measurement Properties evaluated
1.	PFDI-46 Barber et al(62) 2001 USA	Urinary – 28 POP – 16 Colorectal-anal – 17	Symptom Bother	The PFDI assesses symptom distress in women with pelvic floor disorders and has 3 scales: UDI (28 items), Colorectal–anal Distress Inventory (17 items), and Pelvic Organ Prolapse Distress Inventory (16 items)	Content validity Structural validity Internal consistency Reliability Measurement error Responsiveness
2.	PFDI-20 Barber et al(18) 2005 USA	Urinary - 6 POP – 6 Colorectal - 8	Symptom Bother	The short form version of the PFDI has a total of 20 questions and 3 scales (UDI-6, POPDI-6, and CRADI-8)	Content validity Internal consistency Reliability Measurement error Responsiveness
3.	PFIQ-31 Barber et al (62) 2001 USA	Urinary - 31 POP – 31 Colorectal - 31	QoL	The PFIQ assesses life impact and also has 3 scales: IIQ, Colorectal–anal Impact Questionnaire, and the Pelvic Organ Prolapse Impact Questionnaire (31 items each)	Content validity Structural validity Internal consistency Reliability Measurement error Responsiveness
4.	PFIQ-7	Urinary - 8	QoL	There 3 scales	Content validity

	Barber et al (18) 2004 USA	POP – 8 Colorectal - 8		each with 7 items. The PFIQ-7 is scored from 0 (least impact) to 100 (greatest adverse impact) and an overall summary score (0 to 300)	Internal consistency Reliability Measurement error Responsiveness
5.	PISQ 31 Rogers et al(20) 2001 USA	Behavioral - 15 Physical -10 Partner related -6	Symptom QoL	Four functional groups were identified as follows: (1) urinary symptoms, (2) bowel symptoms, (3) sexual symptoms, and (4) other local symptoms	Content validity Internal consistency Reliability Measurement error
6.	PISQ 12 Rogers et al(19) 2003 USA	12 items that predicted long-form scores in the three factors	Symptom QoL	PISQ-12 scores revealed good to excellent correlation with PISQ-31 scores	Content validity Structural validity Internal consistency Reliability
7.	P-QOL Digesu et al (63) 2004 UK	Urinary -7 POP - 22	Symptom QoL	The final version included 20 questions representing nine quality of life domains covering general health, prolapse impact, role, physical and social limitations, personal relationships,	Content validity Internal consistency Reliability

				emotional problems, sleep/energy disturbance as well as measurements of symptom severity. Questions regarding bladder, bowel and sexual function were also included	
8.	ePAQ-PF Radley et al(64-66) 2005 UK	Urinary - 35 POP – 22 Colorectal - 33 Sexual - 28	Symptom QoL Bother	The electronic Personal Assessment Questionnaire Pelvic Floor (ePAQ-PF) was designed to measure symptoms and their impact upon quality of life in women with pelvic floor disorders.	Content validity Structural validity Hypothesis testing Internal consistency Reliability Measurement error Responsiveness
9.	ICIQ-VS Price et al (67) 2006 UK	Vaginal -9 Sexual - 5	Symptom QoL Bother	The ICIQ-VS is a questionnaire for evaluating vaginal symptoms, associated sexual matters and impact on quality of life (QoL) in research and clinical practice across the world.	
10.	POP SS Hagen et al(68) 2009	POP-3 Urinary -2 Colorectal-	Symptom Bother	The POP-SS consists of seven items, each with a 5-point Likert	Content validity Structural validity

	UK	1 Symptom bother -1		response set (0=never, 1=occasionally, 2=sometimes, 3=most of the time, 4=all of the time) A total score (range 0 to 28) is calculated by summing the seven individual symptom responses to derive the POP-SS score.	Hypothesis testing Internal consistency Reliability Measurement error Responsiveness
11.	FPFQ Baessler et al(69) 2009 Australia	Urinary - 15 POP – 5 Colorectal - 12 Sexual - 10	Symptom QoL Bother	Questions regarding bladder (15), bowel (12), and sexual function (10), and pelvic organ prolapse symptoms (five) were grouped according to the physiological functions of the pelvic floor: bladder function, bowel function, prolapse symptoms, and sexual function domains QoL measures and bothersomeness ratings were integrated into the four domains	Content validity Internal consistency Reliability
12.	PFBQ Peterson et al(70)	Urinary - 5 POP – 1 Colorectal -	Bother	The PFBQ was developed by the Cleveland Clinic	Content validity Reliability

	2010 USA	2 Sexual - 1		Pelvic Floor staff based on clinical interviews and review of commonly used surveys, such as the Urinary Distress Inventory and the PFDI and PFIQ

Table 7: Methodological quality of included PROM studies based on the COSMIN quality criteria

Instrument	Content Validity	Structural Validity	Hypothesis Testing	Internal Consistency	Reliability	Measurement error	Responsiveness
			at least 50% of the variance	Cronbach's alpha	ICC / weighted Kappa /Pearson's r	MIC > SDC OR MIC outside the LOA	0.50 OR at least 75% of the results are in accordance with the hypotheses OR AUC 0.70
PFDI-46(62)	++	+	+	+ 0.88	+ 0.89	-	+ 0.50-0.70

PFDI-20(18)	++	+	-	+ 0.8	+ 0.7 (p<0.0001)	? change of 45 points (15% or >1)	+ 0.7-1.28
PFIQ-31(62)	++	-	+	+ 0.97	+ 0.98	-	+ 0.8 -1
PFIQ-7(18)	++	+	+	+ 0.8	+ 0.9 (p<0.001)	? change of 36 points (12% or more)	+ 0.63-0.67
PISQ-31(20)	++	+	-	+ 0.86	+ 0.56 to 0.93	-	-
PISQ - 12(19)	++	-	-	+ 0.93	? (> 0.15)	-	-
P-QoL(63)	++	?	-	+ 0.80	+ (p<0.01)	-	-
ePAQ-PF	++	++	+	+ 0.82	+ 0.70 (p<0.00	+ 2.8	+ 0.8

(64-66)					1)	increase in score	
ICIQ VS(67)	++	?	?	+ 0.81	+ 0.58-1 (p<0.0001)	-	-
POP SS(68)	++	++	++	+ 0.7-0.82	+ 0.5	+ 1.5 or more decrease in score	+ 0.7
FPFQ(69)	++	?	?	+ 0.87	+ 0.5	-	-
PFBQ(70)	++	-	?	+ 0.70	-	-	-

MIC = minimal important change, SDC = smallest detectable change, LoA = limits of agreement

ICC = intraclass correlation coef®cient, DIF = differential item functioning, AUC = area under the curve

+ = positive rating,? = indeterminate rating

- = negative rating

Table 8: Table describing the quality of evidence for the recommended POP measurement properties to be utilised in clinical practise

Measurement property	PFDI 20		POP SS		ePAQ PF	
	Overall rating + /-/?	Quality of evidence High, moderate, low, very low	Overall rating + /-/?	Quality of evidence High, moderate, low, very low	Overall rating + /-/?	Quality of evidence High, moderate, low, very low
Content validity	+	High	+	High	+	High
Relevance	+	High	+	High	+	High
Comprehensiveness	+	High	+	High	+	High
Comprehensibility	+	High	+	High	+	High
Structural validity	+	High	+	High	+	High
Internal consistency	+	High	+	High	+	High
Reliability	+	High	+	High	+	High
Criterion validity	+	High	NA	NA	NA	NA
Hypothesis testing for construct validity	+	High	+	High	+	High

Responsiveness	+	High	+	High	+	High
Measurement error	+	High	+	High	+	High

NA not assessed/not applicable

Discussion

This is the first review to utilize the COSMIN checklist to evaluate patient reported outcome measures (PROMS) for women with POP. In total 12 PROMS were evaluated from 30 studies. In a clinical setting, the PROMs that have demonstrated sufficient quality of evidence are the PFDI SF 20, POP SS and ePAQ- PF. The development and validation studies for these three individual PROMs have been thorough and robust. They have evidence to support all 9 of the measurement properties required of a PROM.

Strengths and limitation

The reviewers have utilized a standardised methodology in evaluating and appraising PROMs in women with POP. A highly specific search strategy was used with aide of the Oxford PROM and Terwee et al filters (59). Therefore, a comprehensive search has been performed in order to identify relevant papers. The scrutiny of the development and validation studies review has highlighted the measurement properties that have been evaluated for each PROM. This allows researchers to review the dearth of information for various PROMs such as the measurement of error, hypothesis testing, structural validity and responsiveness. The introduction of COSMIN tool gives opportunity for researchers developing PROMs to understand that the domains described in the checklist is essential in creating a high-quality

PROM.

The limitation of this study is that the authors limited their evaluation to development studies in English. The research team has noted that the individual PROM may have been translated into various languages, however in order to focus only on the original PROM development paper, cross-cultural validity was not assessed. In addition, the reviewers focused mainly on symptoms of POP. There may be other domains that relate to POP such as self-esteem, body image etc. but these domains were not evaluated by the COSMIN methodology as COSMIN guidance is a relatively new method on analysing and appraising PROMs. Many PROMs were developed prior to this guidance, therefore the reviewers worked on the available information in order extract maximum data from existing articles and some assumptions could have been inferred from the data.

Implications for clinicians

The PFDI-SF 20, POP SS and ePAQ -PF have demonstrated sufficient evidence to be recommended for use in clinical and research settings in order to capture maximum information from the patient.

Implication for research

This systematic review has identified measurement properties that need to be validated in many PROMS. This systematic review supports the need to create a core outcome set in urogynaecology in order to create uniformity in reporting.

CHAPTER FOUR: A RANDOMISED MULTI-CENTRE FEASIBILITY TRIAL TO ASSESS THE EFFECTIVENESS OF LOCAL OESTROGEN TREATMENT IN POSTMENOPAUSAL WOMEN UNDERGOING PELVIC ORGAN PROLAPSE SURGERY (LOTUS - FEASIBILITY TRIAL)

Rationale for the LOTUS study

According to the Cochrane systematic review by Ismail and colleagues, there was limited evidence from existing randomised control trials (RCTs) pertaining to the use of oestrogen for the management and prevention of Pelvic Organ Prolapse (POP). The review recommended further long-term follow up studies were necessary to assess the effectiveness of oestrogen and POP (16).

Whilst there is a plausible argument for using low-dose oestrogen to improve the vaginal environment, there is little evidence to support its effect on the quality of surgical repair, prolapse cure rates or recurrence. Furthermore, there is no information about its effect on prolapse related symptoms, overall quality of life (QoL) and such outcomes, which are important to the women. Finally, the duration of oestrogen treatment and cost-effectiveness compared with current practice are not known.

Before embarking on a large definitive study, we aimed to perform a study that addresses the acceptability of the intervention and information provided to women, the feasibility of recruiting and randomising women in a timely fashion, the compliance with the treatment schedule, the usability of the data collection forms and limited data on the proposed primary outcome measure.

Study Aim

The aim of the feasibility study was to find out if an appropriately powered randomised controlled trial (RCT) can be realistically undertaken.

Specifically, aimed to assess the effectiveness of the patient identification and screening process including reasons for failure to randomise eligible patients; it also evaluated the compliance with the treatment schedule, robustness and usability of data collection processes during and after the hospital episode. We also collected limited data on the proposed primary outcome measure and serious adverse events.

Feasibility study specific objectives:

- To obtain estimates for important aspects of the protocol to allow development of a definitive trial, in particular:

1. Proportion of eligible women of those screened
2. Proportion of eligible women randomised
3. Attrition rates (proportion of completed questionnaires at 6 months)
4. Compliance with treatment
5. Acceptability of outcome measures
6. Estimate the variability of pelvic floor distress inventory short form (PFDI SF20) to inform the sample size calculation for the larger trial

- To derive a realistic understanding of trial processes, in particular:

1. Ascertain robustness of the data collection process during and after the hospital episode
2. Determine the support required in units to ensure successful recruitment

Trial Design

Multicentre feasibility open label trial comparing vaginal low-dose oestrogen with no treatment, in 100 consecutive consenting postmenopausal women who were planning to undergo POP surgery. They were randomly allocated to (Fig 11):

Intervention group (Group A): 6 weeks course of oestradiol 10 µg preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then 10µg oestradiol per vaginum twice weekly from 6-26 weeks postoperatively.

Comparison group (Group B): no vaginal oestrogen treatment

Setting

The women were recruited from 6 NHS hospitals across the United Kingdom involving both district general and tertiary urogynaecology units.

Eligibility

Inclusion criteria:

Postmenopausal women

Consented to undergo surgical intervention for pelvic organ prolapse

Have not received HRT in the last 12 months

Willing to be randomised

Give written informed consent to participate in the study

Exclusion criteria:

Previous breast or uterine malignancy or other hormone- dependant neoplasms

Genital bleeding of unknown origin

Previous thrombo-embolic episodes in relation to oestrogen therapy

Women who cannot understand, speak or write in English

Women known to be allergic to any of the components of vaginal oestrogens

Two or more episodes of culture positive UTI in the last 6 months

Previous POP surgery in the same compartment

Voiding dysfunction (post-voiding residual volume>150ml)

Current or previous POP surgery-involving mesh

Patient is participating in another CTIMP trial.

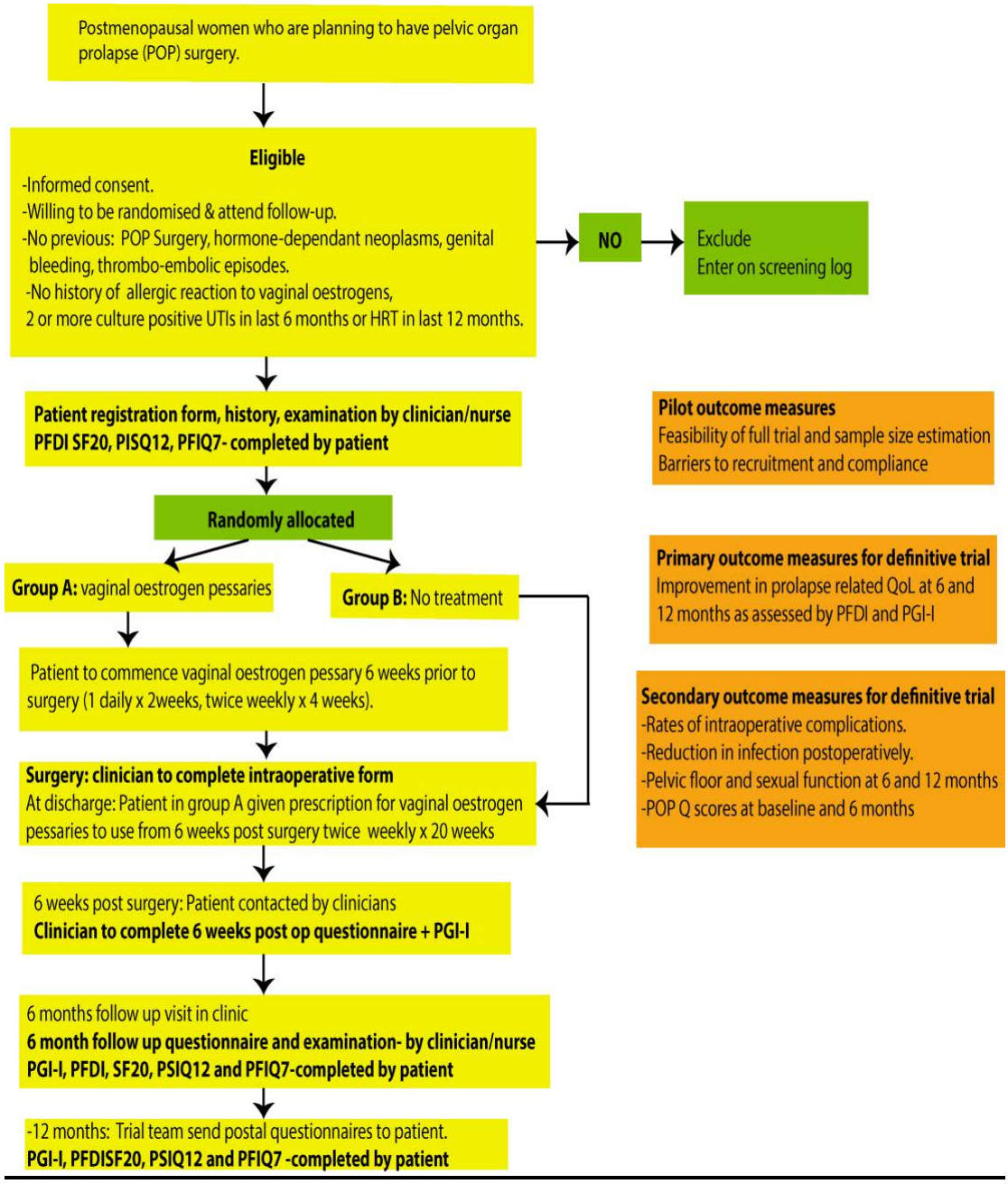

Figure 11: Flow Chart for LOTUS feasibility study

Study set up:

On obtaining ethical and R&D approvals, we commenced screening and recruiting women to the study from July 2015. Initially we set up the study at Birmingham Women's Hospital and presented the protocol to all the urogynaecology consultants and staff members. Subsequently, we conducted site initiation visits at all external sites.

Identification of participants, consent and recruitment process:

We screened and approached eligible women attending the urogynaecology clinics. In addition, we identified potentially eligible women from the GP referral letters at the booking office. The patient information leaflets were sent to the potentially eligible women along with their hospital appointment. Once the women attended their appointment and were classed as eligible to participate in the study, we explained the study process and gave the women adequate time to discuss, think and clear their queries before seeking consent to participate. We obtained a thorough history, performed a clinical examination and graded the prolapse as per pelvic organ prolapse quantification (POP-Q) system. Baseline data including clinical history and symptom related questionnaires were recorded. Intraoperative, post-operative (6 weeks & 6 months) data (including objective assessment of prolapse outcome by POP-Q) were collected at scheduled appointment. Patient outcomes measures were also completed at this time. These included the Pelvic Floor Distress Inventory Short Form 20 (PFDI-SF20), the Pelvic Floor Incontinence Questionnaire (PFIQ-7), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) and Patient Global Impression of Improvement (PGI-I) (Table 9) (Appendix 3).

Written informed consent was obtained for eligible patients and randomisation was performed using a web-based central randomisation system (via Birmingham Clinical Trials Unit) to allocate patients to either vaginal oestrogen pessaries or no treatment in a 1:1 ratio. Minimisation was used to achieve balance between age (<65 years or ≥65 years), parity (<=2, >2 vaginal births), maximum stage of prolapse (I, II or III/IV) and whether a concomitant continence surgery was performed. We randomised 100 women; this number would allow us to measure recruitment and compliance rates with 95% confidence interval (CI) width between 10 and 20%. It would also be enough women to estimate the standard deviation (SD) of PDFI-20, POPDI-6 domain (pelvic organ prolapse distress inventory; the

proposed primary outcome in substantive study) with reasonable confidence for future planning of a larger trial (95% CI for SD would be 7 points, assuming the SD is around 20).

Table 9: Outcome measures collected at specific time points during the LOTUS trial

Data and/or outcome measure collected	At Randomisation	Pre-Surgery	At Surgery	6 Weeks	6 Months	12 Months	Completed by
History, presentation, demographic data	X						Clinician/ nurse
PFDI-SF20 **PFIQ-7** **PISQ-12** **PGI-I**	X X X				X X X X	X X X X	Patient (in clinic at baseline, 6 months and postal at 12 months)
6 weeks questionnaire **PGI I**				X X			Clinician/ research team (to contact patient)
POP-Q	X				X		Clinician
Operative details			X				Clinician
Study drug adverse events		X	X	X	X	X	Clinician
		Spontaneous reporting					Patient

The women allocated to the intervention group were given a prescription to take to pharmacy to obtain the supply of Vagifem pessaries to be used 6 weeks pre-operatively (Table 10). Control group received no vaginal oestrogen treatment. On the day of the surgery, the surgeon completed intraoperative questionnaire on ease of dissection, complications like visceral injury, buttonholing of the vagina and estimated blood loss.

Women in the intervention group were given pessaries at the time of discharge and advised to use it twice weekly from 6 weeks postoperatively for 20 weeks. At 6 weeks postoperatively, the research team contacted the women to record any postoperative complications. At the 6-month follow up, the clinical team with an independent member re-examined the patient including the POP Q, and this was undertaken without knowledge of the findings of the other. Patients completed questionnaires (PFDI-SF20, PFIQ-7 & PGI-I) at 6 months.

Table 10: Dosing schedules in LOTUS study

Starting Time point	Duration	Number of times administered per week
6 weeks before surgery	2 weeks (to 4 weeks before surgery)	Once daily for 2 weeks
4 weeks before surgery	4 weeks (to night before surgery)	Twice weekly for 4weeks
Day of surgery	6 weeks	0
6 weeks after surgery	20 weeks	Twice weekly for 20 weeks

Ineligible patients

We maintained screening logs in order to keep record of the women who were screened but not eligible for the trial. We recorded the minimum identification details, age, ethnicity and reasons for ineligibility. We designed a key for the reason of ineligibility with a view of creating uniformity and ease of documentation throughout all sites.

Study treatment and accountability

At randomisation, the investigational medicinal product (IMP) was supplied by the hospital pharmacy. The pharmacy would receive notification to prepare and dispense the specified treatment schedule. Preoperatively women were given 6 weeks supply of the medication and we prompted women at 6 weeks prior to surgery to commence their medication.

Following surgery and upon discharge the women were given a prescription for a further 6 months supply of the medication. The pharmacy maintained a log of the study drug dispensed.

Statistical analysis

Feasibility outcomes were considered with simple summary statistics, with uncertainty estimates provided by 95% confidence intervals. Clinical and patient reported outcome measures (PROMs) were analysed with point estimates (RR or mean difference) and 95% confidence intervals (CI), adjusting for the minimisation variables. They were not subject to hypothesis testing as the size of the sample would not allow reliable assessment of the effect of the interventions. Participants were considered in the groups they were randomised to regardless of compliance in these summaries (intention-to-treat). The dataset used in this manuscript is available on request from Birmingham Clinical Trials Unit.

Feasibility outcomes

The following outcomes and targets were set a-priori as being indicative that a larger trial would be feasible to conduct. These were: i) patient eligibility rate (the proportion of screened patients eligible) at least 25%; ii) patient recruitment rate (the proportion of eligible patients randomised) at least 25%; iii) compliance rate (the proportion of patients with good compliance to treatment, i.e. at least 75% allocated pessaries used): at least 50%; iv) data completion rate (number of follow-up questionnaires completed at six months): at least 75%.

Results

Patients and follow-up

Recruitment took place over a 13-month period between July 2015 and August 2016 in six urogynaecology centres in the UK (Birmingham Women's Hospital, Croydon University Hospital, Basingstoke and North Hampshire Hospital, Walsall Manor Hospital, Royal Stoke University Hospital, James Cook University Hospital, Middlesbrough). Once the target sample size was reached, the study stopped randomising women.

Of the women who presented with prolapse and wanted surgery, 325 consecutive women were screened for eligibility, 157 were found to be eligible (48%, 95% CI: 40-56%) and 100 (64%, 95% CI 56-72%) of those eligible were randomised (Figure 5). The average age of participants was 66 years and average BMI was 28.2. The parity was over 2 in 47% of the women. The maximum stage of prolapse was III or IV for 40% of participants (Table 13).
Of the 100 randomised women, 89 ultimately had surgery. Of the other 11, 5 could not have surgery due to health issues, 2 changed their mind about surgery, 2 did not attend their surgical appointment and 2 were diagnosed with cancer. At six and 12-month follow-up questionnaires were completed by 79/100 (79%) participants at each time interval. Of those

that had surgery this equated to 79/89 (89%). Of those who had surgery, 100% had completed intraoperative data and 84/89 (94%) had post-operative data recorded at six weeks.

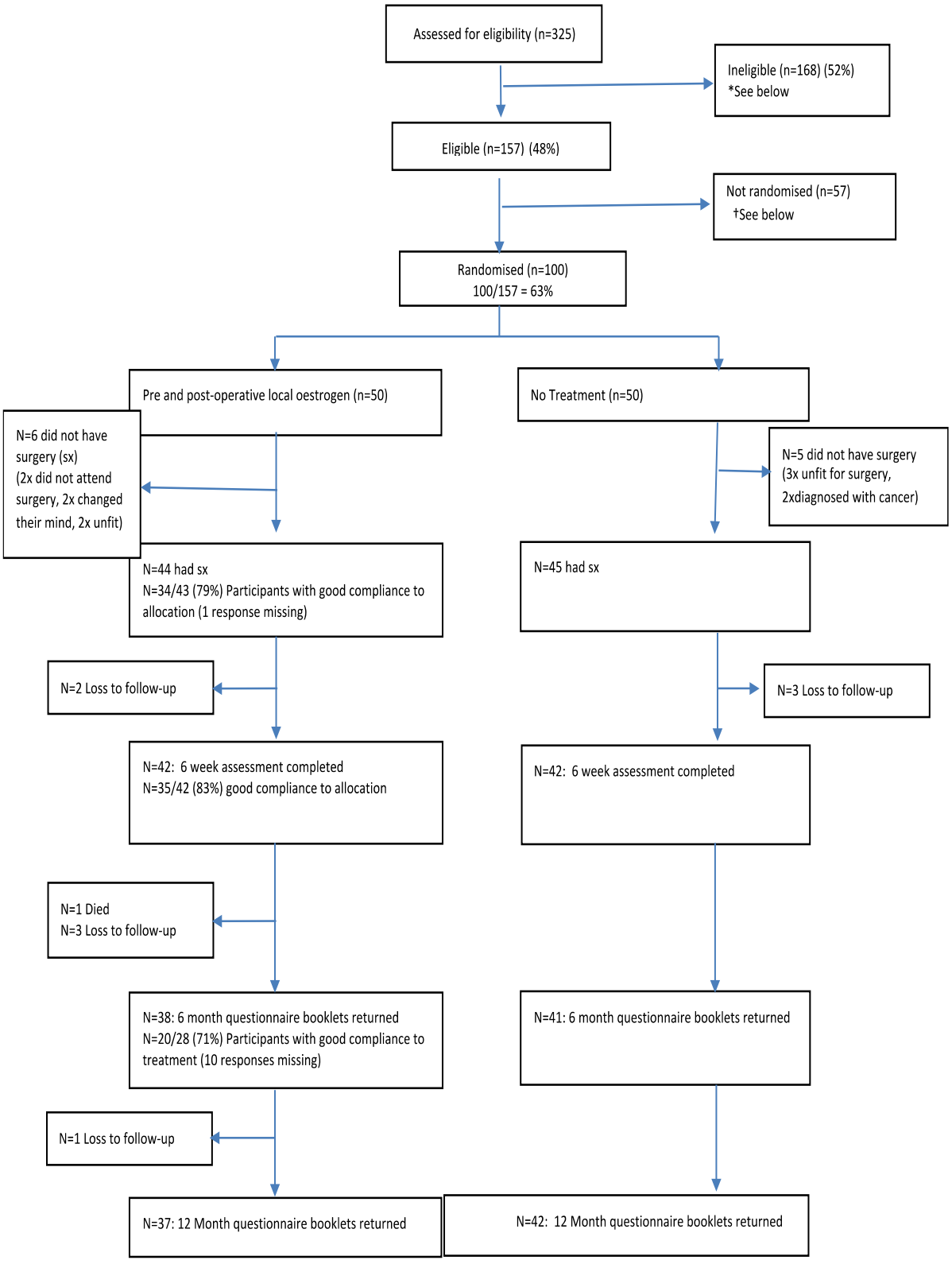

Figure 12: PRISMA Flow of participants through the LOTUS trial

Table 11: Reasons for Ineligibility

Reason	**N=168 (%)**
No prolapse surgery required	38 (22)
Recurrence of prolapse in the same compartment	32 (19)
Previous breast or uterine malignancy	20 (12)
On hormone replacement therapy	17 (10)
Unable to understand English	16 (9)
Genital bleeding of unknown origin	15 (9)
Previous hormone-dependent neoplasms	13 (8)
Previous POP surgery involving mesh	6 (3)
Previous thrombo-embolic episode	4 (2)
Two or more culture positive UTI episodes in the last 6 months	1 (<1)
*Other	6 (3)

**Reasons for other:*

Comorbidities

Wants surgery but at a much later date

Needed bowel surgery prior to prolapse surgery (diagnosed with Bowel Carcinoma)

Table 12: Reasons for Non-Randomisation

Reasons	**N=57 (%)**
Patient did not attend clinic	19 (33)
Not enough time to discuss trial and gain informed consent	14 (25)
Declined Consent/not willing to be randomised	9 (16)
Wants surgical management involving mesh	5 (9)
Not willing to wait 6 weeks for surgery	5 (9)
Unable to gain consent	4 (7)
Did not want to complete questionnaires	1 (2)

Table 13: Baseline Characteristics of participants in the LOTUS trial

Characteristics		Oestrogen (n=50)	No Treatment (n=50)	Overall (n=100)
Age, years[1]	<65	21 (42%)	21 (42%)	42 (42%)
	>=65	29 (58%)	29 (58%)	58 (58%)
	Mean (SD)	65.7 (8.2)	65.9 (8.4)	65.8 (8.3)
Ethnic Group	White	45 (90%)	43 (86%)	88 (88%)
	Asian	2 (4%)	3 (6%)	5 (5%)
	Black	3 (6%)	1 (2%)	4 (4%)
	Mixed	0 (-)	2 (4%)	2 (5%)
	Other ethnic group	0 (-)	1 (2%)	1 (1%)
BMI (mg/k^2)	Mean (SD)	28.1 (5.1)	28.2 (5.9)	28.2 (5.5)
	Missing (N)	2	7	9
Parity[1]	<=2	27 (54%)	26 (52%)	53 (53%)
	>2	23 (46%)	24 (48%)	47 (47%)
Maximum Stage of Prolapse[1]	I	7 (14%)	7 (14%)	14 (14%)
	II	23 (46%)	23 (46%)	46 (46%)
	III/IV	20 (40%)	20 (40%)	40 (40%)

Concomitant continence surgery performed[1]	N (%)	2 (4%)	3 (6%)	5 (5%)
Previous operation for prolapse	N (%)	4 (8%)	4 (8%)	8 (8%)
Anterior	No. of repairs Median (IQR)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)
Posterior	No. of repairs Median (IQR)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)
Hysterectomy	N (%)	12 (24%)	8 (16%)	20 (20%)
Vaginal pessary/ring currently in place	N (%)	5 (10%)	8 (16%)	13 (13%)
Physiotherapy treatment for prolapse/urinary incontinence in last 12 months	N (%)	8 (16%)	10 (20%)	18 (18%)
Drug treatment for urinary incontinence	N (%)	0 (-)	4 (8%)	4 (4%)
Treatment for overactive bladder	N (%)	0 (-)	0 (-)	0 (-)

[1]minimisation variable

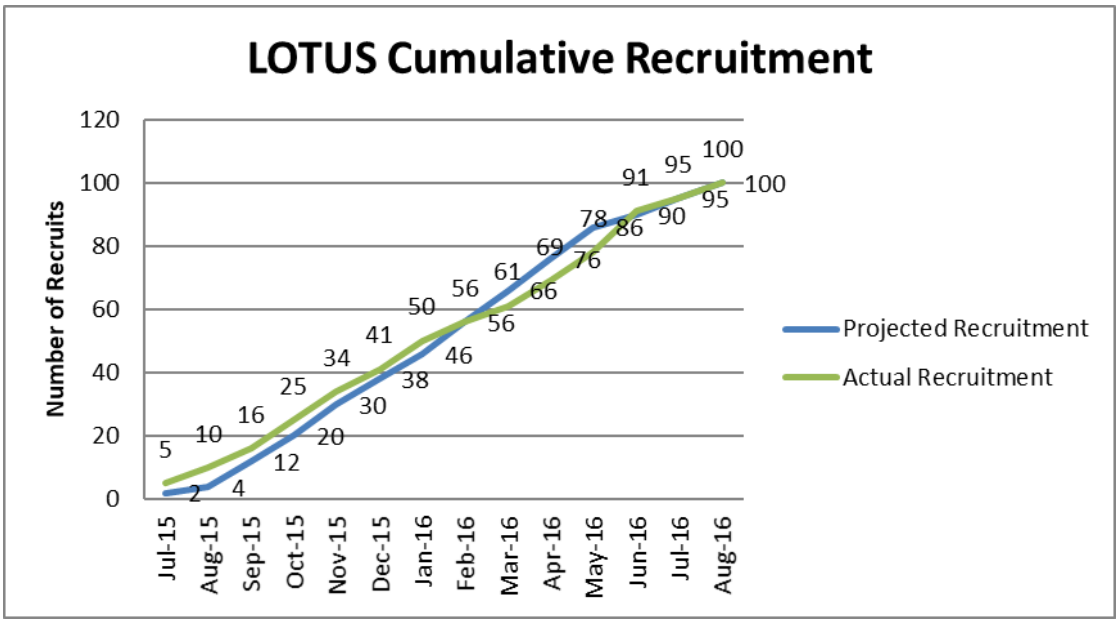

Figure 13: Graph depicting the Lotus recruitment during the 13 months

Table 14: Randomisations by individual centres (100 in total)

Screening centre	**Number eligible**	**Number randomised**	**Conversion rate**
Basingstoke and North Hampshire Hospital	18	5	28%
Birmingham Women's Hospital	79	42	53%
Croydon University Hospital	22	21	95%
James Cook Hospital	13	13	100%
Manor Hospital	16	11	69%
Royal Stoke University Hospital	9	8	89%
TOTAL	**157**	**100**	**64%**

** Trial team noted that in district hospitals, all women being approached were being randomised and therefore the true eligibility was not being captured.

Pre-operation	No. of forms received that were allocated Vagifem **N=44**
Patient used Vagifem as advised preoperatively?	N=31
Did she miss Vagifem pessary insertion during the treatment course?	N=12
Missing	N=1
6 weeks	No. of forms received that were allocated Vagifem **N=42**
Patient used Vagifem as advised post-operatively?	N=35
Did she miss Vagifem pessary insertion during the treatment course?	N=7
6 months	No. of forms received that were allocated Vagifem **N=28**
Patient used Vagifem as advised post-operatively?	N=17
Did she miss Vagifem pessary insertion during the treatment course?	N=10

Missing	N=1

Table 15: Details of compliance of participants in the treatment group

Good compliance with oestrogen treatment (denoted as pessaries used at least >=75% of the expected time) was observed in 79% of participants pre-operatively (34/43), 83% at six weeks (35/42) and 71% at six months (20/28).

Protocol deviations

Table 16: Protocol deviations by group

	Allocated Treatment	
Protocol deviations	**Vagifem**	**No Treatment**
Ineligible patient randomized	0	0
Randomised with no surgery	6[1]	5[2]

[1]Vagifem:

[1] Did not attend (DNA) on the date of surgery 3 times –discharged back to GP; Changed her mind. [2]No Treatment: Reasons for no surgery - Cancer so has not had surgery; DNA surgery 3 times so discharged

Died of cancer; Heart problems so no suitable for surgery; Bowel cancer.

Table 17: Patient reported outcomes – PFDI-SF20

	Vagifem N; Mean (SD)	No Treatment N; Mean (SD)	Difference between groups (95% CI)[3]
PFDI-SF20; POPDI-6 Domain (0-100, higher=worse pain)[1]			
Baseline	N=48; 43.4 (24.8)	N=49; 46.0 (24.4)	
6 Month	N=38; 16.3 (20.3)	N=41; 12.5 (11.6)	4.1 (-3.9, 12.1)
12 Month	N=37 16.7 (20.6)	N=41 14.6 (15.6)	4.4 (-4.7, 13.5)
PFDI-SF20; CRAD-8 Domain (0-100, higher=worse pain)[1]			
Baseline	N=48; 26.0 (25.0)	N=48; 24.3 (18.0)	
6 Month	N=38; 12.7 (14.4)	N=41; 15.2 (13.2)	-2.4 (-7.6, 3.4)
12 Month	N=37 12.8 (14.8)	N=42 15.8 (15.8)	-1.7 (-8.0, 4.6)
PFDI-SF20; UDI-6 Domain (0-100, higher=worse pain)[1]			
Baseline	N=48; 34.8 (22.6)	N=49; 37.9 (26.7)	
6 Month	N=38; 16.4 (17.5)	N=41; 17.2 (18.5)	0.5 (-8.9, 7.9)
12 Month	N=36 20.3 (17.5)	N=42 21.5 (25.3)	0.7 (-9.1, 10.4)
PFDI-SF20; Summary Score (0-300, higher=worse pain)[1]			
Baseline	N=48; 104.3 (62.8)	N=48; 107.0 (57.4)	
6 Month	N=38; 45.4 (43.8)	N=41; 45.0 (37.1)	0.6 (-18.4, 17.2)
12 Month	N=36 49.8 (44.1)	N=41 51.1 (47.7)	4.8 (-16.2, 25.8)

Table 18: Patient reported outcomes – PFIQ-7

	Vagifem N;Mean SD	No Treatment N; Mean (SD)	Difference between groups (95% CI)[3]
PFIQ-7; UIQ-7 Domain (0-100, higher=worse condition)[1]			
Baseline	N=50; 21.0 (25.8)	N=50; 21.5 (24.6)	
6 Month	N=38; 9.6 (21.7)	N=41; 5.9 (11.2)	1.3 (-6.9, 9.5)
12 Month	N=37; 8.9 (16.8)	N=42; 8.0 (13.9)	1.4 (-6.0, 8.8)
PFIQ-7; CRAIQ-7 Domain (0-100, higher=worse condition)[1]			
Baseline	N=50; 12.0 (21.0)	N=50; 8.7 (13.5)	
6 Month	N=38; 4.9 (13.1)	N=41; 2.4 (6.1)	1.6 (-2.5, 5.8)
12 Month	N=36; 4.5 (16.3)	N=42; 2.9 (6.1)	2.2 (-2.8, 7.1)
PFIQ-7; POPIQ-7 Domain (0-100, higher=worse condition)[1]			
Baseline	N=50; 17.7 (21.2)	N=50; 17.1 (22.1)	
6 Month	N=38; 5.0 (13.4)	N=41; 2.3 (6.1)	2.5 (-2.5, 7.5)
12 Month	N=36; 1.9 (6.8)	N=42; 1.7 (5.2)	0.2 (-2.7, 3.1)
PFIQ-7; Summary Score (0-300, higher=worse pain)[1]			
Baseline	N=50; 50.8 (54.8)	N=50; 47.3 (51.9)	
6 Month	N=38; 19.5 (39.8)	N=41; 10.7 (19.8)	6.2 (-8.7, 21.2)
12 Month	N=36; 14.3 (29.1)	N=42; 12.7 (18.3)	4.5 (-6.8, 15.8)

Table 19: Patient reported outcomes – PISQ-12

	Vagifem N; Mean (SD)	No Treatment N; Mean (SD)	Difference between groups (95% CI)[3]
PISQ-12 (0-48, higher=better sexual function)[2]			
Baseline	N=18; 31.2 (6.5)	N=19; 33.1 (7.3)	
6 Month	N=11; 33.1 (4.1)	N=14; 36.1 (5.7)	-2.4 (-7.0, 2.2)
12 Month	N=11; 34.5 (2.7)	N=10; 32.8 (5.1)	3.4 (0.6, 6.2)

[1]<0 indicates less pain/better condition failures with Vagifem
[2]>0 indicates better with Vagifem
[3]Differences are adjusted for baseline score and minimisation variables

Table 20: Patient reported outcomes – PGI-I

PGI-I		**Vagifem**	**No Treatment**	**Relative risk (95%CI)[3]**
6 Week		N=42	N=42	
1 = Very much better	N (%)	22 (52%)	14 (33%)	
2 = Much better	N (%)	16 (38%)	18 (43%)	
3 = A little better	N (%)	4 (10%)	8 (19%)	
4 = No change	N (%)	0 (-)	2 (5%)	
5 = A little worse	N (%)	0 (-)	0 (-)	
6 = Much Worse	N (%)	0 (-)	0 (-)	
7 = Very Much Worse	N (%)	0 (-)	0 (-)	
Better score[1]	N (%)	42 (100%)	40 (95%)	1.05 (0.98 – 1.12)
Worse score[2]	N (%)	0 (-)	2 (5%)	
6 Month		N=38	N=41	
1 = Very much better	N (%)	13 (34%)	18 (44%)	
2 = Much better	N (%)	16 (42%)	17 (41%)	
3 = A little better	N (%)	4 (11%)	5 (12%)	
4 = No change	N (%)	3 (8%)	0 (-)	
5 = A little worse	N (%)	2 (5%)	1 (2%)	
6 = Much Worse	N (%)	0 (-)	0 (-)	
7 = Very Much Worse	N (%)	0 (-)	0 (-)	
Better score[1]	N (%)	33 (87%)	40 (98%)	0.89 (0.78 – 1.02)
Worse score[2]	N (%)	5 (13%)	1 (2%)	
12 Month		N=37	N=42	

1 = Very much better	N (%)	14 (38%)	17 (40%)	
2 = Much better	N (%)	15 (41%)	17 (40%)	
3 = A little better	N (%)	3 (8%)	4 (10%)	
4 = No change	N (%)	4 (11%)	2 (5%)	
5 = A little worse	N (%)	1 (3%)	0 (-)	
6 = Much Worse	N (%)	0 (-)	2 (5%)	
7 = Very Much Worse	N (%)	0 (-)	0 (-)	
Better score[1]	N (%)	32 (86%)	38 (90%)	0.96 (0.81 – 1.12)
Worse score[2]	N (%)	5 (14%)	4 (10%)	

[1]Better score is derived from scores 1 (Very much better) and 3 (A little better)

[2]Worse score is derived from scores 4 (No change) to 7 (Very much worse)

[3]>0 indicates better with Vagifem

Clinical and patient-completed outcomes

Overall, scores from the PFDI-SF20 (POPDI-6 domain) were low at both 6 and 12 months, averaging 14.3 (SD: 16.4) and 15.6 (18.1) out of a maximum of 100, indicating a low level of prolapse-related symptoms (Table 17). Responses from the PFIQ-7 (POP-IQ-7 domain) and PISQ-12 were similarly low (Table 18 and 19 respectively). Scores appeared similar in both groups but with high levels of uncertainty, given the limited size of sample. The number of participants reporting being improved (very much better or better) on the PGI-I was 92% (73/79) at 6 months and 89% (70/79) at 12 months (Table 20). The number of participants with an objective evidence of prolapse failure (from POP-Q) at 6 months was 22/55 (40%) which were mostly grade 2 prolapse or less. Two repeat incontinence surgeries (Botulinum toxin injection) were recorded in the no treatment group over six months, with none in the oestrogen group.

Safety

More UTIs (8/42; 19% versus 4/42; 10%) resulting in antibiotics prescriptions (9/42; 21% versus 5/42; 12%) were reported in the 'no treatment' group than in the oestrogen group. Two serious adverse events were recorded in the oestrogen group - one woman with high temperature was admitted for intravenous antibiotics but culture of vaginal and urine samples were negative; another woman was diagnosed with leukaemia. Neither were thought to be related to treatment. Two incidental hospitalisations were also recorded in the 'no treatment' group (one case of heavy bleeding thought to be unrelated to surgery and another with pancreatic cancer). No concerns were expressed by the independent oversight committee who met halfway through the recruitment period to review the safety data.

Intra-operative observations

Table 21: Intra-operative theatre findings

		Vagifem (n=44)	**No Treatment (n=45)**
POP Surgery performed	Anterior Repair	35 (80%)	34 (76%)
	Posterior Repair	16 (36%)	19 (42%)
	Vaginal Hysterectomy +/- BSO	26 (59%)	25 (56%)
	Sacrospinous Fixation	6 (14%)	6 (13%)
Concomitant Surgery	Sling/TVT	1 (2%)	1 (2%)
	Botox	1 (2%)	1 (2%)
	Suprapublic Catheter	1 (2%)	1 (2%)
Ease of Dissection	Very easy	6 (14%)	5 (11%)
	Easy	22 (50%)	13 (29%)
	Normal	14 (%)	21 (47%)
	Difficult	2 (5%)	5 (11%)

	Very difficult	0 (-)	1 (2%)
Blood loss (g)	N; Median (IQR)	N=44 63 (50 - 125)	N=44 54 (50 - 100)
Visceral Injury	Bladder injury	0 (-)	0 (-)
	Urethral injury	0 (-)	0 (-)
	Ureteric injury	1 (2%)	0 (-)
	Bowel injury	0 (-)	0 (-)
	Button holing of vagina	3 (7%)	1 (2%)
Suture used – Fascial Plication[1]	Vicryl/Polysorb	10 (23%)	10 (22%)
	PDS	35 (80%)	34 (76%)
	Monocryl	0 (-)	0 (-)
	Missing	0	1
Suture used – Vagina[1]	Vicryl/Polysorb	41 (93%)	42 (93%)
	Vicryl Rapide	5 (11%)	6 (13%)
	Monocryl	3 (7%)	1 (2%)
	Vaginal Pack	23 (52%)	28 (62%)
Catheter in theatre	Yes	43 (98%)	42 (93%)
Post-operative complications noted before discharge	Infection	1 (2%)	3 (7%)
	Ureteric injury	0 (-)	0 (-)
	Bladder injury	0 (-)	0 (-)
	Bowel injury	0 (-)	0 (-)
	Vascular injury	0 (-)	0 (-)
	Neurological injury	0 (-)	0 (-)
	blood transfusion	0 (-)	0 (-)
	thromboembolism	0 (-)	0 (-)
	Death	0 (-)	0 (-)

Table 22: Post-operative Questionnaire completed by trial participants at 6 weeks and 6 months

		Vagifem pessary (n=42) N (%)	No treatment(n=42) N (%)
6 Week Post-operative			
Complications			
UTI		4 (10)	8 (19)
Vaginal infection		1 (2)	1 (2)
Secondary bleeding		0 (-)	2 (5)
Iron Therapy		0 (-)	0 (-)
Other Post-op complications[1]		7 (17)	12 (29)
Antibiotics prescribed		5 (12)	9 (21)
Antibiotics duration	3 Days	0 (-)	0 (-)
	5 Days	4 (80)	5 (56)
	7 Days	0 (-)	4 (44%)
	Other[2]	1 (20)	0 (-)
More than one course prescribed		1 (2)	2 (5)

	Vagifem pessary (n=28) N (%)	No Treatment (n=34) N (%)
6 Month Post-operative		
Repeat/incontinence surgery	0 (-)	2 (6)
Recurring vaginal infection	1 (4)	0 (-)

[1]Vagifem Group: Patient was admitted with a fever and unidentified source of infection; Patient had 4 courses of antibiotics due to UTI infection and an anaerobic infection. Patient has had to delay the start of her Vagifem as advised by her GP; irritable bladder; still feels a lump; hot sweats-stopped taking the Vagifem; Mild discharge; Vomited day one, post op stay 1 night.

No Treatment Group: Given wrong dosage of Warfarin, patient was treated and the dose brought down and patient feeling very well; Had a lot of pain; feeling sore since stitches came out; patient concerned that she can still feel a bulge.; patient was re-admitted due to bleeding heavily (4.03.2016-07.03.2016) & treated with antibiotics.; patient had a severe cold which after lots of coughing has caused her to have a prolapse, seeing a consultant at clinic; problems with bowels 3/52 after surgery; had blood tests and UTI test but no antibiotics prescribed; infection from stitches; none but the patient has mentioned that although she feels so much better she can feel a drop sensation; pains in stomach; stabbing pain below

[2]Vagifem Group: 4 Courses.

Discussion

In this open label randomised study we sought to examine the feasibility of randomising post-menopausal women undergoing POP surgery to receive vaginal oestrogen. Our four key feasibility indicators were met and we have shown that a large multicentre randomised controlled trial (RCT) is feasible. It is possible to randomise and follow up patients with high fidelity over at least 12 months. Oestrogen treatment in the form of vaginal pessaries was well tolerated and consistently applied by most women. As this was a feasibility study with an open-label design, no inferences can be made about the treatment's therapeutic efficacy. However, the data does suggest that further research is warranted. There was evidence that the majority of women in both trial groups did report improvement in their prolapse symptoms, aspects of urinary and sexual function as well as related Quality of life. The effect was sustained for at least the first six months after surgery irrespective of oestrogen treatment.

Among women planning to undergo surgical repair for prolapse, four studies have reported on preoperative vaginal oestrogen by various methods, compared with placebo or no treatment, with a total of 111 participants (12-14). Follow up varied from 12 weeks to three years postoperatively. No vaginal oestrogen was given following surgery. The overall quality of evidence was poor. Use of vaginal oestrogen improved the vaginal maturation index, a histological measure of the status of the vaginal epithelium, at the time of surgery and increased vaginal epithelial thickness (15). Vaginal oestrogen application for six weeks preoperatively increased synthesis of mature collagen and increased thickness of the vaginal wall, suggesting this intervention improves both the substrate for suture placement at the time of repair and maintenance of tissue integrity of the pelvic floor (15). Local oestrogen therapy plays an important role in the activation of immune system within the local vaginal

environment, limiting the undesirable ECM degradation, which supports the strengthening of vaginal ECM in post-menopausal women, therefore resisting menopause/age-related changes and inducing urogenital tract tissue regeneration (71). In our study, we did not monitor the vaginal maturation index but we did note that there were fewer UTIs observed in the group that received vaginal oestrogen pre-operatively although the study was not powered for this outcome. The clinicians reported easier planes of dissection in women in the intervention group.

Mikkelsen et al described the three-year postoperative outcomes after preoperative treatment with vaginal oestradiol or placebo tablets before POP repair (13). They included a questionnaire of patient satisfaction, but no standardised or validated metric of prolapse symptoms, discontinuation rates and reasons were reported. They suggested that if vaginal oestrogen does improve tissue integrity then therapy may need to be continued postoperatively until the time of complete scar maturation (13). There is no clear evidence to state how long when a women would have adequate scar maturation after a prolapse surgery as this could be dependent on various factors of wound healing. In the LOTUS study women in the intervention group continued oestrogen up to 20 weeks post- surgery. The overall improvement in symptoms was comparable at 6 and 12 months post surgery in the groups. The majority of participants undergoing prolapse surgery in both groups demonstrated improvements in prolapse symptoms (90%) at 12 months, indicating that the. The benefit of vaginal oestrogen may be marginal, with the majority of improvement in patient symptoms pertaining to surgery. This is hypothetical as there has been no RCT with long term follow up on these patients randomised to postoperative local oestrogen vs placebo or no treatment.

Surgical failures requiring repeat POP repairs on an average occur within 2 years after

primary surgery. The PROSPECT study reported that 2% (6/395 standard repair) repeat surgeries were required as early as 1 year after primary surgery and 5% (16/348 standard repair) repeat surgery within 2 years (72). The authors concluded that follow up of patients for a minimum of 5 years would be required to assess recurrence of symptoms following POP surgery (72). We need to consider the pros and cons of long term maintenance treatment with vaginal oestrogen in the intervention group in a definitive study including costs, compliance, plateauing of benefits and regression of changes on stopping the treatment. The potential outcomes measured in long-term studies could include recurrence rates, interval of recurrence of prolapse symptoms from index surgery, reduction in urinary tract symptoms, sustained QoL improvements and cost effectiveness analysis.

Despite the feasibility study running smoothly, there were aspects in the design, patient participation, dropouts post consent and randomisation. Twelve trial meetings took place during the recruitment, and more importantly during analysis phase with a couple of meetings to discuss planning of definitive trial after conclusion of the feasibility study. Conclusions drawn from these meetings suggested that a number of changes would be required to develop a fully functioning and successful trial design and protocol.

The feasibility study allowed the team to identify the problems within the trial as well as come up with solutions to resolve the potential issues. We based our decision-making process as per the ADePT Algorithm for Decision-making after Pilot and feasibility Trials (Figure 14 and Table 23).

Figure 14: Algorithm depicting the decision making process based on the findings from the LOTUS feasibility study based on the ADePT flow chart

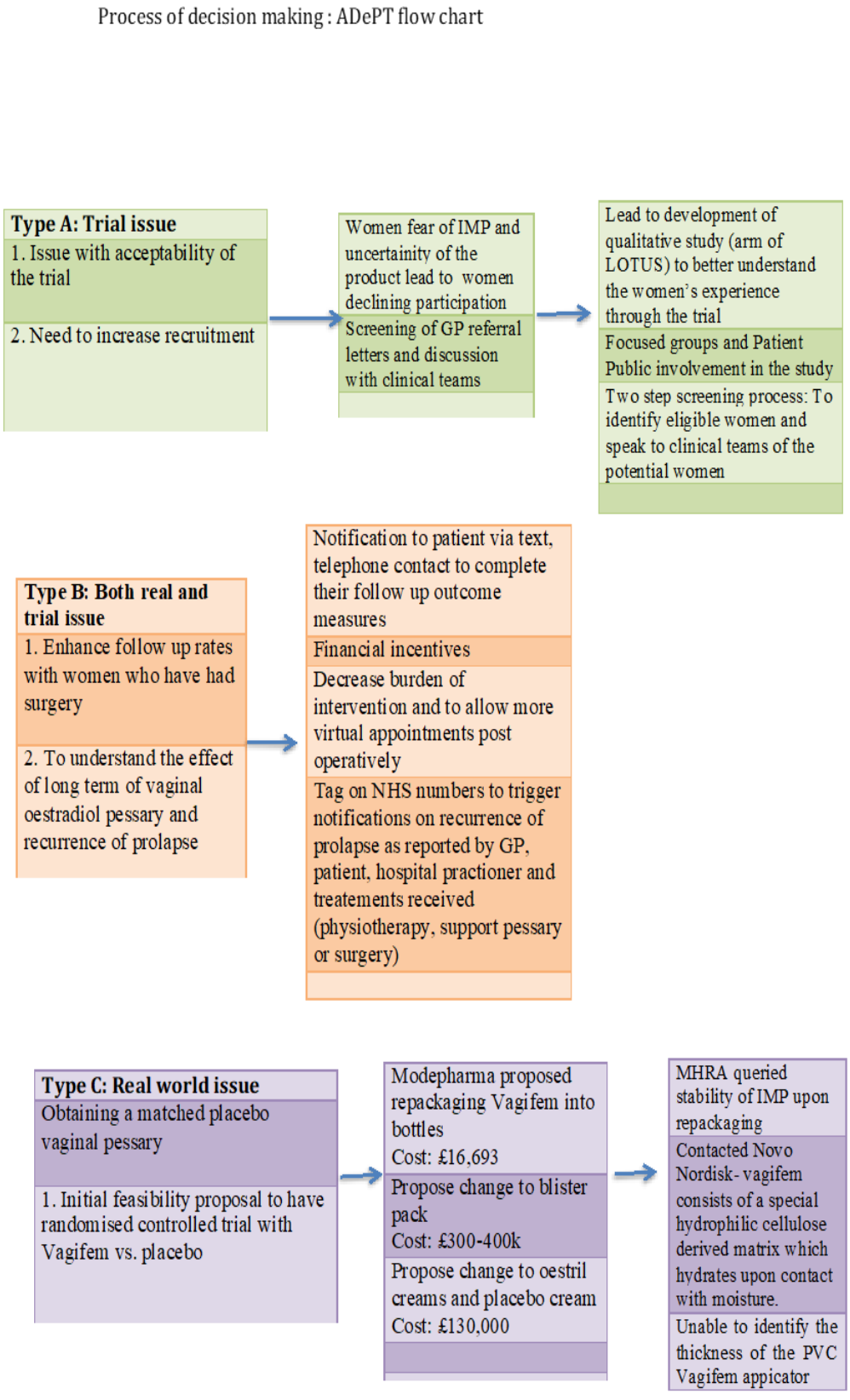

Table 23: Summary of findings from feasibility trial for designing definitive trial

	Methodological issues	**Findings**	**Evidence**
1.	Did the feasibility/pilot study allow a sample size calculation for the main trial?	Sample size: To detect a difference of 0.33SD (small to moderate effect size; approximately 8 points) in prolapse QoL score of the PFDI-SF20 with 90% power (p=0.05) will require 191 per group, 382 in total.	To allow for 10% who fail to have surgery post-randomisation and a further 20% loss to follow- up this will be inflated to a target of 532 women in total.
2.	What factors influenced eligibility and what proportion of those approached were eligible?	Screening of GP referral letters prior to women's attendance to clinic assisted in identifying eligible women. Clinicians input along with active research teams	325 women with POP and desiring surgery were screened for eligibility, with 157 found to be eligible (48%, 95%CI: 40%-56%)
3.	Was recruitment successful?	Yes	Recruiting sites were able to meet their targets on month
4.	Did eligible participants consent?	Yes	100/157 of these women (64%, 95%CI: 56%-72%) were randomised over a 13-month period (July 2015 to August 2016).
5.	Were participants successfully randomized and did randomization yield equality in groups?	Yes	Minimisation was used to achieve balance between age (<65 years or ≥65 years), parity (<=2, >2 vaginal births), maximum stage of prolapse (I, II or III/IV) and whether a concomitant continence surgery was performed
6.	Were blinding procedures adequate?	Difficult to blind as it was open labelled trial. The statistician	Blinding procedure could only be enhanced with

		was blinded. In order to enhance blinding procedure we endeavoured for women to be examined by an independent clinician post operatively.	presence of placebo.
7.	Did participants adhere to the intervention?	Yes	32/41 (78%), 34/41 (83%) and 21/27 (78%) of those allocated oestrogen pessaries reported good compliance with treatment (taking treatment as advised at least >=75% of the time) pre-operatively, at six weeks and six months respectively.
8.	Was the intervention acceptable to the participants?	Yes	Interviewed participants had a positive experience reporting that they felt well informed by trial staff about the trial. The consent process was undertaken well and patients felt reassured by explanations of randomisation. The main aspect of the trial that may benefit a revisit are the questionnaires, as a number of patients found that the format repetitive and lengthy. Qualitative analysis identified themes motivating women e.g. altruism, clear and transparent information, potential health benefit. Among those who declined participation themes were: lack of time, uncertainty, dependant on others due to age

9.	Was it possible to calculate intervention costs and duration?	Yes	Various models of intervention costs and duration were proposed to the funding body involving the help of various pharmaceuticals.
10.	Were outcome assessments completed?	Yes	Of the 85 participants who had surgery, 85/85 (100%) had completed intraoperative forms and 83/85 (98%) completed post-operative forms at six weeks. Only minor discrepancies in their completion were noted by the trial team.
11.	Were outcomes measured those that were the most appropriate outcomes?	Yes	The pooled (over both groups) standard deviation of the PFDI-SF20 POPDI-6 domain at six months was: 16.4 points (95%CI: 11.0 – 18.5).
12.	Was retention to the study good?	Yes	77/100 (77%) six-month follow-up questionnaires were returned. Of those that had surgery, this equated to 77/85 (91%).
13.	Were the logistics of running a multicenter trial assessed?	Yes	Multiple Trial management meetings along with Independent oversight committee took place throughout the feasibility study process to check and assess the logistics of running the trial
14.	Did all components of the protocol work together?	Yes	The objectives of the feasibility study were met within the time frames proposed.

The problems that pertained mainly to the trial are the following:

1) Identification of a matched placebo

2) In order to assess the recurrence rates after POP and effect of oestrogen - discussion revolved around what would be the ideal number of years of follow up following primary surgery

3) Identification of whether and which subjective or objective outcomes would be best to infer satisfaction or improvement after surgery

4) Identification of a process that would involve primary care to participate within the definitive study and prescribe oestrogen via GPs

5) Training recruiting centres on POP -Q assessment in order to improve uniformity in the objective reporting

The problems involving mainly trial and real world issues are the following:

1) In the feasibility study we found that there were significant dropouts post pre-assessment of potential patients for surgery

2) Multiple appointments post surgery was potentially leading to high drop out

Strengths

This feasibility study was conducted over a period of 13 months during which the trial achieved its target recruitment of 100 women from 6 centres in the UK. The study

efficiently met all their target criteria within the given time frame and showed that a substantial trial will be achievable.

We were able to capture patient responses by using validated PROMs such as the PFDI - SF20, PFIQ7 and PSIQ 12. The feasibility study has been reported in line with the CONSORT reporting guideline for feasibility/ pilot studies. It has allowed the trial team to identify areas in the study process that require fine-tuning ahead of a larger trial. We are considering long term follow up of participants for a minimum of 5 years in order to capture the recurrence rates and relapse of POP symptoms after index surgery. In addition, we are considering offering participants in the intervention group to continue with long-term maintenance therapy with vaginal oestrogen.

Limitations

Ideally, we would have liked to conduct a RCT comparing vaginal oestrogen with a placebo pessary. All of the symptom related outcome measures are patient-completed and potentially prone to reporting bias if the participant is aware of the treatment allocation. However, despite extensive discussions with clinical trial suppliers, we were unable to procure a placebo without it being prohibitively expensive. Oestrogen pessaries are supplied in individually packaged, single-use plastic applicators, which cannot be replicated with a placebo due to the trademark on the packaging. Disassembling the pessary from the applicator to repackage in an unbranded applicator and container would require additional stability testing to confirm the bioavailability of the oestradiol hemihydrate. The manufacturer of Vagifem, Novo Nordisk, declined to provide assistance. Oestradiol is also available as a cream, and a placebo cream could be procured, but the acceptability and adherence to a cream as the route of treatment was not evaluated in this pilot and we should not extrapolate adherence based on pessaries. There is some evidence from a trial of vaginal pessary versus cream for atrophy which suggested that significantly more patients who were

using the vaginal tablets rated their medication favorably than did patients who were using the vaginal cream ($p \leq 0.001$). Patients who were receiving the vaginal tablets also had a lower incidence of patient withdrawal (10% versus 32%) (73).

A few patients post randomisation could not undergo surgery as they were deemed to be unfit. To avoid this from happening, the patients could have undergone pre-operative assessments to determine surgical and anaesthetic risk and randomised once they were scheduled for surgery. We could potentially have sent telephone, email or text reminders to the participants to improve compliance with the post-operative pessary use but besides being expensive it will not reflect a real-life situation.

CHAPTER FIVE: WILLINGNESS OF POSTMENOPAUSAL WOMEN TO PARTICIPATE IN A STUDY INVOLVING LOCAL VAGINAL OESTROGEN TREATMENT AS AN ADJUNCT TO PELVIC ORGAN PROLAPSE SURGERY: A QUALITATIVE STUDY

Published article

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ORIGINAL ARTICLE

Willingness of postmenopausal women to participate in a study involving local vaginal oestrogen treatment as an adjunct to pelvic organ prolapse surgery: a qualitative study

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Abstract

Background Pelvic organ prolapse (POP) negatively affects many women's quality of life. The ability to develop improved therapeutic approaches for POP patients is hampered by low patient recruitment and retention rates in clinical trials.

Objective Our objective was to explore the motivational factors and barriers to recruitment and participation in clinical trials among postmenopausal women with POP who are intending to have surgical management.

Design Qualitative study based on in-depth face-to-face interviews with postmenopausal women attending urogynaecology clinics in the UK intending to have surgical management for pelvic organ prolapse. These women were eligible to participate intheon-goingclinicaltrialontheuseoflocalvaginaloestrogenasanadjuncttosurgicaltreatment.Twenty-twopostmenopausal women aged 52–76 years were interviewed. Interviews were analysed using thematic analysis method.

Results Many women participated because of altruistic motivations; however, we found that clarity of information provided, timing of approach and acceptability of study design played a pivotal role in women. Of the women who declined participation, the following themes emerged: uncertainty of the investigational product, fear of experimentation, logistical concerns and regret that their condition was trivialised at an early stage.

Conclusion We have gained a valuable insight into women's views and experience in the decision making process. Understanding the elements that will enhance trial participation such as clarity of information provided, balance between professional guidance whilst maintaining equipoise, easy access to trial teams and timing of approach will ultimately enable us to improve our recruitment to clinical trials.

Keywords Postmenopausalwomen.Oestrogen.Qualitativedesign

Introduction

Pelvic organ prolapse is a chronic condition affecting millions of women. The condition negatively impacts on their quality of life through effects on their urinary and bowel symptoms, body image and chronic backache [1]. The severity of symptoms is not, however, correlated with the level of POP. Women are offered varied treatment options from expectant, conservative and surgical management.

One of the main recommendations of the UK government Life Science Strategy was for the National Health services (NHS) to respond to the growing readiness of patients to participate in research studies [2]. The strategy recommended researchers to respond to patient choices to enhance participation within a trial. However, there is extensive evidence from the NHS acute hospital sector that poor patient recruitment or retention of patients to clinical researchiswidespread, leading

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NHS Research Ethics Committee (NRES Committee West Midlands, REC number 15/WM/0092)

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to delays in commencement or completion of both academic and commercially funded research [3]. This results in wastage of public resources and opportunities for patient participation.

We performed a study to assess the feasibility of patient screeningandrecruitmentprocesstostudytheeffectivenessof Local Oestrogen Treatment in Postmenopausal Women Undergoing Pelvic Organ Prolapse Surgery (LOTUS) https://doi.org/10.1186/ISRCTN46661996. This study was in preparation for a large definitive randomised controlled study to determine whether pre- and postoperative local oestrogen treatment is more effective in improving prolapse- related patient-reported outcomes and reducing recurrence of prolapse symptoms when compared to no treatment.

The research team identified the women eligible to participate in the feasibility trial by screening the GP referral letters. Potential eligible women were sent patient information leaf- lets before the clinic appointments in order to give the women an opportunity to consider participation in the clinical trial. The trial team comprised of a research fellow, research nurses and urogynaecologist from district and tertiary hospitals acrosstheUK.Onceeligibilitywasreconfirmed,womenwere given sufficient time to obtain informed written consent and collect baseline data. Randomisation was performed using a web-based central randomisation system (via Birmingham Clinical Trials Unit) to allocate patients to either oestrogen or no treatment in a 1:1 ratio. Minimisation was used to achieve balance between age (< 65 years or ≥ 65 years), parity (≤ 2 or>2 vaginal births) and maximum stage of prolapse (I, II or III/IV).

Women allocated to oestrogen (oestradiol hemihydrate 10 mcg vaginal pessaries; Vagifem™, Novo Nordisk) were instructed to use the oestrogen pessaries 6 weeks prior to surgery(oncedailyfor2weeksandtwiceweeklyfor4weeks)up to the night before surgery. Treatment was restarted 6 weeks postoperatively, administering twice weekly for 20 weeks. Women were encouraged to insert the pessaries into the vagi- na at the same time of day. However, if a dose was missed, patients were advised it should be administered as soon as possible thereafter, provided the next dose was not due. Participants allocated no treatment received the usual care of the randomising centre. The surgical approach to POP repair was at the discretion of the urogynaecological surgeon. The researchersconductingthequalitativeinterviewswereblinded to the participant's intervention allocation within the study.

Approximately quarter of women opt for surgical repair of POP [4]. There are few studies seeking to explore the experienceofpostmenopausal womenwithPOPplanning onundergoing surgical repair. Therefore, alongside the LOTUS feasibility study, we undertook a qualitative study with the objectiveofexploringthefactorsthatmotivatethisgroupofwomen to participate in clinical trials. Some women see POP as a sensitive and embarrassing condition; therefore, to prepare for our planned future trial, we aimed to identify barriers to recruitmentandparticipationinclinicaltrialsamongpostmenopausal women with pelvic organ prolapse intending to have surgical management.

Methods

We conducted semi-structured, in-depth, audio-recorded interviews with postmenopausal women eligible to participate in the LOTUS study (Table 1). Interviews were conducted from October 2015 until July 2016 from Birmingham Women's and Children's NHS Foundation Trust. The research team proposed a priori sample size at the time of initial proposal of ten interviews with a further stopping criterion of five interviews. The essence of these interviews was to obtain information and shared beliefs until data saturation was achieved [5–8]. The research team ultimately interviewed 22 women individually. Along with this a focused group interview (10 women) was used to expand on and verify the emerging themes from individual themes.

Of the 22 women interviewed, 7 who had initially declined participation in the LOTUS trial were willing to take part in the qualitative arm ofthe study.Participationinthe qualitative arm of the study was purely voluntary among those who participated or declined participation in the LOTUS trial. The study aimed for a diverse, maximum variation sample of participants. Participants were sent a patient information sheet, had the study explained to them and signed a consent form beforetheinterview.Thewomenwhoconsentedtoparticipate in the qualitative arm of the study were given the choice of placewheretheywouldprefertohavetheinterviewinorderto make sure that the women were most comfortable and free to voice their thoughts. Women were interviewed in informal non-clinical settings such as quiet rooms in hospitals or at the comfort of their own homes via teleconference sessions. This allowed the women to chose the most convenient time and place; therefore, they never felt pressured or rushed. The interview had two parts:

- An unstructured narrative section, in which participants wereasked totell their own story with aslittleinterruption as possible, to capture their own accounts of their experience with POP, what brought them to the hospital and aspects of the trial that they felt were important to them.
- A series of prompts, used by the interviewer to explore particular issues further in a semi-structured part of the interview

The interviews lasted 45 to 90 min each. The interviews weretranscribedverbatimandanalysedthematicallyusingthe organisational support of NVivo 10 software. Transcripts were read and re-read carefully by the interviewer, and a coding framework was developed. A second researcher checked

Table 1 Qualitative Interview guide

Regarding pelvic organ prolapse	When did you first start experiencing symptoms of prolapse?
	• How did it affect your day-to-day life?
	• What did you understand about prolapse
	• When were you diagnosed?
	• How did you feel about the diagnosis?
	• Did you try another treatment?
	Tell me about your experiences of usingpessaries/ physiotherapy for prolapse
	• How effective was this treatment?
Views on Medical Trials [General]	What do you think about medical trial?
	• for individuals?
	• for medical science?
	What do you think about randomisation?
	• Understandings of randomisation/how treatment is allocated
	• Is randomisation acceptable to you?
	• Is the possibility of not getting treatment acceptable?
Views on participation in LOTUS study	What are your thoughts about the trial?
	• NB: Expand into an open-ended discussion about the
	trial ° Hopes for the trial
	° Concerns about the trial
	What would motivate/motivated you to take part in the trial? What would you hope to get out of participating in this study?
	What are your main concerns about participating in the trial?
	• What would be a barrier to you
	participating? ° Personal factors?
	• Past experiences with treatments or trials
	• Time or travel
	costs ° Trial factors?
	• Concerns about treatment availability
	• Concerns about treatment choice and randomisation
	What did you think about the study after reading the patient information leaflet for the study?
	° Did you feel the leaflet gave you enough information?
Experiences of hormone replacement treatment (HRT)	What do you understand by HRT:
	• Have you used HRT before? For how long?
	• Do you have any concerns regarding HRT?
	• Have usedoestrogenpessaries or creams in thepast?Whichwould you prefer to use?

the transcripts (LL) and independently coded the first few interviews; results were compared and discussed. The coding framework was revised and further developed. A qualitative interpretativeapproachwasutilised,combiningthematicanal- with constant comparison continuously looking for anticipatedandemergentthemes[6,7].Fieldnotesweremadeafter every interview process in order for the interviewer to capture theunderstandingandbodylanguageaspectsofpatientduring the interview when talking on certain aspects of the condition and the trial. A modified grounded theory approach using the "one sheet of paper" method ensured that all the coded ex- tracts within the theme were included and compared in the analysis.Theapproachensuredthateveryinstanceandnuance was considered importantly including deviant cases. Qualitative data collection and analysis often proceed iteratively to achieve data saturation, with analytic categories saturated when data from new interviews do not add any more to the analysis [6, 7].

Results

Twenty-two women with symptomatic POP were recruited for the qualitative study. Symptomatic POP was defined as

presence of a vaginal bulge and/or other symptoms from the bladder orbowel.The womenwereassessedusingthe POP-Q classification system [9]. Recruitment was according to purposive sampling, i.e., the greatest variation of characteristics such as age, parity, BMI and stage of prolapse in order to capture wide narratives from the informants (Table 2). The results are summarised in Table 3.

Factors that facilitated recruitment

Theme 1: probably help another woman

Themajorityofwomenwhowereapproachedtoparticipatein the LOTUS trial were willing, as they wanted to help other women and hoped that their contribution and/or participation would help other women in their similar situation. Interestingly, it was the group of women who had struggled for many years with prolapse who readily wanted to participate rather than those who received a new diagnosis. The women who declined regretted that they did not request to be seen at tertiary care earlier and felt that primary care did not offer them much help with their symptoms.

P3: As I sat in the waiting room just looking at the trial poster and after reading through the leaflet, there was this inclining in me to participate, I have had just enough with my symptoms, if I can participate in this trial and if it would help another woman I would be really happy.

P5: I'm retired now and I have participated in other trials and I think thisstudy reallymakes sense,I think thiswill make a change for the future generation.

P6: I am 76 years old and suffered with a prolapse for so manyyears,Iknowageingis aprocessandhavingaprolapse may be part of it, but I think more women should talk about it…These are present day problems and studies like this will startconversations,whichIthinkisessential.Youdonotoften hear women's hour talking about vaginal prolapse (laughs). Yes, I would definitely take part, I hope the study triggers women to talk more about vaginal prolapse, this should help.

P11: I wish I did not carry on with these pelvic exercises, now the gynaecologist offers me surgery. There should be some time limits in place. My doctor examined me once and nofurther,perhapsIcouldhaveavoidedsurgery!Iratherjust get on have surgery with no further delays in my treatment.

Theme 2: Easy to understand protocol and research team accessibility

This study reinforces that clear and easy to understand protocols playeda vital roleinencouragingwomentoparticipate in the study. Reading and understanding a study consent form has been shown to be critical to enrolment in a trial. The women within the study felt that they had the ability to access the trial team at any point during the study and felt reassured. This was a safety net that many of them felt convinced would help them through the process without just becoming a trial number to the research. Many felt that interaction between themselves and the trial team gave them the confidence to complete the trial from start to end.

P12: I received the leaflet prior to me coming for my appointment; it was quite straightforward and simple. I had a few questions, which the researcher answered for me.

P10: The clinician made it very easy for me to understand the process; we had a really long chat. I was able to make my

Table 2 Background characteristics of participants

Characteristics of participants	Total
Age	
	< 65 years
	≥ 65 years
Ethnic group	White
	Asian
	Black
	Mixed
Parity	≤ 2
	> 2
BMI (mg/kg²)	Mean (SD)
Maximum stage of prolapse	Stage I
	Stage II
	Stage III/IV
Marital status	Married
	Single
	Widow
Occupation	Employed
	Retired

Table 3 Summary of results

Facilitating factors to recruitment	Barriers to recruitment
Altruism	Uncertainty of treatment proposed
Simplicity of trial protocol	Logistical factors—number of clinic appointments, parking charges,transport dependence, leave from work
Clear and succinct patient information leaflets	False perception of delay in receiving treatment if participates in clinical trial
Easy accessibility to research teams via contact telephone numbers and email addresses	Time constraints for patients
Activeclinicianinputandcollaborationwithtrial units	Trivialisation of condition by primary care
Screening GP referral forms prior to clinic appointments	
Sending information leaflets to potential participants before the clinic appointment	

and access to research team. These women felt part of the research team that shaped the study from a patient's point of view. This even led two of participants becoming part of the patient and public involvement (PPI) group.

Theme 3: Senior clinician input and collaboration between the research and clinical teams

The recruitment process itself is often complex and involves several linked activities performed by clinical and research staff within and between different centres. We found that the women who participated in the trial felt that input from the clinicians gave them a security and confidence in enrolling in a randomised control study.

P20: I found that talking to the clinician made be more confident in the trial. She seemed to explain the ins and outs ofthistrial.Shehelpedunderstandwhattheywerelookingfor and why they were conducting the clinical trial. I trust the clinical team; I mean they were the ones that took my symptoms seriously and I am finally being offered some kind of surgery.

P15: The clinician really understood my condition; she explainedwhatwashappeningandthereasonwhyIamprobably having these symptoms. I guess this oestrogen might help; that's if I get that and if not then I am only being offered what the rest the women with my condition are receiving on the NHS.

Two-step approach

The researchers in this study screened the GP referral letters and were able to identify potential women who could be invited to participate in the study. The potential women were sent patient information leaflets prior to them attending their clinic appointments. This process assisted in preparing women regarding the clinical discussion and the clinical trial.

P2: I received a leaflet along with my clinic letter; I was able to read through this prior to me attending this appointment. This leaflet was quite helpful and I was able to identify many of my symptoms from just reading the leaflet. I felt more confident; I knew I was attending the right clinic. I did read about the trial as well; I was able to chat with my husband about the study and ask a few more questions to the clinician regarding it.

P7: I think this method of sending the details about the study is helpful; it really saves time. I had time to think about the study and I was able to make up my mind regarding participation.

P14:IhadloadsofquestionsbeforeImetthedoctor,Ieven wrote my queries on the leaflet. You need the time to think about these things.

P17: I knew I was in the right place, I took my time deciding whether I should participate. I read the information and spoke to the clinician. I went home and then after discussing with my family, I was able to contact the trial team and informed them that I wanted to participate. I think it's easier to make up your mind when you are in your own home. Loads of things went through my head when I was in clinic. We talked about so many things, the surgery and the study.

Barriers to recruitment

Theme 4: Uncertainty

Themajorbarriertothisstudywastheuncertaintyofthestudy product. The women who declined participation expressed that they had a fear of experimentation and were concerned of developing cancer. The number of discrepancies regarding hormone replacement therapy fuelled this uncertainty. Participants felt that their GPs were not confident in prescribing long-term hormone replacement therapy. Few participants did not like to be "a guniea pig" inthe process of the trial. The

conflictinginformationthattheyhavereceivedinthepastwith regard to HRT made them worry about participation.

P14: I am not sure about hormone replacement; I had spoken with my GP on a previous occasion regarding taking oestrogen replacement and he did not want me to have therapy for long term.

P10: I worry about developing cancer; I know this is a low dose but who knows? Why would you want to put yourself in such a position?

P3: This is conflicting information; you hear about the ill effects of HRT and its relation with cancers like breast. I am here for is being described as a chronic problem; if the surgery can fix my prolapse why would I take any other medication? I would be quite anxious of developing any side effects.

Theme 5:Logistic factors

There were various logistical factors that were highlighted by the women who feltthatinhibitedthemfor participatinginthe trial.

P20: Coming to clinic appointments are really very difficult for me; I need my daughter to be available to bring me to the clinic appointments. I do not want to be more of a burden to her. I guess the lesser appointments the better.

P16: The parking charges in this hospital are really ridiculous; I mean if I participate it would mean that I would probablybeherelongerandifparticipationwouldwavethese charges perhaps I would consider participating.

P14: So many clinic appointments; I think the lesser time I am at the hospital the better! I think I am always in the hospital and lesser at home (laughs).

P17:I needtobethereformyhusband;heneeds roundthe clock care. I would not have come to this clinic; it has only been because I started to have some bleeding that I did come to this appointment. I would have just continued to ignore my symptoms otherwise. I do not think I can possibly participate at this point in my life; there is just too much going on.

Theme 6: Time between intervention and surgery

As per the study protocol, after randomisation participants in the intervention arm were requested to commence medication for a period of 6 weeks prior to their surgery. Some of the women who were approached felt that they did not want to wait for approximately 6–8 weeks for surgery. These women perceived that time between commencing the investigational product and surgery was a delaying factor and thought this would disadvantage them on the waiting list for surgery.

P6: I was told that I require surgery; I do not want to wait for another 2 months until I have surgery.

P15: I have put with these symptoms far too long, I would just like to get on and have the surgery now. I think I have postponedmytreatmentfartoolong; I thinkifI doparticipate I will just be delaying the process.

Theme 7: Trivialisation of the condition

During the interview process, many women voiced their thoughts regarding their condition and symptoms. Deprioritisation of their own symptoms for several years before they presented to medical team was recognised as a theme among the women. Some felt embarrassed to come forward while others feltregret for leaving their symptoms for solong. Interestingly, some women were not self-aware of the worsening of their condition. They were not sure what impact prolapse could have on their bladder or bowel. The recognition of these worsening symptoms would assist the women and their GPs for a referral to tertiary care.

P4: I went tomyGPyears agoandatthatpointshe didnot say that my prolapse would worsen; all she said was to do pelvicfloorexercise.Ithinkdoctorshavebeentellingmetodo this since I had my son nearly 30 years ago. I did not realise I would need a surgery.

P8: Ialwayshadsymptomsofprolapseandinfact I wasso embarrassed; I avoided going to the gym I was so worried I would leak or others could notice my prolapse. Everyone said it was part of ageing process…maybe I should have gone to the doctor earlier.

P10: I am so irritated I always kept voicing my concern with my GP. I do not think any one examined me in the past. Now I am being told that I would require surgery. I just want to get the surgery over with. I wish some had paid more attention to my symptoms earlier.

The initial and emerging codes have been complied in Table 4.

Discussion

We have sought to produce an understanding of 22 individuals with POP and their experience within the trial and their decisions making process as to what compelled them to take part or refuse participation in the trial. We have demonstrated that there was considerable variation among our participants, but there were some strong common themes as well without downplaying the uniqueness of each person's view.

This study has helped us to understand factors that would be likely to motivate or detract from patient participation and retention within our planned trial. The factors that we identified were part of procedural, communication and resource issues. The minimum contact must have a very specific structure and the research team must follow the structured guidelines until the woman feels sufficiently comfortable. There must be a minimum adherence plan for the entire multicentre clinical trial in the developmental stages of the trial [10].

Table 4 Coding index

Themes	Initial categories
Clarity in information	Trial teams gave maximum information
	Individualised their concerns
	Easy to understand
	Not very complex patient information leaflet
	Faith in clinical teams
	Co-ordination between clinical and research teams
Timing of approach and environment	Two step approach
	Given enough time
	Ability to contact trial teams
	Easier to make a decision at home
	Dedicated clinics for the trial purposes
	Opportunities to ask questions
Acceptability of study design	Understand the process of randomisation
	Recall the design
	Understand and maintain equipoise
Uncertainty	Fear of cancer
	Varied information online
	Unpredictable outcomes
	Concerns of side effects
Logistical concerns	Dependent on family and friends
	No monetary incentives
	Timing between intervention and surgery
	Other co-morbidities
	Multiple appointments
Trivialisation	Let down by clinical team
	Prioritising other family issues over symptoms
	Carer for family members
	Embarrassed by the condition/ symptoms
	Ageing process

During the trial, researchers should be perceptive to the feedback and information received from patients at the time of recruitment. Despite numerous strategies present in the literature, gaps remain. Gul and Ali [11] identified that the majorityofrecommendedinterventionsforenhancingtherecruitment and in clinical studies are 'piecemeal' and take little account of how local practices of recruitment work influence the effectiveness of such interventions [11].

Taking part in research is a complex decision. Multiple factors play a role in decision-making. Altruism may have existed in many participants and is seen across all clinical studies [12]; however, in this group there was also an element of their symptoms finally receiving recognition and acknowledgement of a problem, which was ultimately taken seriously when they enrolled into the trial. The majority felt that their symptoms had been trivialised in the past. They voiced the need for forums for women to talk openly about POP and welcomed research in this area. Prolapse symptoms hindered their quality of life and with an ageing population, there are necessities to not only prolong life expectancy but equally importance to quality of life. Participants experienced barriers to trial participation including additional demands such as attendingappointmentsandassociatedtime,effortorfinancial costs, discomfort associated with trial procedures, the risk of not being allocated to their preferred treatment and uncertain outcomes. Likewise, Fogel et al. reported burdens including potential side effects from treatment, additional tests that would have to be endured, financial concerns (including loss ofjobsupport andworkdisruption)anda general worryabout the unknown future, including whether or not the study drug assigned would be beneficial [13, 14]. Sometimes patients are not presented with a clear rationale for why their participation is important and receive minimal feedback.

Women who received the leaflets prior to coming to their designated clinic appointment found it easier to make their decision on trial participation. This two-step approach of

screening potential participants and sending out information to the women prior to as well as having dedicated clinics for potential participants gave the optimum time for women to think over their options [15]. Screening patient records, identifying eligible patients, preparing recruitment material and ensuring that the relevant clinicians were informed about the study, were useful strategies practised by the research teams. Similar strategies are echoed in various other clinical trials as well [16, 17]. Chhatre et al. found that contacting potential participant prior to clinical appointment helped streamline therecruitmentprocess[18].Furthermore,aneasilyaccessible research team and the quality ofinformation provided tothese patients gave the women an added confidence not only with the clinician but with the research team as well.

The practicalities and co-ordination of balanced information provision for patients about both treatments can be challenging. Clinicians may be comfortable explaining interventionstheyroutinelydeliverbuttheymaywellbelessconfident conveying the effectiveness of treatments outside their specialist remit. However, the research team were able to maintain equipoise better than the clinicians in informing patients of the treatment choices. The research team at several points had anxiety regarding the eligibility of women into the study.

In the LOTUS trial there were a few patients who were flagged at multi-disciplinary team (MDT) meetings as potentiallyeligible for the trial.These decisions were sharedbetween the clinical and research team and this assisted in giving the research team confidence in having an open conversation with the potential participant. The research team were given training and assisted by clinicians to provide similar clinical message to all involved participants through their journey in the trial. Clinicians who maintained ongoing involvement with clinical studies and positive relationship with the research staff and accessiblity to the participants generated trust and together helped the recruitment and retention efforts. Studies report that up to 76% of patients expected their physician to alert them about appropriate clinical trials and that physician referral was one of the most useful recruitment strategy [19, 20].

This team approach enhanced the patient's final understanding of the study as well maintaining equipoise and therefore ultimately increasing the likelihood of participation and randomisation [21]. Similar MDT meetings are in practise in cancer studies and they have found similar results [22].

Strengths

This is one of the few urogynaecology studies that looked at the complexities in decision-making in women with prolapse priortoembarkingonclinicaltrials.Thestudyhasbroughtout themes that are relevant when planning studies for POP. We were able to identify the factors that facilitate and detract women from participation. We gained insight into the women's experience and thereby were able to tailor the consenting process. It highlighted the individual differences and the desire for information.

The suggestions voiced by the participants were taken into consideration and helped in framing a definitive trial that was more patient friendly. Two of the women agreed to be part of the patient and public involvement group for the proposed definitive trial.

Limitations

The views obtained from a small cohort of women who participated in the LOTUS trial. We obtained saturation with a small sample size. However, the research teams did explore and ultimately interviewed 22 women individually and a focused group interview to ensure and verify the emerging themes from individual themes. We do acknowledge there were other women in the trial who participated who may have had unique views and reasons for participation in the trial. In addition it is always challenging to distinguish between various personality types. The study was open label and therefore this could have influenced patient's experience through the trial process. Some of the themes that emerged were limited to the trial itself and certain elements may not be transferrable outside this setting.

Conclusion

The benefits of RCTs have been universally appreciated. However, RCTs need to be more sensitive to women's views and understanding of their trial journey.

From this qualitative study, the researchers found that factors that enhanced participation were maintenance of simplicity in patient leaflets, easy accessibility to research teams and providing clarity in information disseminated, devoid of medical jargon. The barriers to recruitment were uncertainty regarding the investigational product, logistical elements such as physically attending multiple appointments, time constraintsand false patient perceptionofdelay inreceiving treatment if participating in a clinical trial.

Thesethemesidentifiedinthisstudywillhelpshapeamore efficient and productive definitive study. For successful completion ofclinicaltrials, futurevaginal prolapsestudies should design their trials keeping the woman's point of view as paramount importance.

Author participation TS Verghese: Project development, Data collection, Manuscript writing.
A Merriel: Manuscript editing.
L Leighton: Data collection.
P Latthe: Project lead, manuscript edition.

Compliance with ethical standards

Conflict of interest None.

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CHAPTER SIX: PROPOSED DEFINITIVE PROTOCOL FOR LOCAL OESTROGEN TREATMENT IN POSTMENOPAUSAL WOMEN UNDERGOING PELVIC ORGAN PROLAPSE SURGERY (LOTUS) II

LOTUS II

PROTOCOL

QUESTION	Does vaginal oestrogen treatment of postmenopausal women undergoing pelvic floor repair surgery lead to improved patient reported outcomes in relation to urinary, bowel, sexual function and prolapse related quality of life (QoL)?
CONSIDERED FOR ENTRY	Postmenopausal women who are going to have prolapse surgery for pelvic organ prolapse
STUDY ENTRY	Eligible and consenting women having prolapse surgery will be studied. Consent will be obtained from women after

	written and oral information has been provided.
INTERVENTIONS	Intervention: 6 weeks course of 10µg oestradiol preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then 10µg oestradiol per vaginum twice weekly from 6-52weeks postoperatively. Comparison: no vaginal oestrogen treatment
OUTCOME ASSESSMENT	Primary outcome: prolapse related quality of life (QoL) at 12 months, as assessed by Pelvic Floor Distress Inventory Short Form 20 (PFDI-SF20).
CO-ORDINATION	**Local**: by local lead Gynaecologist and Research Nurse. **Central**: by Study Office in Birmingham **Overall**: by the Project Management Group and overseen by the Steering Committee and the Data Monitoring Committee.
FUNDING	To be submitted to funding body

Summary

Pelvic Organ Prolapse is the bulging or dropping of any pelvic organs (bladder, uterus, bowel) into the vagina. Prolapse is a common gynaecological condition caused by weakening of the supporting tissues of the pelvic floor, especially in women after the menopause. Prolapse operations may include vaginal hysterectomy (removal of the womb vaginally) or pelvic floor repair (tightening of the front or back wall of the vagina or support the top of vagina). Hormone replacement might improve the condition of the vaginal wall and help strengthen the pelvic floor, reducing complications of surgery e.g., water infections and improving the quality of the surgical repair. Postmenopausal women with vaginal dryness are sometimes treated with oestrogen in the form of tablets (pessaries) or cream they insert into the vagina. However, it's not known whether vaginal application of oestrogen might reduce complications during operations for prolapse and improve long-term postoperative outcomes.

The aim of our study is to establish whether treatment with vaginal oestrogen, before and after prolapse repair surgery, improves prolapse-related quality of life (QoL) at two years following surgery.

We propose a randomised clinical trial of 532 women, half of whom would receive oestrogen vaginal pessaries and half who would get no medication. The allocation will be at random by computer. All women in the treatment arm would be given vaginal oestrogen pessary with disposable applicators, to be used for 6 weeks before the prolapse surgery at a dose of once daily for 2 weeks then twice weekly for 4 weeks. There would be gap of 6 weeks after the surgery to allow the wound to heal. A member of the research team will contact participants by telephone to check on

progress, and then ask the women to use the vaginal pessary twice weekly for a further 46 weeks. Apart from receiving either active oestrogen or no medication, there would be no other difference in the treatment pathways. All participants will complete questionnaires related to symptoms, incontinence, sexual function and general quality of life before starting using the cream, then again at 6, 12 and 24 months after surgery.

We will also assess whether surgical complications are reduced, how often the prolapse returns and if there are any side effects of using the pessaries.

We have completed a study to assess the feasibility of conducting a larger study. We

randomised 100 women from 6 centres in 13 months. We found 157 women eligible and 100 consented to participation. A high proportion of women have completed the questionnaire at 6 months after their surgery (87%). We are confident that these results show that a larger study recruiting over 500 women over 2 years is possible. Interviews with participants showed that improvements that are sustained over the long term are important, so we propose to follow-up participants for 2 years after surgery.

The study results will provide reliable advice regarding the extent of benefit and side effects of local oestrogen alongside surgery for reducing surgical risks and increasing effectiveness of the outcomes. Whatever the result, we will communicate the results to gynaecologists, surgeons and GPs via the medical literature and conferences. We would expect professional organisations such as NICE to include the results in their guidance and information to be available on reliable patient sites e.g., NHS Choices.

This protocol describes a major multicenter UK trial to establish whether vaginal

oestrogen treatment of postmenopausal women undergoing pelvic floor repair surgery leads to improved patient reported outcomes. The study is designed to be as simple as possible both for those participating and for those involved in clinical care.

Research Nurses and gynaecologists in each centre will identify and recruit postmenopausal women undergoing prolapse surgery and collect descriptive information and baseline prolapse measurements. Those who are eligible will be invited to enter a randomised trial. All women will be followed up at 6, 12, 24 and 60 months after surgery.

Introduction

There are 12 million women over the age of 50, and increase of 14% on the decade before in the UK, (Mid-2015 Population Estimates UK Office for National Statistics, 2016) of whom 41% will have some amount of POP (74). Women have a lifetime risk of prolapse surgery of 12-19% (24). There were over 21,515 vaginal repair surgeries performed in England in2014/15, incurring a hospital stay of 2 days each on average (HES data, Q08.9, P23.1). Efforts to reduce perioperative complications of POP surgery and enhance long term benefit will reduce urinary and bowel symptoms, reoperations and improve QoL in this group of ageing population. If 20% of all repairs are reoperations and local oestrogen could decrease this figure by just 20%, 857 fewer procedures would be needed each year. At an average tariff of £3,666, £3.14m could be saved annually in England alone by preventing recurrence. Conversely, oestrogen is inexpensive, at £5.30 per patient for the regimen proposed for this study, so even a 2%reduction in repeat operations would be cost-effective.

The 2010 Cochrane review did not find clear evidence to suggest whether oestrogens

help in reducing POP symptoms, but recommended that an adequately powered, long-term RCT was needed to identify benefits or risks (16). Whilst there is a plausible argument for using low-dose oestrogen to improve the vaginal environment and reduce urinary tract infections (UTIs) at the time of prolapse surgery, there is little evidence on its effect on the prolapse cure rates or recurrence (15). Furthermore, there is no information about any effect in terms of prolapse symptoms and QoL, which is important to women.

The economic benefits will not just be from reduced repeat surgeries, but also from the cost of treating wound infections, UTIs and vaginal atrophy. Reports suggest that as many as 41% of women who underwent prolapse repair, had antibiotics for pyrexia, UTI or vaginal discharge (secondary to surgical wound infection)(75). By reducing these adverse events, this intervention might reduce the costs and demand on NHS services. It is worth remembering that the physical burden and emotional cost of prolapse to the women, her partner and family remains unquantified.

Sustained Interest

We performed a survey in April 2013 of the British Society of Urogynaecology (BSUG) membership (87/385 responded). We noted that 44% of the respondents recommend local oestrogens before POP surgery and 77% of the BSUG members were willing to recruit patients into the trial due to equipoise.

Our 2-year feasibility study demonstrated that the study was able to randomise 100 postmenopausal women from 6 centres in one year. The study addressed the acceptability of the intervention, the feasibility of recruiting and randomising women

in a timely fashion, the compliance with the treatment schedule, the usability of the data collection forms and follow up rates. The study has demonstrated that a larger trial is feasible and good recruitment, adherence rates and follow-up over six months are achievable.

Research question

Does vaginal oestrogen treatment of postmenopausal women undergoing prolapse repair surgery lead to improved patient reported outcomes in relation to urinary, bowel, sexual function and prolapse-related QoL.

Secondary questions are:

Does using vaginal oestrogen reduce recurrence of prolapse related symptoms?
Is vaginal oestrogen cost-effective?

Population: Postmenopausal women undergoing POP surgery (excluding mesh procedures)

Intervention: Local oestrogen pre-operatively and 1 year postoperatively

Comparison: No treatment

Primary Outcome:

Prolapse related QoL at 12 months as assessed by PFDI SF20.

Secondary Outcomes:

1. Prolapse related QoL at 24 months assessed by PFDI SF20, PGII in patients who continued vs discontinued local oestrogen treatment

2. Sexual function at 12 & 24 months using PISQ 12.

3. Intraoperative complications e.g. tearing or button holing of the vagina and blood loss.

4. Incidence of surgical wound infection and urinary tract infections postoperatively.

5. Cost per QALY (SF12) and cost per clinically significant improvement in prolapse-related QoL.

Design: Randomised controlled open labelled multicentre trial with economic evaluation involving a cost-effectiveness and cost-utility analysis.

Setting: Up to 25 UK urogynaecology clinics

Target population: Postmenopausal women planning to have pelvic organ prolapse (POP) surgery.

Inclusion criteria: Consenting postmenopausal women having either initial POP surgery, or if repeat surgery, in a different compartment.

Exclusion criteria: Hormone replacement therapy in 12 months prior to randomisation; previous breast or uterine malignancy or other hormone dependant neoplasms; genital bleeding of unknown origin; previous thrombo-embolic episodes related to oestrogen therapy; allergic to any components of vaginal oestrogens; POP surgery involving mesh.

Health technologies being assessed: Intervention: 6 weeks course of oestradiol pessary preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for 4 weeks) and then oestradiol pessary per vaginum twice weekly from week 6-52 postoperatively.

Comparison: No treatment or placebo

Outcomes:

Primary: prolapse related quality of life (QoL) at 12 months, as assessed by Pelvic Floor Distress Inventory Short Form 20 (PFDI-SF20).

Secondary: Sexual function related QoL at 12 & 24 months assessed by POP/Urinary Incontinence Sexual Questionnaire (PISQ-12); Patient Global Impression of Improvement (PGI-I) at 6, 12, and 24months; intraoperative complications e.g. tearing or button holing of the vagina, blood loss; surgical wound infection, post-operative urinary tract infection (UTI); serious adverse events; POP recurrence using the POP quantification system (POP-Q).

Follow-up at 24 months to assess attenuation of effects posttreatment, recurrence and reoperation.

Economic: cost of prescription of vaginal oestrogen, health resources used in primary and secondary care, generic health-related QoL using SF-12. Perspective: NHS and personal care.

Sample size: To detect a difference of 0.33SD (small to moderate effect size; approximately 8 points) in prolapse QoL score of the PFDI-SF20 with 90% power (p=0.05) will require 191 per group, 382 in total. To allow for 10% who fail to have surgery post-randomisation and a further 20% loss to follow up this will be inflated to a target of 532 women in total.

Project timetables including recruitment rate:

Prior to grant: Protocol development, trial staff recruitment.

Months 1-6: REC and MHRA approval, local site permission, training, database development.

Months 7-30: Recruitment in minimum 25 sites over a 24 month period (5 lead sites recruiting 8 patients/month and 20 sites recruiting 14 patients/month).

Months 10-36: Questionnaire and clinical data follow-up.

Months 37-42: analysis and write-up.

Months 31-54: two year follow-up

Eligibility criteria

Inclusion criteria:

Postmenopausal women

Consented to undergo surgical intervention for pelvic organ prolapse

Have not received HRT in the last 12 months

Willing to be randomised

Give written informed consent

Exclusion criteria:

Previous breast or uterine malignancy or other hormone- dependant neoplasms

Genital bleeding of unknown origin

Previous thrombo-embolic episodes in relation to oestrogen therapy

Women who cannot understand, speak or write in English

Women known to be allergic to any of the components of vaginal oestrogens

Two or more episodes of culture positive UTI in the last 6 months

Previous POP surgery in the same compartment

Voiding dysfunction (post-voiding residual volume>150ml)

Current or previous POP surgery involving mesh

Patient is participating in another CTIMP trial.

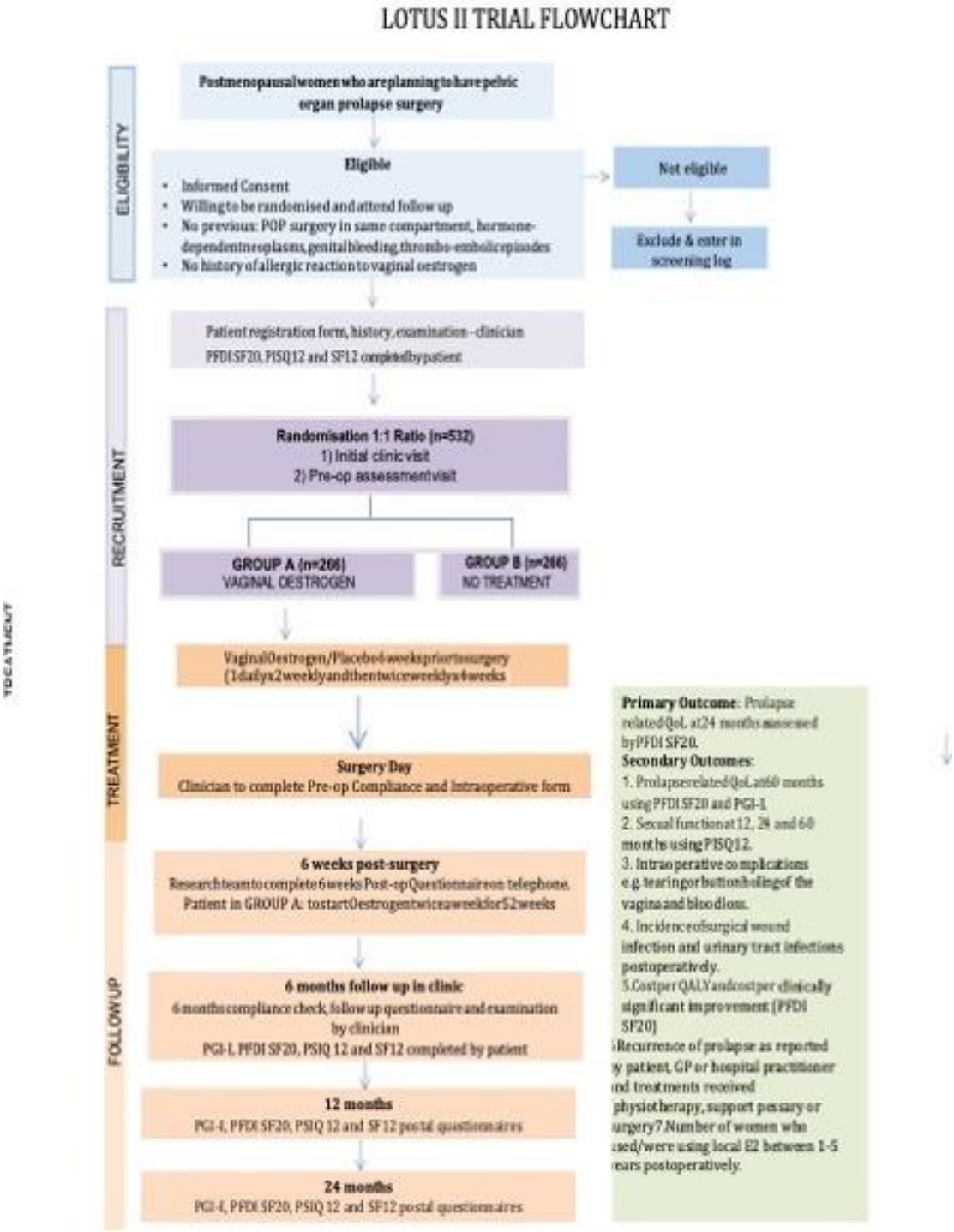

Figure 15: LOTUS II TRIAL FLOWCHART

Identification of participants and consent

Ideally consent should be sought under unhurried circumstances when entry criteria are fulfilled by the researcher. Consent should be sought face to face. Consent is sought in several stages. We aim to use the same pattern of identification of participants as in the feasibility study. A two-step process was used in which the researcher would review the referral letters sent by GP to the urogynaecology consultants. The potential participants are identified and a patient information leaflet is sent out to the patient along with the appointment letter. The evidence of successful recruitment of patients utilising the two step process has been highlighted in the feasibility study (LOTUS).

Once the patient visits the hospital and is deemed to be eligible to participate in the study, consent will be sought by the researcher (face to face consent). Enough time will be given to discuss the study, ask any questions before seeking consent. The researcher will perform a clinical examination including grading the prolapse with pelvic organ prolapse quantification (POPQ) scoring. All women will then be requested to answer baseline questionnaires. The researcher will randomise the patient. The researcher will randomly allocate the patient to either the intervention group (Group A) or the control group (Group B). Timing of randomization in LOTUS II can be perfomed either at clinic appointment or after obtaining pre assessment fitness for surgery. This ensures decreasing the number of dropouts after pre assessment.

The patient allocated to the intervention group will be given a prescription to take to pharmacy to obtain the supply of study pre-operative treatment. The prescription will advise the patient to commence the vaginal pessary six weeks prior to surgery (daily insertion of pessary for first two weeks followed by twice weekly insertion for the next 4 weeks). Control group will receive no vaginal oestrogen treatment. On the day of the surgery, the surgeon will be asked to complete intraoperative questionnaire on ease of dissection, complications like visceral injury, button-holing of the vagina and estimated blood loss. Blood loss will be measured intra-operatively by weighing the swabs or nearest estimate. The patients in the intervention group will be given a supply of pessaries at the time of discharge from the hospital with advice to use it on a twice weekly basis from 6 weeks postoperatively for 20 weeks. Women will be advised to telephone and seek advice from the hospital if they develop any signs of UTI or surgical site wound infection in the first 6 weeks. At 6 weeks postoperatively, the women will be contacted by the research team by telephone to record any postoperative complications encountered and to remind the intervention group to start using the vaginal oestrogen again twice a week. At the 6 months follow up, the clinical team with an independent member will re- examine the patient including the POP Q, and this will be undertaken without knowledge of the findings of the other. Patients will complete questionnaires (PFDI-SF20, PISQ-12 & PGI-I). Postal questionnaires will be sent out at 12 months and subsequently again at 24 months.

Number of centres involved

We aim to recruit women from approximately 25 centres across the UK.

Randomisation and Study Drug supply

Randomisation

Participants will be randomised individually into the study in an equal 1:1 ratio. A 'minimisation' procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables. Strata used in the minimisation will be:

1.age (<=65, >65 years)

2.parity (< =2, >2 vaginal births)

3.Maximum stage of prolapse (Stage I, II or III/IV)

The arrangement for group allocation following randomisation ensures that both the groups are nearly equal in demographics and prevents allocation bias.

Supply of Study Treatments

The study drugs will be supplied and released from normal stock “off shelf” by the hospital pharmacy.

Study Treatment Dispensing and Accountability

At randomisation, the first supply of study drugs will be provided by the hospital pharmacy. The pharmacist will receive email notification via the study database of the name and trial number of the randomised woman and will prepare the specified study treatment for dispensing. The woman in the intervention group (Group A) will be given a prescription by the research team to take to the pharmacy to obtain the vaginal pessaries. The trial treatment will contain 6 weeks’ supply of pessaries for initial use by the participant. The investigator or research nurse will trigger a second dispensation of study treatment upon the patient’s discharge following POP surgery.

The supply will contain a further 12 month study treatment for that participant. The pharmacist should keep accurate records of study drugs dispensed using a pharmacy log. Women will be advised to keep the study drugs in a cool, dry place.

Investigational Medicinal Products

Oestradiol vaginal pessary

The investigational medicinal product (IMP) is oestradiol hemihydrate (Vagifem^{TM}) in the form of vaginal pessary, available in the dose of 10µg.

The up-to-date Summary of Product Characteristics for oestradiol hemihydrate can be found at http://emc.medicines.org.uk.

Dose and route of administration

The study treatment for Group A will be initiated after randomisation and initiated 6 weeks prior to the date of surgery. The study treatment is to be administered preoperatively once daily for 2 weeks followed by twice weekly for 4 weeks. The treatment will be restarted 6 weeks postoperatively, administered twice weekly per vaginum for 40 weeks.

Withdrawal from treatment

Withdrawal from treatment is a decision of the participant however, withdrawn patients can bias trial results and reduce the power of the trial to detect important differences, so women should be encouraged to allow data collection to continue even if she ceases to use the study treatment.

Withdrawal of treatment will also be necessitated in cases where a known serious adverse reaction to the trial drug occurs or a suspected unexpected serious adverse reaction occurs. Women will be given a prompt card to show to emergency doctors to indicate that they are trial participants and that they are taking oestrogen pessaries.

The patient is free to withdraw from the trial, at any time, for any reason, without prejudice to future care and with no obligation to give reason for withdrawal. These will be recorded and a request made to utilise the data accumulated prior to withdrawal.

Protocol violations and compliance monitoring

Any incidences of study participants not receiving the specified treatment allocation by randomisation will be recorded. Women will be analysed according to group allocation, by intent-to-treat analysis and also per protocol analysis.

Women in group A will be advised to use pessaries preoperatively and postoperatively. Importance of compliance to drug treatment will be stressed at the time of recruitment, on commencement of the study treatment, and at follow-up appointments. Women will be asked to rate their compliance with treatment schedule. Women who fail to attend follow up appointments will be contacted on telephone and offered further follow-up.

If women are unable to have their surgery 6-weeks after taking the pre-operative treatment schedule of oestrogen due to reasons such as possible infection on day of surgery, theatre list cancelled due hospital/Trust difficulties then the centre is advised to give a new date for POP surgery within 4 weeks of initial proposed date. No additional oestrogen is required for the patient in the treatment arm. However, if the

surgery is postponed further than 4 weeks from initial proposed surgery date then participants will be logged as protocol violators and oestrogen treatment continued until surgery.

Safety Monitoring Procedures

Serious Adverse Event (SAE) Report Form

Serious adverse events will be recorded using a standard SAE CRF form. The SAE form will be used to record details of any serious adverse events. Adverse events will be categorised using the IUGA/ICS Classification of Complications coding systems.

Methods to protect against sources of bias

Ensuring standardisation of intervention and outcome measurement (avoiding performance bias)

Both specialist urogynaecologists and general gynaecologists can recruit and randomise women, thus extending the generalisability of the trial and the future transfer of skills. All gynaecologists will be proficient in performing the POP-Q method of objective quantification of prolapse.

All gynaecologists will complete a Surgical Standardisation Form to provide details of their preferred operative techniques. Any additional training required will be conducted by the clinical grant applicants and will be directed towards ensuring standardisation of their existing techniques and outcome measures.

The Research Nurses and the surgeons will complete a Recruitment Officer Case Report Form (ROCRF) (developed for VUE and adapted for LOTUS II) at the time of surgery to

ensure a complete record of all surgical techniques and materials used and any intra-operative difficulties or complications. The Research Nurses in each centre will ensure completeness and accuracy of data

Loss to follow up (attrition bias)

We have used a conservative estimate of 15% loss to follow up in the power calculations. We will take very active measures to minimise such loss, such as phoning the women, using retention incentives and checking with their GPs in case of non-contact.

In addition, we will try to obtain consent from the women to enable us to access centrally-held NHS data for example via the NHS Strategic Tracing Service in England and Wales

.

Other sources of bias (detection bias)

Group allocation will be concealed from the ward staff if clinically possible, although blinding in theatre is not possible given this is a surgical trial.

Outcome assessment is largely by participant self-completed questionnaire, so avoiding interviewer bias. The clinical review at 6 months in Outpatient department (secondary outcome) will be conducted by staff blinded to allocation, performing the POP-Q examination.

Research staff who are blinded to allocation will conduct the data collection, data entry and analysis, using Study Numbers only to identify women and questionnaires. All women will be actively followed up, with analysis based on the intention-to-treat principle. All analyses will be clearly predefined to avoid bias.

Sample size

In the LOTUS feasibility study we planned to randomise 100 women; this number would

allow us to measure recruitment and compliance rates with 95% confidence interval (CI) width between 10 and 20%. We screened 325 consecutive women for eligibility, 157 were found to be eligible (48%, 95%CI: 40%-56%) and 100 (64%, 95% CI 56-72%) of those eligible were randomised.

To detect a difference of 0.33SD (small to moderate effect size; approximately 8 points) in prolapse QoL score of the PFDI-SF20 with 90% power (p=0.05) will require 191 per group, 382 in total. To allow for 10% who fail to have surgery post-randomisation and a further 20% loss to follow- up this will be inflated to a target of 532 women in total.

Data Collection and Processing

Follow up will continue for 24 months from the date of surgery. It is not part of this protocol or the current study to follow up the women beyond this time. However, consent will be sought to make this possible in the future, and long term follow up (5 years) is planned.

Proposed outcome measures

The outcomes are identical to those piloted and used successfully in LOTUS. We are using standardised outcome instruments developed by International Continence Society (ICS) recommendations for terminology and standard techniques. We have liaised with our patient representative to ensure that all relevant issues are covered, the patient information and survey instruments are acceptable to the women and the outcome measures relevant. The outcome measures were trialled in the feasibility study LOTUS. In LOTUS six-month follow-up questionnaires were completed by 79/100 (79%) of participants. Of those that had surgery this equated to 79/89 (89%). Of those who had surgery, 100% had completed intraoperative data and 84/89 (94%) had post-operative data recorded at six weeks. Overall, scores from the PFDI-SF20 (POPDI-6 domain) were low at both 6 and 12 months, averaging 14.3 (SD: 16.4) and 15.6 (18.1) out of a maximum of 100, indicating a low level of prolapse-related symptoms at these times. Responses from the PFIQ-7 (POP-IQ-7 domain) were similarly low.

Therefore in LOTUS II, we have decided to continue to use the PFDI SF 20 questionnaire along with PSIQ 12 questionnaire in order to capture information relating to the various domains mainly prolapse symptoms, urinary, bowel and sexual function pre and post surgery.

Economic outcome measures

The cost of prescription of vaginal oestrogen, health resources used in primary and secondary care, generic health-related QoL using SF-12. Trial participants will be asked to complete the questionnaire at baseline and at 6, 12 and 24 months after their operation and randomisation, respectively. This instrument will provide the quality of life (QoL) weights to compute the QALYs. The economic evaluation will be based on the following:

Cost and use of NHS services;

Cost to the women and their families/carers;

QALYs estimated from the responses and

The incremental costs, QALYs and incremental cost per QALY derived by the economic model over a longer term time horizon.

Data Processing

Research Nurses or Researcher will enter locally-collected data in the centres. Staff in the Trial Office will work closely with local Research Nurses to ensure that the data are as complete and accurate as possible. Follow up questionnaires to women will be sent from and returned to the Trial Office. Extensive range and consistency checks will further enhance the quality of the data.

Change of Status Procedures

Participants will remain on the trial unless they chose not to receive further questionnaires . We will retain their data and their permission to access health care records unless consent for

these activities is explicitly withdrawn.

Statistical analysis

A single principal analysis is anticipated at 12 months after the last woman has had her operation. The Data Monitoring Committee will determine the frequency of confidential interim analyses, but at present these are planned on three occasions during the data collection period.

All outcomes in both trials will be described with the appropriate descriptive statistics where relevant: mean and standard deviation for continuous and count outcomes, or medians and inter-quartile range if required for skewed data, numbers and percentages for dichotomous and categorical outcomes (for example subjective recurrence of prolapse).

Analysis of the primary outcome (PFDI SF20) will estimate the mean difference (and 95% confidence interval) between intervention and control groups at 12 months after randomisation using a general linear model that adjusts for the minimisation covariates and other important prognostic covariates, including the baseline symptom score. Clinical and patient reported outcome measures (PROMs) will analysed with point estimates (RR or mean difference) and 95% confidence intervals, adjusting for the minimisation variables A similar analysis will be used to analyse the primary outcome at six months after surgery.

The ways in which these data will be analysed are set out in the LOTUS Statistical Analysis Plan. All study analyses will be according to a statistical analysis plan that will be agreed in advance by the LOTUS II Steering Committee and compatible with that rehearsed in LOTUS study.

Objective Measurement Analysis

Each of the POP-Q stage analyses consists of a comparison of the ordinal distributions from Stage 0 to 4, along with a dichotomised comparison of the proportion beyond the hymen (>0cm).

In order to standardise the POP Q analysis, the LOTUS II analysis of objective measurements will be adapted according to the analysis performed in PROSPECT and VUE studies (72). We intend that, at baseline and (for randomised women) at 6 months after surgery, women would have objective measurements of their prolapse compartments. Objective prolapse staging was carried out using the POP-Q system. This measures the maximum descent of each of the three prolapse compartments (anterior, posterior and upper) relative to the hymen (at 0 cm): measurements inside the vagina are negative, whereas those outside are positive. A measure of prolapse (classified from stage 0 to 4) is determined for anterior, posterior and uterine/vault, with the leading edge of the most descended compartment used to define overall stage. An algorithm will be used to ensure that POP-Q staging is correctly calculated from the component measurements of the POP-Q [Aa, Ba, C, D, Bp, Ap and total vaginal length (TVL)] in which common recording errors (e.g., Ba measurement less than Aa) will be corrected or queried. If data are discrepant, they will be corrected by consultation with the local hospital records to obtain additional data. If POP-Q data is missing, we will then accept the surgeon's qualitative record of stage, both overall and in individual compartments (i.e., surgeons could specify the stage without giving the POP-Q measurements).

Usually, using the classic Bump et al criteria (23) for the POP-Q system, any measurement from -1 cm (inside the hymen) to 1 cm outside counts as stage 2. However, we further subdivided stage 2 into prolapse at the hymen or within (-1 cm to 0 cm; stage 2a or less) compared with prolapse at > 0 cm (stage 2b). Thus, women were classified as having

objective prolapse if the leading edge was at any point outside the hymen (measured at > 0 cm, stage 2b, 3 or 4).

Organisation

A detailed plan and timetable of study organisation is presented in the Gantt chart. (Figure 9). The Gantt chart indicates when it is anticipated that the major study events will occur, including recruitment, study progress and meetings. There will be 3-monthly project management meetings, five meetings of the Steering Committee and four of the Data Monitoring Committee. Two meetings are planned for collaborators (including gynaecologists, local Research Nurses, consumer participants and members of BSUG), the first timed to occur when all the sites have been identified and the second when results are available.

These time-related milestones will be used to enable close monitoring of progress.

Local organisation in centres

Lead Gynaecologist (Local Principal Investigator)

Each collaborating centre will identify a Lead Gynaecologist who will be the point of contact for that centre. The responsibilities of this person will be to:

• establish the study locally (for example, by getting agreement from clinical colleagues; facilitate local regulatory approvals; identify, appoint and train a local Research Nurse; and inform all relevant local staff about the study (eg other consultant gynaecologists, junior medical staff, secretaries, ward staff))

• take responsibility for clinical aspects of the study locally (for example if any particular concerns occur)

• explain the different surgery options to them, and ensure that study documentation has been provided and that informed consent has been obtained

• notify the Study Office of any unexpected clinical events which might be related to study participation

• provide support, training and supervision for the local Research Nurse(s)

• represent the centre at the collaborators' meetings.

ii) Local Research Nurse

Each collaborating centre will appoint a local Research Nurse to organise the day-to-day recruitment of women to the study. The responsibilities of this person will be to:

keep regular contact with the local Lead Gynaecologist, with notification of any problem or unexpected development

maintain regular contact with the LOTUS II Study Office

keep local staff informed of progress in the study

contact potential participants by: providing the Patient Information Sheet to women being admitted electively for prolapse surgery; identifying any eligible women at pre-assessment clinics or on the ward while they are in hospital for their prolapse surgery; explain the study and the potential for participation in a trial if they are eligible; explaining what is intended by research access to their NHS data; and describing the possibility of long-term follow up and participation in other research

Collect and complete all the questionnaires and enter details into the database

Obtain written consent after checking eligibility with lead clinicians

File all relevant study documents in the medical records of the patient

LOTUS II Trial Office

The Trial Office at the BCTU will be responsible for providing all trial materials, including the trial site file and folders containing printed materials. These will be supplied to each collaborating centre, after relevant NHS permission for that site been obtained. Additional supplies of any printed material can be obtained on request. The Trial Office will provide the central randomisation service and will be responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment), for reporting of serious and unexpected adverse events to the Co-sponsors. The Chief Investigator will be responsible for ad hoc and annual progress and safety reporting to the REC and MHRA. The Trial Office will help resolve any local problems that may be encountered in trial participation.

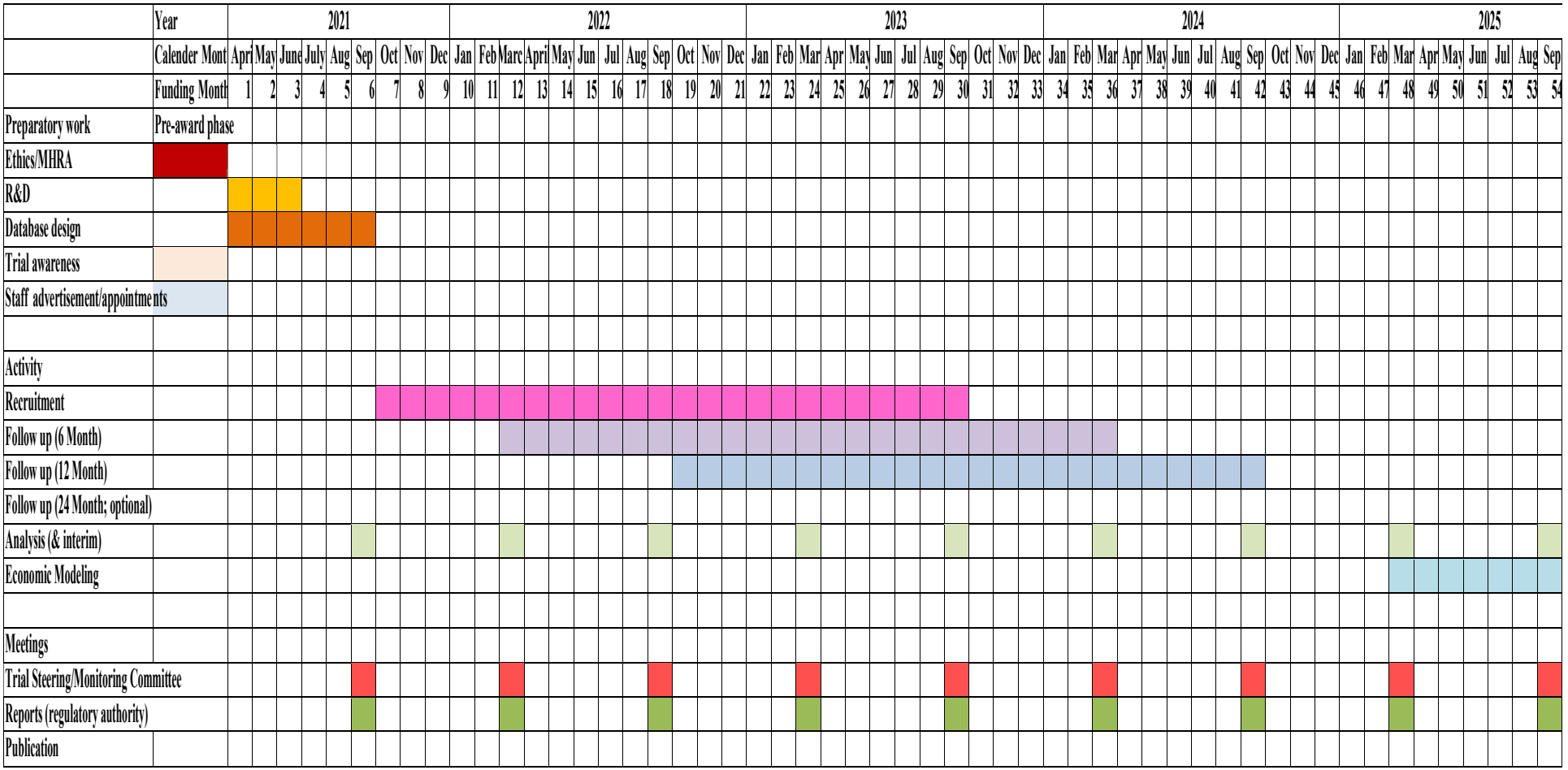

Figure 16: GANTT Chart for proposed definitive study

CHAPTER SEVEN: CONCLUSION

Summary

The National Institute of Health Research (NIHR) and the Research for Patient Benefit (RFPB) champion feasibility studies as a phased approach to the designing and development of large scale RCTs. Feasibility studies have the ability to identify uncertain parameters and describe methods that improve precision in the main study. This phased approach ensures a better chance of success in a definitive study.

In Chapter 2, I collated the existing knowledge of the prevalence of POP by performing a systematic review to further understand the worldwide burden of the disease. This systematic review comprehensively summarised the prevalence of POP in developing and developed countries. From the review, I was able to generate epimaps, which created a visual aid for clinicians to use and emphasize the need to target health resources in this area of women's health. I recommended using a dual combination of validated questionnaires along with gynaecological examination (POP-Q) for determination of true prevalence of prolapse.

In Chapter 3, I performed a systematic review to assess the various PROMs utilized in POP. In order to select the best outcome measurement instrument, one requires high quality studies that document the evaluation of the measurement properties (in total- nine different aspects of reliability, validity, and responsiveness) of relevant outcome measurement instruments in the target population. There was strong evidence supporting internal consistency and moderate evidence supporting construct validity for the Pelvic Floor Distress Inventory (PFDI), PFDI SF20 while the Pelvic Organ Prolapse Symptom Score (POP-SS) and ePAQ-PF had moderate evidence of internal consistency, test-retest reliability and construct validity.

In Chapter 4 of my thesis: I have evaluated the LOTUS feasibility study and I have summarised the key findings of the feasibility study as follows:

- 325 women with POP and desiring surgery were screened for eligibility, with 157 found to be eligible (48%, 95%CI: 40%-56%). 100/157 of these women (64%, 95%CI: 56%-72%) were randomised over a 13-month period (July 2015 to August 2016).

- Of the 100 randomised women, 85 ultimately had surgery. Of the other 15, 6 could not have surgery due to health issues, 3 changed their mind about surgery and 6 did not turn up for their surgical appointment.

- In the treatment group, 32/41 (78%), 34/41 (83%) and 21/27 (78%) of those allocated oestrogen pessaries reported good compliance (taking treatment as advised at least >=75% of the time) pre-operatively, at six weeks and six months respectively.

- Of the participants who had surgery, 85/85 (100%) had completed intraoperative forms and 83/85 (98%) completed post-operative forms at six weeks. Only minor discrepancies in their completion were noted by the trial team.

- At 6 months follow up, 77/100 (77%) questionnaires were returned. Of those that had surgery, this equated to 77/85 (91%).

- The pooled (over both groups) standard deviation of the PFDI-SF20 POPDI-6 domain at six months was: 16.4 points (95%CI: 11.0 – 18.5).

- An independent Oversight Committee indicated no safety concerns during the study.

- Interviewed participants had a positive experience reporting that they felt well informed by trial staff about the trial. The consent process was undertaken well and patients felt reassured by explanations of randomisation. The main aspect of the trial that may benefit

a revisit are the questionnaires, as a number of patients found that the format repetitive and lengthy. Qualitative analysis identified themes motivating women e.g. altruism, clear and transparent information, potential health benefit. Among those who declined participation themes were: lack of time, uncertainty, dependent on others due to age.

- Staff felt positive about recruitment although there were some challenges such as difficulty to get patients scheduled for surgery within the time frames and scheduling follow up appointments. Clinical staff were supportive of the trial; they found that the trial processes and procedures were very straightforward including randomisation and completion of the case report forms.

Our four key indicators were met and we conclude that a large multicentre RCT of vaginal oestrogen pessaries is feasible. It is possible to randomise and follow up patients with high retention over six months. Some minor modifications to the study protocol, such as flexibility in timing of randomisation, reducing the length of forms would help to further improve recruitment, retention and follow-up figures. Patients and staff interviewed were very receptive to the study; staff in particular felt study processes was straightforward. The majority of clinicians surveyed would be happy to randomise patients in any future trial.

In Chapter 5, the qualitative research work gave enormous insight into understanding research trials from the women's point of view. From the emerging themes, I found that factors that enhanced participation were maintenance of simplicity in patient leaflets, easy accessibility to research teams and providing clarity in information disseminated, devoid of medical jargon. The more vital parameter identified were the barriers to recruitment: such as

uncertainty regarding the investigational product, logistical elements like physically attending multiple appointments, time constraints and false patient perception of delay in receiving treatment if participating in a clinical trial. Participation and engagement of women in research projects leads to better understanding of the working of a trial and gives the clinician ability to respond to their needs.

Utilising the feasibility results, in Chapter 6, I have designed and prepared a proposal for a definitive study. This work required several meetings with vital members of the research and clinical teams. We collated and brainstormed the various trial and real-world issues, evaluated the problem as well as the solutions. This brainstorming has been depicted in the ADEPT flow chart (Figure 14). The proposed definitive trial design is now ready, and the team has prepared expression of interest for funding bodies.

Implications for clinical practice:

- Amongst gynaecologists, there is variation in belief regarding the effectiveness of vaginal oestrogen for postmenopausal women needing surgical interventions for POP. These beliefs range from substantial benefits to slight harm. Gynaecologists await further research to understand the effect the vaginal oestrogen.

- Clinicians who maintained ongoing involvement with clinical studies and positive relationship with the research staff and accessibility to the participants, generate trust and together help the recruitment and retention efforts in clinical trials.

- In developed countries the highest prevalence of POP is within the age group 45-75 years, which is as high as 59.4%. This rate is higher in developing countries within the same age criteria of 45-75 years, which is reported at 70-75%. In developed countries, the reporting trend decreases to 10-22% beyond the age of 76 years. This

estimation of disease burden should be considered by policy makers when planning gynaecological services

- We suggest considering the use of ePAQ and/ or PFDI SF -20 in clinical practice and the POP-SS for use in women with POP in research in order to get maximum information on patient reported outcomes.

Implications for research:

- The uncertainty in effectiveness of vaginal oestrogen in postmenopausal women with POP undergoing surgical interventions indicates that a large-scale scientific clinical trial is warranted to resolve this uncertainty.

- The prevalence of POP systematic review has highlighted the need for reporting from many countries. I recommend that standardization in reporting by utilising validated questionnaires and POP-Q examination will assist in homogenous reporting from both developed and developing countries

- The systematic review on PROMS has identified that there is vital work needed to completely evaluate measurement properties in order to validate their use in a clinical or research setting. There is need to create core outcome sets that are readily accessible for clinicians and researchers.

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APPENDIX

Appendix 1: Search strategy for PROM

1.(woman).ti,ab OR (women*).ti,ab OR (lady).ti,ab OR (ladies).ti,ab OR (female).ti,ab OR (females).ti,ab)

AND

2. ((vaginal prolapse).ti,ab OR (pelvic organ prolapse).ti,ab OR (cystocele).ti,ab OR (uterine prolapse).ti,ab OR (uterine descent).ti,ab OR (enterocele).ti,ab OR (rectocele).ti,ab))

AND

3. ((questionnaire).ti,ab OR (questionnaires*).ti,ab OR (outcome measure*).ti,ab OR (outcome assessment*).ti,ab OR (health status indicator*).ti,ab)) AND ((reproducib*).ti,ab OR (method*).ti,ab OR (valid*).ti,ab OR (reliab*).ti,ab)) AND ((reproducib*).ti,ab OR (method*).ti,ab OR (valid*).ti,ab OR (reliab*).ti,ab OR (internal consistency).ti,ab OR (ceiling effect).ti,ab OR (coefficient of variation).ti,ab OR (observer variation).ti,ab OR (psychometric*).ti,ab OR (validation study*).ti,ab OR (discriminative).ti,ab OR (precision).ti,ab) OR (Instrumentation or method* or Validation Studies or Comparative Study).mp. or psychometrics/ or psychometr*.mp. or clinimetr*.mp. or clinometr*.mp. or outcome assessment health care/ or outcome assessment*.ti,ab. or outcome measure*.mp. or observer variation/ or observer variation*.ti,ab. or Health Status Indicators/ or reproducibility of results/ or reproducib*.ti,ab. or discriminant analysis/ or reliab*.ti,ab. or unreliab*.ti,ab. or valid*.ti,ab. or coefficient of variation.ti,ab. or coefficient*.ti,ab. or homogeneity.ti,ab. or homogeneous.ti,ab. or internal consistency.ti,ab. or cronbach*.ti,ab.) and alpha*.ti,ab.) or item*.ti,ab.) and correlation*.ti,ab.) or selection*.ti,ab. or reduction*.ti,ab. or agreement.mp.

or precision.mp. or imprecision.mp. or precise value*.mp. or test-retest.ti,ab. or test.ti,ab.) and retest.ti,ab.) or reliab*.ti,ab.) and test.ti,ab.) or retest.ti,ab. or stability.ti,ab. or interrater.ti,ab. or inter-rater.ti,ab. or intrarater.ti,ab. or intrarater.ti,ab. or intertester.ti,ab. or inter-tester.ti,ab. or intratester.ti,ab. or intratester.ti,ab. or interobserver.ti,ab. or inter-observer.ti,ab. or intraobserver.ti,ab. or intra-observer.ti,ab. or intertechnician.ti,ab. or inter-technician.ti,ab. or intratechnician.ti,ab. or intra-technician.ti,ab. or interexaminer.ti,ab. or interexaminer.ti,ab. or intraexaminer.ti,ab. or intra-examiner.ti,ab. or interassay.ti,ab. or inter-assay.ti,ab. or intraassay.ti,ab. or intra-assay.ti,ab. or interindividual.ti,ab. or inter-individual.ti,ab. or intraindividual.ti,ab. or intra-individual.ti,ab. or interparticipant.ti,ab. or inter-participant.ti,ab. or intraparticipant.ti,ab. or intraparticipant.ti,ab. or kappa*.ti,ab. or kappa's.ti,ab. or repeatab*.mp. or replicab*.mp. or repeated.mp.) and measure*.mp.) or finding*.mp. or result*.mp. or test*.mp. or generaliza*.ti,ab. or generalisa*.ti,ab. or concordance.ti,ab. or intraclass.ti,ab.) and correlation*.ti,ab.) or discriminative.ti,ab. or known group.ti,ab. or factor analysis.ti,ab. or factor analyses.ti,ab. or factor structure.ti,ab. or factor structure.ti,ab. or dimension*.ti,ab. or subscale*.ti,ab. or multitrait.ti,ab.) and scaling.ti,ab. and analysis.ti,ab.) or analyses.ti,ab. or item discriminant.ti,ab. or interscale correlation*.ti,ab. or error.ti,ab. or errors.ti,ab. or individual variability.ti,ab. or interval variability.ti,ab. or rate variability.ti,ab. or variability.ti,ab.) and analysis.ti,ab.) or value*.ti,ab. or uncertainty.ti,ab.) and measurement.ti,ab.) or measuring.ti,ab. or standard error of measurement.ti,ab. or sensitiv*.ti,ab. or responsive*.ti,ab. or limit*.ti,ab.) and detection.ti,ab.) or minimal detectable concentration.ti,ab. or interpretab*.ti,ab. or minimal.ti,ab. or minimally.ti,ab. or clinical.ti,ab. or clinically.ti,ab.) and important.ti,ab.) or significant.ti,ab. or detectable.ti,ab.) and change.ti,ab.) or difference.ti,ab. or small*.ti,ab.) and real.ti,ab.) or detectable.ti,ab.) and change.ti,ab.) or difference.ti,ab. or meaningful change.ti,ab. or ceiling effect.ti,ab. or floor effect.ti,ab. or Item response model.ti,ab. or

IRT.ti,ab. or Rasch.ti,ab. or Differential item functioning.ti,ab. or DIF.ti,ab. or computer adaptive testing.ti,ab. or item bank.ti,ab. or cross-cultural equivalence.ti,ab

Appendix 2: Consort checklist for randomised controlled trials checklist

	Item No	Checklist item	reported
Title and abstract	1a	Identification as a randomised trial in the title	√
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	√
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	√
	2b	Specific objectives or hypotheses	√
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	√
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	√
Participants	4a	Eligibility criteria for participants	√
	4b	Settings and locations where the data were collected	√

Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	√
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	√
	6b	Any changes to trial outcomes after the trial commenced, with reasons	√
Sample size	7a	How sample size was determined	√
	7b	When applicable, explanation of any interim analyses and stopping guidelines	√
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	√
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	√
Allocation concealment	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	√

mechanism			
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	√
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	-
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	√
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	√
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	√
	13b	For each group, losses and exclusions after randomisation, together with reasons	√
Recruitment	14a	Dates defining the periods of recruitment and follow-up	√

	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	√
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	√
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	√
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	√
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	√
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	√
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	√

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	√
Other information			
Registration	23	Registration number and name of trial registry	√
Protocol	24	Where the full trial protocol can be accessed, if available	√
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	√

Appendix 3: Outcome measures utilised in the feasibility trial

1. PGI-I Questionnaire

Tick the number that best describes how your post-operative condition is now, compared with how it was before you had the surgery
1. Very much better
2. Much better
3. A little better
4. No change
5. A little worse
6. Much worse
7. Very much worse

PFDI-20	**For each question, please tick yes or no. if you tick yes please STATE HOW MUCH IT bothers you.**						
Qu	**Do you……**	**Yes**	**No**	**If yes, how much does this bother you?**			
1	usually experience pressure in the lower abdomen?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
2	usually experience heaviness or dullness in the pelvic area?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
3	usually have a bulge or something falling out that you can see or feel in your vaginal area?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
4	ever have to push on the vagina or around the rectum to have or complete a bowel movement?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
5	usually experience a feeling of incomplete bladder emptying?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
6	ever have to push up on a bulge in the vaginal area with your fingers to start or complete urination?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
7	feel you need to strain too hard to have a bowel movement?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐

8	feel you have not completely emptied your bowels at the end of a bowel movement?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
9	usually lose stool beyond your control, if your stool is well formed?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
10	usually lose stool beyond your control, if your stool is loose?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
11	usually lose gas from the rectum, beyond your control?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
12	usually have pain when you pass your stool?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
13	experience a strong sense of urgency and have to rush to the bathroom to have a bowel movement?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐

Qu	Do you……	Yes	No	If yes, how much does this bother you?			
14	experience part of your bowel ever pass through the rectum and bulge outside, during or after a bowel movement?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
15	usually experience frequent urination?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
16	usually experience urine leakage associated with a feeling of urgency, that is, a strong sensation of needing to go to the bathroom?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
17	usually experience urine leakage related to coughing, sneezing or laughing?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
18	usually experience small amounts of urine leakage (that is, drops)?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
19	usually experience difficulty emptying your bladder?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
20	usually experience pain or discomfort in the lower abdomen or genital region?	☐	☐	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐

PFIQ-7 Questionnaire and PSIQ 12 Questionnaire

Qu	**How do symptoms or conditions in the following, usually affect your……**					
1	Ability to do household chores (cooking, laundry, housecleaning)?	Bladder or Urine	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
		Bowel or Rectum	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
		Vagina or Pelvis	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
2	Ability to do physical activities, such as walking, swimming or other exercise?	Bladder or Urine	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
		Bowel or Rectum	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
		Vagina or Pelvis	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐
3	Entertainment activities, such as going to the cinema or concert?	Bladder or Urine	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐

1. How frequently do you feel sexual desire? This feeling may include wanting to have sex, planning to have sex, feeling frustrated due to lack of sex, etc?			**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐
		Rectum					
		Vagina or Pelvis	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐	
4	Ability to travel by car or bus for a distance greater than 30 minutes away from home?	Bladder or Urine	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐	
		Bowel or Rectum	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐	
		Vagina or Pelvis	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐	
5	Participating in social activities outside your home?	Bladder or Urine	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐	
		Bowel or Rectum	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐	
		Vagina or Pelvis	1: Not at all ☐	2: Somewhat ☐	3: Moderately ☐	4: Quite a bit ☐	

2. Do you climax (have an orgasm) when having sexual intercourse with your partner?	**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐
3. Do you feel sexually excited (turned on) when having sexual activity with your partner?	**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐
4. How satisfied are you with the variety of sexual activities in your current sex life?	**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐
5. Do you feel pain during sexual intercourse?	**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐
6. Are you incontinent of urine (leak urine) with sexual activity?	**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐
7. Does fear of incontinence (either stool or urine) restrict your sexual activity?	**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐
8. Do you avoid sexual intercourse because of bulging in the vagina (either the bladder, rectum or vagina falling out)?	**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐
9. When you have sex with your partner, do you have negative emotional reactions such as fear, disgust, shame or guilt?	**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐

10. Does your partner have a problem with erections that affects your sexual activity?	**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐
11. Does your partner have a problem with premature ejaculation that affects your sexual activity?	**Always** ☐	**Usually** ☐	**Sometimes** ☐	**Seldom** ☐	**Never** ☐
12. Compared to orgasms you have had in the past, how intense are the orgasms you have had in the past six months?	**Much less intense** ☐	**Less intense** ☐	**Same intensity** ☐	**More intense** ☐	**Much more intense** ☐