UNIVERSITY OF BIRMINGHAM

Birmingham Women's NHS
NHS Foundation Trust

Local Oestrogen Treatment in Postmenopausal Women Undergoing Pelvic Organ Prolapse Surgery (LOTUS) - Feasibility Study

PROTOCOL

NHS
National Institute for Health Research

Version 2.0 Date 02.03.2017

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Version Number

1.2 (dated 18.05.2016)

Protocol Versions

1.1 (dated 09.10.2015) Submission to REC and MHRA

1.0 (date 02.03.2015) Submission to REC and MHRA

ISRCTN 46661996

EUDRACT 2014-000179-18

Funding Body

National Institute for Health Research, Research for Patient Benefit Programme

Sponsor and Sponsor Roles

Co-Sponsorship: The University of Birmingham and Birmingham Women's NHS Foundation Trust.

Chief Investigator: Dr Pallavi Latthe

Birmingham Women's NHS Foundation Trust is responsible for obtaining necessary approvals, for pharmacovigilance and overseeing good clinical practice

The University of Birmingham is responsible for randomisation and statistical analysis.

The Investigators are responsible for obtaining informed consent and care of the participants.

Signatures

The investigators and the sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

Chief investigator Dr P Latthe		23/02/2015
Birmingham women's hospital	Signature	Date
Sponsor		
University of Birmingham	Signature	Date

Birmingham Women's NHS Foundation Trust	Signature	Date

Abbreviations

AE	Adverse event
AR	Adverse reaction
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
BMI	Body Mass Index
BSUG	British Society of Urogynaecologists
CI	Chief Investigator
CTU	Clinical Trials Unit
DMEC	Data Monitoring Ethics Committee
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GP	General Practitioner
IMP	Investigational Medicinal Product
IRAS	Intergrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
HRT	Hormone Replacement Therapy
MHRA	Medicines and Healthcare Products Regulatory Authority
MRC	Medical Research Council
NHS	National Health Service
PI	Principal Investigator – the local lead investigator for the LOTUS Trial
POP	Pelvic Organ Prolapse
PPI	Patient and Public Involvement
RCT	Randomised Controlled Trial
R & D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
S D	Standard Deviation

SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TOC	Trial Oversight Committee
TSC	Trial Steering Committee
UTI	Urinary Tract Infection

CONTENTS

1 BACKGROUND

The International Continence Society and International Urogynaecological 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. A departure from normal sensation, structure, or function is experienced by the woman in reference to the position of her pelvic organs.[1] and a protrusion of the vagina, uterus, or both towards or out of the introitus may be observed.[2]

In the Women's Health Initiative Study, 41% of women aged 50–79 years showed some amount of POP, including cystocele in 34%, rectocele in 19% and uterine prolapse in 14%.[3] 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. In the UK, POP accounts for 20% of women on the waiting list for major gynaecological surgery.[4] and at least 10% of women undergo surgery for POP in their lifetime. 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 year age group.[5] The anterior vaginal wall is both the most common site of pelvic organ prolapse, with 81% of surgical repairs involving the anterior wall, and the most frequent site of operative failure.[6] Recurrence following POP surgery requiring reoperation was reported to occur in 10% to 30% of the women in various studies.[7,8]

Prolapse may be associated with weakening or atrophy of the genital tract. Oestrogen deficiency secondary to menopause results in weakening of the supporting ligaments of the pelvic organs and the pelvic floor muscles worsening the symptoms of prolapse. The vagina also contains oestrogen receptors and is sensitive to changes in circulating levels of oestrogen. Low oestradiol levels after the menopause lead to reduced vascularity of the tissues, along with a 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. [9]This may lead to overcolonization of the vagina, irritation and discharge. A decrease in oestrogen levels also results 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.[9,10]

1.1 Current surgical practice and complications

A common surgical complication continues to be surgical site infection, occurring in up to 5% of patients. Consequences of surgical site infection include longer hospitalization and increased healthcare costs.[11] Selective use of antibiotic prophylaxis has been one of the major advances in infection control practices. Preoperative, single-dose antimicrobial prophylaxis is recommended for women undergoing clean contaminated surgery like vaginal repair .[12]

Efforts to reduce perioperative complications of POP surgery and enhancement of long term cure are of utmost importance in the present and future management of rapidly growing ageing population. In postmenopausal women with vaginal atrophy, surgical dissection may be difficult during anterior and posterior vaginal wall repairs due to thinning of the vaginal walls and this may increase the risk of visceral injury. Also women in this age group may be at a higher risk of surgical site wound infection secondary to changes in the vaginal flora.[4]

1.2 The use of peri-operative oestrogen

Oestrogen treatment can be used to reduce thinning of the vaginal and pelvic tissues. This may help to reduce or prevent the symptoms of prolapse, or may be used to make other prolapse treatments work better. The different preparations of topical hormone replacement therapy (HRT) (creams, pessaries, tablets and the estradiol vaginal ring all appear equally effective for treating vaginal atrophy but the evidence on their effectiveness in reducing symptoms related to prolapse or indeed reducing the risk of recurrence of prolapse postoperatively is non-existent.[13]

1.2.1 Current evidence for the use of oestrogen peri-operatively for pelvic organ prolapse surgery

Replacement of oestrogen, even in small amounts, is effective in reversing vaginal atrophy and increasing vaginal lubrication.[4] In an randomised controlled trial (RCT) by Karp *et al*, early administration of local oestrogen after vaginal surgery via an oestradiol-releasing ring 2 weeks (for 12 weeks) after pelvic floor repair resulted in improved markers of tissue quality (vaginal maturation, reduced or absent granulation tissue) compared to placebo.[10] In a study evaluating the role of 2-12 weeks' preoperative local oestrogen in increasing vaginal wall thickness prior to POP surgery, there was no statistically significant increase in the thickness of the vagina in the treatment group compared to the group with no intervention, but the vaginal cytology was restored.[14]

When used preoperatively, vaginal oestrogens for three weeks did not reduce the recurrence rates of pelvic organ prolapse in an RCT of 43 postmenopausal women.[15] The subjective cure rate was 67% in the preoperative vaginal oestrogen group and 74% in the placebo group at the end of 3 year follow up. Methodological weaknesses in this study were the small sample size and short duration of oestrogen use.

Urinary tract infection (UTI) with the incidence of 6-9% is the most common postoperative adverse event in prolapse surgery.[16,17] In the RCT of 48 women by *Felding et al*, use of preoperative oestrogen unexpectedly reduced the incidence of postoperative culture positive UTI in the first 4 weeks after surgery. The use of preoperative vaginal oestrogens may also reduce the incidence of postoperative complications, e.g. haematoma.[18]

1.3 Rationale for the LOTUS Trial

To date, there has been no robust data on the benefits of pre and postoperative oestrogen treatment in postmenopausal women undergoing POP surgery. A Cochrane review published in 2010 did not find any clear evidence to suggest whether oestrogens help in reducing the symptoms of POP.[13] However due to frequent use, it was recommended that adequately powered RCTs with long term follow up is needed to identify benefits or risks.[13] We have done an up to date search and there have been no trials published or registered till December 2014. Highlighting this lack of evidence, we performed a survey of the British Society of Urogynaecology BSUG membership in April 2013 and noted that whilst 87% of the clinicians who returned the questionnaires (23% response rate) believed that postmenopausal women undergoing prolapse surgery would benefit from the use of low dose oestrogens, only 44% of the clinicians (out of the 39/89 respondents) recommend use of local oestrogen preoperatively before POP surgery (and not postoperatively regularly) (BSUG), The

reason behind this discrepancy may be the lack of conclusive evidence to support the change in clinical practice to use low dose oestrogens or the uncertainty regarding the potential adverse effects of this therapy. Encouragingly, 77%(69/89) of the respondents were willing to recruit patients into the trial to study the effectiveness of this intervention.

Whilst there is a plausible argument for using low-dose oestrogen to improve the vaginal environment and reduce UTIs at the time of prolapse surgery, 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 any effect in terms of prolapse related symptoms, overall quality of life and outcomes important to the women. Finally, the duration of oestrogen treatment, and cost-effectiveness compared with current practice are not known.

A high quality randomised controlled trial, with economic evaluation, is clearly needed to address these questions. However, before embarking on a large scale project, we aim to perform a feasibility study that addresses the acceptability of the intervention and information provided to women, the feasibility of recruiting and randomizing 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.

2 RESEARCH AIMS AND OBJECTIVES

2.1 Study Aim

The aim of the feasibility study is to find out if an appropriately powered randomised controlled trial (RCT) can be realistically undertaken. The feasibility study will also allow the research team to identify any barriers to recruitment and compliance, and fine tune study procedures such as data collection and prescription of the study treatments.

The aim of the definitive study would be to test the hypothesis that vaginal oestrogen treatment of postmenopausal women undergoing pelvic floor repair surgery leads to improved patient reported outcomes in relation to urinary, bowel, sexual function and prolapse related quality of life (QoL).

2.2 Feasibility study specific objectives:

1. To obtain estimates for important aspects of the protocol to allow development of a definitive trial
2. To derive real- time data on the design aspects of the study
   I. Proportion of eligible women of those screened
   II. Proportion of eligible women randomised
   III. Attrition rates (proportion of completed questionnaires at 6 months)
   IV. Compliance with treatment
   V. Acceptability of outcome measures
   VI. Estimate the variability of PFDI SF20 to inform the sample size calculation for the larger trial
3. To derive a realistic understanding of trial processes, in particular:
   I. Ascertain robustness of the data collection process during and after the hospital episode
   II. Determine the support required in units to ensure successful recruitment
   III. Why patients decline participation or withdraw after randomisation

2.3 Definitive Trial Objectives

2.4 Primary Objective of the definitive trial

Improvement in prolapse related QoL at 12 months as assessed by PFDI SF20. [19]

Secondary Objectives of the definitive trial:

1. Improvement sexual function related quality of life (QoL) at 12 months with the use of PISQ 12. [20]
2. Reduction of intraoperative complications like tearing or button holing of the vagina and blood loss.
3. Reduction in the incidence of surgical wound infection and urinary tract infection postoperatively.
4. Validate Patient Global Impression of Improvement (PGI-I)[21] in relation to the POP surgery, PFDI SF20 and PFIQ-7.

3 TRIAL DESIGN

3.1 Design

Multicentre feasibility open label trial comparing vaginal low-dose oestrogen with no treatment, in 100 consenting postmenopausal women who are planning to undergo POP surgery. They will be randomly allocated to:

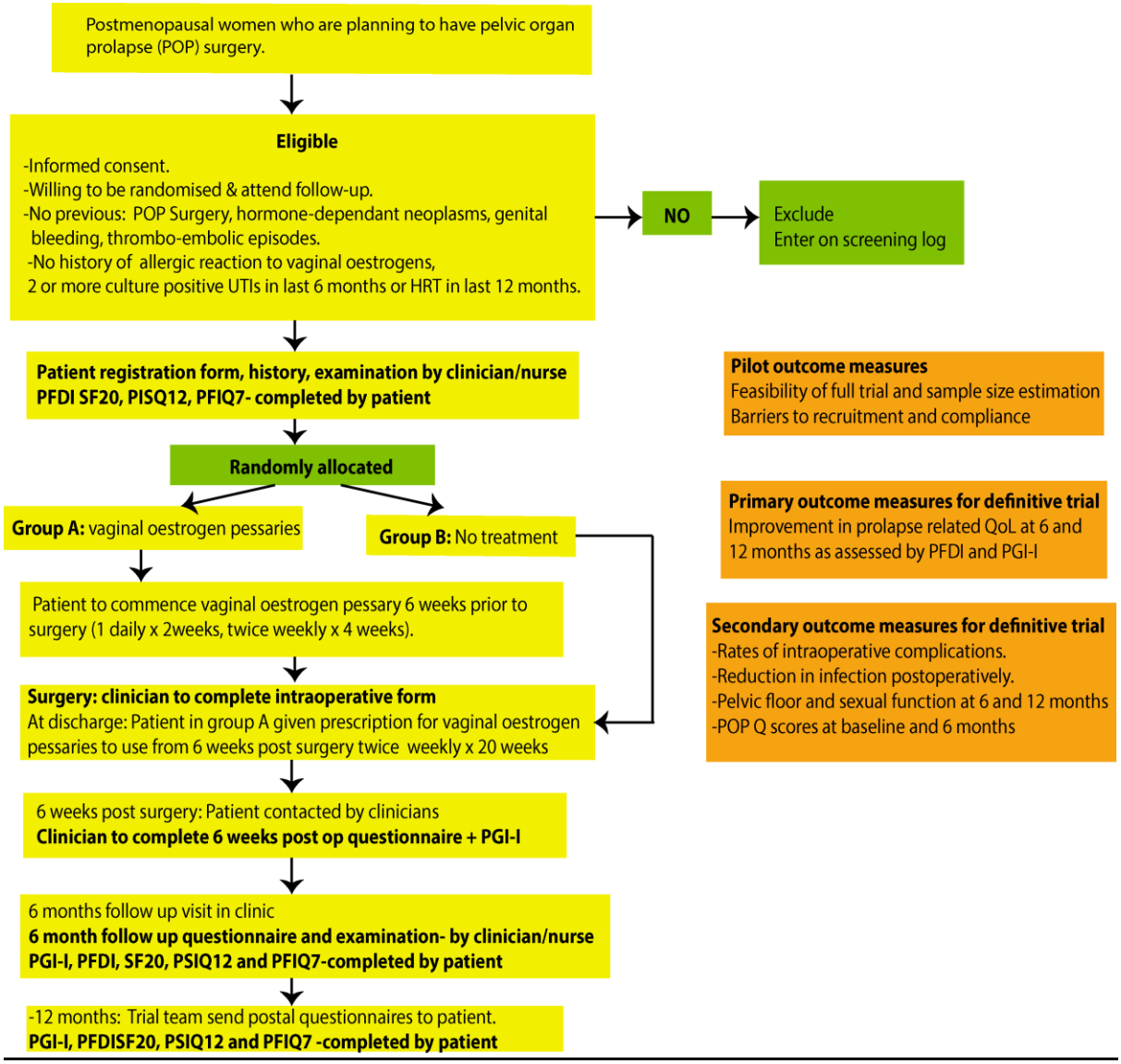
I. Intervention group (Group A): This will comprise of 6 weeks course of oestradiol 10 µg preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then 10µg oestradiol per vaginum twice weekly from 6-26 weeks postoperatively.
II. Comparison group (Group B) will receive no vaginal oestrogen treatment

3.2 Setting

Four to six urogynaecological centres in the UK

3.3 Participants flow through the trial

Study Flow Chart for LOTUS trial



4 ELIGIBILITY

4.1 Inclusion criteria:

1. Postmenopausal women
2. Consented to undergo surgical intervention for pelvic organ prolapse
3. Have not received HRT in the last 12 months
4. Willing to be randomised
5. Give written informed consent
6. POP surgery required in a different compartment if prior POP surgery performed

7.

4.2 Exclusion criteria:

1. Previous breast or uterine malignancy or other hormone- dependant neoplasms
2. Genital bleeding of unknown origin
3. Previous thrombo-embolic episodes in relation to oestrogen therapy
4. Women who cannot understand, speak or write in English
5. Women known to be allergic to any of the components of vaginal oestrogens
6. Two or more episodes of culture positive UTI in the last 6 months
7. Previous POP surgery in the same compartment
8. Voiding dysfunction (post-voiding residual volume>150ml)
9. Current or previous POP surgery involving mesh
10. Patient is participating in another CTIMP trial.

4.3 Identification of participants and consent

Ideally consent should be sought under unhurried circumstances when entry criteria are fulfilled by the researcher. Consent is sought in several stages. We aim to identify patients with POP by scanning GP referral letters. These women will be sent a Patient Information leaflet by post along with the hospital appointment.

Once the patient visits the hospital and is deemed to be eligible to participate in the study, consent will be sought and the paperwork completed by the researcher during face to face consultation). 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 (a copy of this should be filed in the patients notes) . 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). 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. We will also endeavour to record the difference between pre and post op haemoglobin wherever it has been done. 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 (the 6 week postoperative form will be filed only at the trials unit and not in the patients hospital notes). At the 6 month 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, PFIQ-7 & PGI-I). However if the patient's follow up appointment is delayed then the BCTU will post the 6 month (post randomisation) questionnaire to the patient who will return the form in a free post envelope.

The BCTU will post the 12 month post randomisation follow up questionnaire to the patient who will return the form in a free post envelope to the trials office once completed.

4.4 Informing participants GP

Women will be asked to consent to their GP being informed about their participation in the study and also to contact the GP if we need to trace the participant for follow up. A specimen "Letter to GP" is supplied.

4.5 Ineligible patients

If a woman undergoing POP surgery is screened but is not eligible for the LOTUS trial or consent for randomisation is not given, a record of the case will be kept in the screening log. The log will collect hospital number, patient's initials, date of birth, age, ethnic group, BMI and reason not eligible for the trial. The log should be kept in the centre's site file and a copy (in an anonymised format – removing initials and hospital number) sent to BCTU. This will inform screening and recruitment predictions for the definitive study. No further information will be collected on ineligible patients. Women who decline to participate in the study, will be invited to participate in a telephone/ face to face interview and encouraged to discuss their thoughts on the trial, information sheets and reason for non participation.(section12).

The screening logs will be maintained and information is to be collected on:

1. Ineligible patients and reason for ineligibility (Key provided with possible reason)

-No surgery required
-Cannot read/speak English
-Using local HRT
-On systemic HRT
- use of any HRT in the last 12 months
-Reaction to oestrogen
-Previous Breast/uterine malignancy/hormone dependent tumour
-PMB unknown reason
-VTE related to oestrogen therapy
-2 or more UTIs
-PVR >150ml
-Not menopausal
-Previous POP surgery with mesh
- Previous POP surgery in the same compartment

2. Eligible patients and reason for not randomising (Key provided with possible reason)

-Does not want to participate in research
-Not willing to be randomised

-Unable to gain informed consent (mental health reasons)
-Not willing to wait 6 weeks for surgery
-Did not attend appointment
-Wants conservative management (support pessary/ physiotherapy)
-Does not want surgery presently (family reason/ carer)

4.6 Co-Enrolment

Women randomised to the LOTUS trial should be excluded from participation in any further trial of investigational medicinal products (IMPs) for the treatment of gynaecological disorders or urological disorders. If the woman has withdrawn from the trial treatment but is still contributing to data collection, any further treatments within trials for her prolapse should be noted, for example if she chooses to participate in a trial of different methods of surgery for recurrent prolapse.

Women already participating in another trial of an IMP for a non-gynaecological reason are able to participate in LOTUS, provided careful consideration of the interactions between that IMP and the oestrogen is undertaken. Women already participating in non-IMP trials can be considered for LOTUS, including trial of different methods of prolapse surgery, providing mesh is not used.

5 RANDOMISATION AND STUDY DRUG SUPPLY

5.1 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)
4. Concomitant continence surgery performed

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

5.2 Supply of Study Treatments

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

5.3 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 6 months 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.

6 INVESTIGATIONAL MEDICINAL PRODUCTS

6.1 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.

6.2 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 20 weeks.

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 4wks
Day of surgery	6 weeks	0
6 weeks after surgery	20 weeks	Twice weekly for 20 wks

Women will be told that the study treatment is not to be taken orally. Women will be encouraged to insert the pessaries at the same time of day, for example just before bedtime. However, if a dose is missed, it should be administered as soon as possible thereafter, provided the next dose is not due.

6.3 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. Study personnel may ask why a participant has decided to withdraw, and record a reason if given. However, it should be noted that it is the participants right to withdraw without giving a reason.

6.4 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 (see Section 8.1.4). Women who fail to attend follow up appointments will be contacted on telephone and offered further follow-ups.

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.

7 SAFETY MONITORING PROCEDURES

7.1 Safety profile of oestradiol

Oestradiol pessaries at the dose of 10µg when used once daily for 2 weeks and then twice weekly for 10 weeks are known to be safe with no change in the systemic oestrogen levels after 12 weeks of use.[22] Oestradiol when used for 12 months at 10µg daily for 2weeks followed by twice weekly for 52 weeks resulted in a total annual oestradiol exposure of only 1.14 mg and did not stimulate the endometrium in postmenopausal women. There were no cases of endometrial hyperplasia or carcinoma in these women.[23] As there is no data available on its effect on the breast or on women predisposed to thromboembolic episodes, we have excluded women with previous history of breast malignancy or thromboembolic episodes from participation in this study.

Systemic absorption of oestrogen and the adverse effects of increased circulating hormone were found to be more common when oestrogen cream was used compared to 25µg estradiol tablets. ($p < 0.001$) Endometrial proliferation or hyperplasia was more common in the cream using group compared to tablets though the difference did not reach statistical significance.[24] In our study, we

are planning to use 10µg oestradiol tablets, which is a much lower dose, compared to other studies mentioned in the literature.

7.2 General definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 define categories of adverse events, the responsibilities of the investigators to notify adverse events to the Trial Office and for the Sponsor, or designated delegate, to report to the regulatory authority and ethics committee. It is therefore imperative that all investigators have a thorough understanding of anticipated adverse events and the reporting process of these events.

7.2.1 Adverse Events (AEs)

An AE is any:

I. Unintentional, unfavourable clinical sign or symptom.
II. New illness or the deterioration of existing illness.

The following are not AEs:

I. A pre-existing condition (unless it worsens significantly during treatment)
II. Recurrence of prolapse
III. Urinary tract infection
IV. Dysuria
V. Vaginal pain or burning sensation

7.2.2 Adverse Reactions (ARs)

An AR is an adverse event that is considered to have a "reasonable causal relationship" with study drug. The known minor ARs for oestradiol, as Vagifem™, refer to SmPC link in Appendix A.

7.2.3 Serious Adverse Events (SAEs)

An SAE, in the context of the LOTUS Trial, is an untoward event which:

I. Results in death
II. Is life-threatening
III. Requires hospitalisation or a longer than anticipated stay in hospital
IV. Results in a persistent or significant disability

7.2.4 Expected SAEs

In addition to the ARs, there are a number of potential serious SAEs discussed in the current SmPC for Vagifem™ as potentially associated with use of a higher dose of oestradiol, but considered very rare (<1 in 10,000 patient years exposure), listed in **Error! Reference source not found.**. These events do not meet the criteria of a suspected, unexpected serious adverse reactions (SUSAR) unless for reason of their severity.

Other serious adverse events have been reported in association with oestrogen treatment, but risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments. Those listed in the SmPC, and any others meeting the definition of a SAE, should be reviewed to determine if they are SUSAR.

In considering SAES, the most updated SmPC should always be used, available at http://emc.medicines.org.uk/.

7.2.5 Suspected unexpected serious adverse reactions (SUSARs)

A SUSAR is an SAE suspected to be related to a product, which is of a type or severity which is NOT consistent with the up-to-date SmPC.

7.3 Reporting AEs, SAEs, SUSARs

There is a degree of overlap between some minor adverse events from oestrogen and anticipated complications of POP surgery, for example vaginal discharge, so consideration of the timing of the event in relation to the surgery is necessary.

7.3.1 Reporting AEs

Specific adverse events related to surgery and forming part of the outcome assessment will be collected from the first administration of study treatment until the end of the study participation, whether observed directly or reported by the patient. Non-serious, expected adverse reactions or events are not required to be reported.

7.3.2 Reporting SAEs

All SAEs meeting the definition in Section 7.2.3 must be recorded on a SAE Form and faxed to the BCTU on 0121 415 9136 within 24 hours of the research staff becoming aware of the event. As women may not present to their gynaecologist with a SAE, participants will be given a prompt card to encourage reporting directly to the Trial Office of any hospitalisations. The LOTUS Trial Office will alert the original gynaecologist to make contact with via the participant's GP or treating doctor. Once the nature of the SAE is established, the local Principal Investigator (or other nominated clinician) has to assign seriousness, causality and expectedness to the SAE before reporting.

For each SAE, the following information will be collected, from the gynaecologist, treating doctor or woman herself:

I. Full details in medical terms with a diagnosis, if possible
II. Its duration (start and end dates; times, if applicable)
III. Action taken
IV. Outcome
V. Causality, in the opinion of the investigator
VI. Whether the event would be considered expected or unexpected (refer to the most recent and relevant SmPC)

Assessment of causality and expectedness must be made by a doctor. If a doctor is unavailable, initial reports without causality and expectedness assessment should be submitted to the BCTU by a healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter, ideally within the following 24 hours. An SAE which is assessed as possibly, probably or definitely related to trial treatment is classified as a Serious Adverse Reaction (SAR).

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors and provide

further follow-up information as soon as available. If a participant dies, any post-mortem findings must be provided to the BCTU.

SAEs still present at the end of the trial must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the patient finishes the study treatment.

The BCTU will report all SAEs to the Trial Oversight Committee (TOC, see Section 10.3) approximately 6-monthly. The TOC will view data blinded to treatment but will be able to review unblinded data if necessary. The CI will also report all SAEs to the main REC and MHRA annually, and to the Trial Steering Committee 6-monthly. The main REC, MHRA and TSC will only view data blinded to trial treatment. Local Investigators are responsible for reporting SAEs to their host institution, according to local regulations, but they do not need to inform MHRA or main REC as this will be done by the BCTU as detailed above.

7.4 Reporting SUSARs

SAEs categorised by the local investigator as **both** suspected to be related to the trial drug **and** unexpected are SUSARs, and are subject to expedited reporting.

All SUSARs must be recorded on a SAE Form and faxed to the BCTU on 0121 415 9136 immediately or within 24 hours of the research staff becoming aware of the event. The CI or nominated individual will undertake urgent review of SUSARs within 24 hours of reporting and may request further information immediately from the patient's clinical team. The CI will not overrule the causality, expectedness or seriousness assessment given by the local investigator. If the CI disagrees with the local investigator's assessment, further clarification and discussion should take place to reach a consensus. If a consensus cannot be reached, both the opinion of the local investigator and the CI should be provided in the report to the Medicines and Healthcare and Regulatory Agency (MHRA) and the MREC.

The BCTU will report all SUSARs, unblinded, to the MHRA and the MREC on behalf of the co-sponsors. If the SUSAR resulted in death or was life-threatening this will be done within 7 days of the initial report being received, or within 15 days for any other SUSAR.

If information is incomplete at the time of initial reporting, or the event is ongoing, the BCTU will request follow-up information, including information for categorisation of causality, from the local investigator and will send the follow-up information to the MHRA and MREC within an additional 8 days for fatal or life-threatening SUSARs and as soon as possible for any other events.

7.5 Pharmacovigilance responsibilities

7.5.1 Local Principal Investigator (or nominated individual in PIs absence):

I. To record **all** SAE/SARs that occurs in the subjects taking part in the trial. This excludes non-serious, expected adverse events or reactions listed in the current SmPC (Refer to link in Appendix A)
II. Medical judgement in assigning seriousness, expectedness and causality to SAEs.
III. To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
IV. To report SAEs to local committees if required, in line with local arrangements.
V. To sign an Investigator's Agreement accepting these responsibilities.

7.5.2 Chief Investigator (or nominated individual in CIs absence):

I. To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment
II. To review all events assessed as SAEs in the opinion of the local investigator
III. To review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and CI with regards to SUSAR status, local assessment will not be over-ruled, but the CI may add comments prior to reporting to MHRA.

7.5.3 Birmingham Clinical Trials Unit:

I. To immediately report SUSARs to co-sponsors.
II. To report SUSARs to MHRA and MREC within required timelines as detailed above, on behalf of the co-sponsors
III. To prepare annual safety reports to MHRA, MREC and TOC.
IV. To prepare SAE safety reports for the TOC at 6-monthly intervals. Data will be presented blinded to treatment, but the TOC will be able to review unblinded data if necessary.
V. To report all fatal SAEs to the TOC for continuous safety review

- To notify Investigators of SUSARs which compromise patient safety

7.5.4 Trial Oversight Committee (TOC):

I. To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies.
II. To review data, patient compliance, completion rates, adverse events (during treatment and up to end of follow-up).
III. To make recommendations to the TMG on protocol modifications.
IV. To review (initially at approx 6-monthly intervals) overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis

8 OUTCOME MEASURES

8.1 Process outcomes for the feasibility study

8.1.1 Proportion of eligible women of those screened.

All women with a POP diagnosis being scheduled for POP surgery will be screened against the eligibility criteria, and a count of the clinical reasons for ineligibility will be kept.

8.1.2 Proportion of eligible women randomised.

Eligible women who have received information regarding the trial will be approached for consent, and a count of those that decline, and their reasons, where stated, will be collected.

8.1.3 Attrition rates

The proportion of randomised women who complete the proposed primary outcome measure at six months will be calculated. The proportion of outcome measures captured at the first attempt at contact will be noted, alongside the response rate after subsequent contacts, and the methods of contact, will be captured. Reasons for loss to follow-up and withdrawal of consent to contact will be noted wherever possible.

Women will be checked for compliance with treatment on the day of surgery, at the 6 weeks telephone call and at 6 months follow up visit. The research nurse/clinician will receive the empty/partially used/unused treatment bottles at the local centres, and will document this in the database for each trial participant. In an effort to improve compliance, women who fail to return the treatment bottles, whether empty or not, will be contacted by telephone or email by the Clinical Coordinator for advice and support.

Women will also be asked to subjectively state whether they used their treatments always (used them exactly as scheduled), almost always (over 75% on schedule), mostly (50-75% on schedule), some of the time (25-50% on schedule), hardly at all (less than 25% on schedule) or never.

8.1.4 Acceptability of outcome measures

The completion rate of each outcome measure will determine the user acceptability of the patient reported outcome measures.

8.1.5 Data to inform the sample size calculation for the larger trial

Responses from the PFDI-SF20 will be used to derive a pooled group standard deviation to inform the design of a larger trial.

8.1.6 Ascertain robustness of the data collection process during and after the hospital episode

Patients will be asked at the 6 month hospital visit about the details of postoperative complications. This will be cross referenced with already existing data collected during the hospital stay and the 6 week telephone follow up.

8.1.7 Determine the support required in units to ensure successful recruitment

The eligibility and consent rate, together with feedback from the research nurses and investigators, will determine the NHS support requirement for the substantive trial. The experience of the trial and clinical coordinators, will inform the research costs.

8.2 Clinical and Patient Reported Outcome Measures

8.2.1 Prolapse specific quality of life measures – PFDI-SF20 and PFIQ-7

The Pelvic Floor Distress Inventory- Short Form 20 (PFDI-SF20) assesses symptom distress in women with pelvic floor disorders The short-form version of the PFDI has a total of 20 questions and 3 scales (Urinary Distress Inventory, Pelvic Organ Prolapse Distress Inventory, and Colorectal-Anal Distress Inventory).

The Pelvic Floor Incontinence Questionnaire (PFIQ-7) is a seven question self-report measure assessing pelvic floor impact on QOL, daily activities and emotional health. Originally, the PFIQ was 93-item patient report outcome, with a short version subsequently derived. Upon assessment it was found that the long form and short form were substantially close in reliability and validity. The short form questionnaires are more commonly used due to similar psychometric property values as well as decreased administration time.[19,25]

The PFDI and PFIQ are responsive to change in women undergoing surgical and nonsurgical treatment for pelvic organ prolapse. In one study, the PFDI was found to be more responsive than the PFIQ.[26] Both the questionnaires will be completed to ascertain if the completeness rate are similar and if one questionnaire is more responsive to change, in comparison to a global impression of change.

8.2.2 General measures of improvement – PGI-I

The Patient Global Impression of Improvement (PGI-I) is a global index that may be used following prolapse surgery. It is a simple, direct, easy to use scale that is intuitively understandable to clinician. The PGI-I has been found to have excellent validity.[21] Sexual function outcome – PISQ-12

The short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire PISQ-12 is a reliable, consistent and valid instrument to evaluate sexual functioning in women with urinary incontinence and/or pelvic organ prolapse. It is easy to understand that it may be easily administered and self-completed by the women.[27]

8.2.3 Clinical assessment

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 intraobserver reliability.[28]

There are six defined points for measurement in the POPQ system – Aa, Ba, C, D, Ap, Bp and three others landmarks: GH, TVL, PB (see Figure 1). 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).

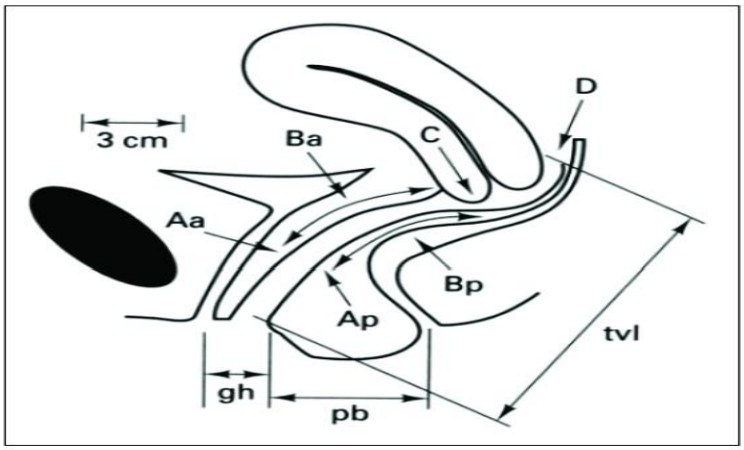


Figure 1 Anatomical landmarks for the POP-Q assessment

Clinicians will be requested to complete the POP-Q three by three grid (see Figure 2) and to document the maximum stage of prolapse as stage I, II or III/IV. 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.

anterior wall **Aa**	anterior wall **Ba**	cervix or cuff **C**
genital hiatus **gh**	perineal body **pb**	total vaginal length **tvl**
posterior wall **Ap**	posterior wall **Bp**	posterior fornix **D**

Figure 2: POP-Q grid

8.2.4 Operative complications

Wound infection is defined by the Centre for Disease Control [12] as infection which occurs within 30 days after the operation. For the LOTUS Study, the infection appears to be related to the operation and involves superficial and/ or deep soft tissues. In addition, at least *one* of the following:

1. Purulent discharge from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision that spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination.

Incidence of wound infections, duration and subsequent treatment will be recorded at 6 weeks post-surgery at the routine clinical follow-up assessment. Women having symptoms before then would report to their treating gynaecologist or GP, as would be usual practice. A urinary tract infection (UTI) (also known as acute cystitis or bladder infection) is an infection that affects part of the urinary tract. When it affects the lower urinary tract it is known as a simple cystitis (a bladder infection) and when it affects the upper urinary tract it is known as pyelonephritis (a kidney infection). Women will be asked to report episodes of UTIs, and whether they were confirmed by their gynaecologist or GP, or else self-treated, at 6 weeks and 6 and 12 months.

8.2.5 Follow-up and timing of assessments

Table 1:The outcome measures, the frequency of collection and by whom they are collected.

Data and/or outcome measure collected	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 in clinic or postal 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		X	X	X	X	X	Clinician
		Spontaneous reporting					Patient

events			

Table 1 Assessment schedule for the LOTUS Trial

Initial follow up will be carried out 6 weeks after surgery and this will be by telephone, by the research team, who will ask about the details of postoperative recovery, complications after discharge and will advise the participant in Group A to commence vaginal pessaries for 20 weeks. Hospital follow up will be carried out by the randomising gynaecologist at 6months following surgery where they will be examined for POP-Q scoring and requested to complete the questionnaires. If follow up appointments are delayed then the questionnaire will be collected by the BCTU. A postal follow-up will be carried out 12 months by BCTUat, with questionnaires to be sent back in the self-addressed envelope provided. Patients will be contacted if they fail to attend follow up appointment and agree to complete the questionnaire over the telephone.

8.3 Definition of the End of Trial

The definition of the end of the interventional phase of the trial will be when the last participant has completed 26 weeks post-surgery and ceased the study treatment. The end of the observational phase will be at 12 months post-surgery, once all attempts have been made to obtain the relevant 12 month outcome assessments.

9 ACCRUAL AND ANALYSIS

9.1 Sample size

The LOTUS feasibility study will enrol 100 women. This number will allow us to measure recruitment and compliance rates with 95% confidence interval (CI) width between 10 and 20% (e.g. if we assume a good compliance with treatment rate of 70%, we could rule it out being less than 60%). It would also be enough women to estimate the standard deviation (SD) of PDFI-20 with reasonable confidence for future planning of a larger trial (95%CI for SD would be 7 points, assuming the SD is around 20 points).

9.2 Analysis

The size of this feasibility study will not allow reliable assessment of the effect of the intervention on outcomes and so hypothesis testing is not proposed. Analyses of feasibility and patient reported outcomes will primarily take the form of simple descriptive statistics (e.g. proportions & interquartile ranges, means and standard deviations) and where appropriate, point estimates of effects sizes (e.g. mean differences and relative risks) and associated 95% confidence intervals. In the first instance, for patient reported outcomes, women will be kept in the groups they were allocated, regardless of compliance with treatment (intention-to-treat). Analysis will be completed once all patients have completed the primary timepoint at six month follow-up, with 12 month follow-up analysed subsequently. A Statistical Analysis Plan will be generated for review by the TOC before any analysis takes place.

9.3 Handling missing data

Missing data for the primary outcome should be limited at baseline and 6 months, as patients will be asked to complete questionnaires in clinic. There is a potential for some missing data to occur at 12 month follow-up, however, both BCTU and clinicians will be involved in contacting patients for any missing data via telephone and post. Imputation of missing responses is not proposed for patient reported outcomes as this not a definitive trial and no hypothesis testing will be performed.

10 DATA ACCESS AND QUALITY ASSURANCE

10.1 Data management and confidentiality

Personal data and sensitive information required for the LOTUS feasibility study will be collected directly from trial participants and hospital notes on data collection forms, coded with the participant's unique trial number and initials. Participants will be informed about the transfer of this information to the LOTUS trial office at the BCTU and asked for their consent. The consent and randomisation forms will also be faxed or sent as attachments on emails between nhs.net email accounts, to the study office, as these are the sole documents with identifiable details, again with consent from the participant. The data will be entered onto a secure computer database, either directly via the internet using secure socket layer encryption technology or indirectly from paper by BCTU staff.

All personal information received in paper format for the trial will be held securely and treated as strictly confidential according to BCTU policies. All staff involved in the study (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server at Birmingham Clinical Trials Unit (BCTU) under the provisions of the Data Protection Act and/or applicable laws and regulations. Only the clinical coordinator, trial coordinator and study statistician will have access to the database until completion of the analysis. Investigators will only have access to personal information on their own patients.

10.2 Data Quality Assurance and Validation

The study will adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry of paper questionnaires will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables. Source data verification of clinical outcomes will only be employed if there is reason to believe data quality has been compromised, and then only in a sub-set of practices.

Good clinical practice in relation to data collection will begin with simple, unambiguous data collection forms, and the need for complete and valid data collection reiterated at site initiation. Reports will be available to investigators indicating missing clinical and questionnaire data for all participants at that centre.

10.2.1Monitoring and Audit

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by the Trial Coordinator, providing direct access to source data and documents as requested. Trusts may also be subject to inspection by the Medicines and Healthcare Products Regulatory Agency and/ or by the Research and Development Manager of their own Trust and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

10.3 Trial Oversight Committee

As this is a feasibility study, there will be no formal trial steering or data monitoring committee. Instead a Trial Oversight Committee will be appointed, which will consist of three non-recruiting members. The Committee will provide supervision and advice for the study, and ensure the study is conducted as applicable to the MRC Guidelines for Good Clinical Practice in Clinical Trials. Trial data provided to the TOC will be anonymised but study group allocation may be provided, if it is necessary for their deliberations regarding serious adverse events.

10.4 Long-term storage of data

In line with the Medicines for Human Use (Clinical Trials) Regulations, once data collection is complete on all participants, all data will be stored for at least 5 years. This will allow adequate time for development and completion of a substantive study, if deemed feasible. Limited data on the participants and records of any adverse events may be kept for longer if recommended by an independent advisory board, and archived in long-term offsite data archiving facilities. The BCTU has standard processes for both hard copy and computer database legacy archiving. After the end of the trial, the site files from each centre will be archived at the site.

11 ORGANISATION AND RESPONSIBILITIES

The Chief Investigator, Dr Pallavi Latthe, takes primary responsibility for the design, conduct and reporting of the study. The University of Birmingham Lead, Dr Jane Daniels, takes responsibility for the conduct and delivery of those parts of the study, which are according the co-sponsorship agreement, managed or overseen by the BCTU. The BCTU is a registered CTU with the UK Clinical Research Collaboration.

All investigators are responsible for ensuring that the research they undertake follows the agreed protocol, for ensuring that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, serious adverse reactions and other events or suspected misconduct through the appropriate systems.

11.1 Local Co-ordinator at each centre

Each Centre should nominate a doctor to act as the local Principal Investigator and bear responsibility for the conduct of research at their centre. The responsibilities of the local Principal Investigator will be to ensure that all medical and nursing staff involved in the care of LOTUS patients are well informed about the study and trained in trial procedures, including obtaining informed consent. The local Principal Investigator should liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

11.2 Nursing Co-ordinator at each centre

Each participating centre may also designate one nurse as local Nursing Coordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The research nurse and non-clinical staff who are appropriately trained, can take responsibility for all aspects of local organisation including identifying, consenting, randomising and data collection for the participants. Again this person would be sent updates and newsletters, and would be invited to training and progress meetings.

11.3 The LOTUS Trial Office

The Trial Office at the BCTU is 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 also provides the central randomisation service and is 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 is 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.

11.4 Research Governance

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework for Health and Social Care and the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended in 2006 and any subsequent amendments.

All local Principal Investigators will be required to sign a Site Principal Investigator Declaration, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. All host NHS Trusts will be required to sign a Clinical Study Agreement, countersigned by the Co-sponsors, listing the responsibilities of each party. Deviations from the agreement will be monitored and the Co-sponsors will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

The Co-Sponsors will ensure any researchers not employed by an NHS organisation who may be in position to influence the care of patients, or require access to patient notes, obtain a research passport or letter of access.

11.4.1 Ethical and NHS Permission

The trial protocol and related documents have been granted a favourable ethical opinion by West Midlands Research Ethics Committee (REC). Any subsequent protocol amendments will also be submitted to the REC and MHRA for approval, as appropriate.

The Local Comprehensive Research Network will conduct global governance checks. The participating Trusts' Research and Development departments will assess the facilities and resources needed to run the trial, in order to give host site permission. The Trial Office is able to help the local Principal Investigator in the process of the site specific assessment by completing much of Site Specific Information section of the standard IRAS form as possible. The local Principal Investigator will be responsible for liaison with the Trust R & D department with respect to locality issues and obtaining the necessary signatures at their Trust.

As soon as NHS Permission has been obtained, the Trial Office will send a folder containing all trial materials to the local Principal Investigator. Potential trial participants can then start to be approached

11.4.2 Clinical Trial Authorisation

The Trial Office has obtained Clinical Trials Authorisation from the Medicines and Healthcare Regulatory Authority and has obtained a unique EudraCT number for the trial. Any subsequent protocol amendments will also be submitted to the REC and MHRA for approval, as appropriate.

11.5 Funding and Cost implications

NHS support costs associated with the trial, e.g. gaining consent, are estimated in the Site Specific Information section of the standard IRAS form. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

11.6 Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored trial and so ABPI/ABHI guidelines on indemnity do not apply. The normal NHS indemnity liability arrangements for research detailed in HSG96(48) will operate in this case.

However, it should be stressed that in terms of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical trial.

11.7 Dissemination of results

This feasibility study is designed to identify if a substantive trial is possible, although the findings of this study may be of scientific interest to others in their own right. We plan the dissemination strategy in a number of ways: A report will be prepared for the funders and ethics committee. Findings will be more widely available via the trial study website. The feasibility findings will also be presented at local and national meetings such as the British Society of Urogynaecology or British Menopause Society. This will capture an extremely large audience of national and international clinicians. We will seek all opportunities to assess the willingness to participate throughout the feasibility study and gain research community support for in a substantive trial should such a RCT be proven feasible.

12 Qualitative Study

12.1 Purpose of qualitative interviews

Randomised controlled trials (RCT) are considered to be the most robust method by which researchers can determine the effectiveness of an intervention. The success of an RCT depends largely on the ability to recruit and retain a target population in adequate numbers in order to answer the scientific question. It is often challenging to recruit older women than younger participants to clinical trials due to numerous reasons.[29 30] The reasons for difficulty recruiting that are unique to older women are that many of them are dependent on family members for transport or they themselves are caregivers in their family. Other frequent challenges identified are time constraints, presence of co-morbid conditions that make older women reluctant to enrol over an extended period of time.

It has been noted that large emphasis is devoted to designing the intervention for a clinical trial. However, it is equally important to dedicate time towards planning recruitment strategies and identify the reasons for or against participation by the targeted populations.

There is lack of information focusing on women's views on their experience of prolapse and the use of local hormonal replacement therapy. Several quantitative studies investigate issues of POP, however utilising qualitative research alongside may be a complementary tool to capture the experience or perceptions of these women.[21] Qualitative interviews from a subgroup of women in the feasibility study will be valuable in assisting in the planning of definitive clinical trials.

12.2 Aim of qualitative study

To identify the motivations for, and barriers to recruitment and participation in clinical trials among postmenopausal women with POP intending to have surgical management.

12.3 Qualitative assessment of barriers and facilitators to recruitment to LOTUS study

The ability to recruit and retain participants in randomised control studies pose a major challenge. It is essential to identify the reasons for or against participation during the feasibility phase of an RCT so this may assist the researchers in adequate planning of the recruitment process for the definitive trial. To obtain this valuable information, conducting face to face or telephone interviews with participants willing to or declined to participate in the feasibility study will help enhance our understanding of the factors that influence participation in a RCT.

12.4 Identification of participants to the qualitative arm of the feasibility study

We aim to recruit eligible women who have entered the feasibility study as well as women who have declined participation into the trial but have agreed to discuss their reason for not participating, their experience of POP and their views on the trial. Gaining the perspectives of both groups of women will provide the research team with key insight into trial recruitment barriers.

Eligible women will be identified and recruited through their GP letters and from urogynaecology clinics. Information sheets regarding the study are sent to the women along with their letter of invitation. The information sheets include a description of the interview process, the nature and purpose of the interview in relation to the trial and how the research findings would be used. A purposive sample of 10-15 women from the each group of participants will be interviewed. Additional women will be interviewed until data saturation is reached. It is anticipated that 10 women in each group will be sufficient to reach theoretical saturation, this will depend on the variability in the sample and properties of the data, recruitment will continue until no new themes emerge from additional data collection. The small number of patients will ensure that the interviewer has the opportunity to allow patients to explore and describe the experiences regarding POP and the trial.

Interview process will be conducted either at the time of women's decision making of participation/ non-participation in the trial or soon after. The interview process will be conducted either by a face-to-face process or via telephone interview. The women will be invited to discuss and explore their willingness to participate in the study in general, their views of the use of HRT, the use of placebo arm and their needs regarding the information sheets provided. The participants are encouraged to generate discussion regarding the study. An interview guide will be available consisting of open-ended questions addressing different topic areas to ensure that the aims of the study are achieved. A clinical research fellow will conduct interviews.

12.5 Consent and withdrawal

Written informed consent will be obtained either prior to or at the time of the interview process. If at any point the women feel that they want the interview stopped, this will be respected. If women decide to withdraw from the interview study completely this will be observed.

12.6 Interview process and anonymity

The interview process may last up to 30-45 minutes. Interviews will be digitally audio- recorded and will then be transcribed by the researcher. Transcripts will be audited for accuracy. No names will be used in the transcription. Women will be offered notification of any publications of the study findings in medical journals. Any direct quotations used in any publication will be anonymised.

12.7 Storage of data

Digital recordings will be stored in an electronic file, which only the research team will have access to. Only those required to transcribe the recordings will listen to them. Once transcribed and checked for accuracy the digital file will be destroyed. All data will be stored and archived in line with the BCTU policies.

12.8 Analysis

We will use qualitative content analysis to develop a series of coding units from the interview process and identify key descriptive themes within the qualitative data. Data will be coded using the NVivo software and analysed thematically. The coding categories will be systematically approached and data analysis will be conducted. To address validity, two researchers will crosscheck the data independently, the themes will be cross-referenced and these results will be combined. Brief quotations from individual women will be provided for illustrative purposes

APPENDIX A: ADVERSE REACTIONS OF OESTRADIOL

The manufacturer may change the SmPC's for this study as new information becomes available. The study will therefore adopt the manufacturer's current SmPC's.

The study team will monitor and review changes to the SmPC's and consider the impact on the study and revise documents if required. The SmPC's are published on the electronic Medicines Compendium (eMC)

https://www.medicines.org.uk/emc/medicine/23819

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