Joint Research Management Office (JRMO) Research Protocol for Research Studies

Full Title	*Preventing Endometrial Cancers: Comparing Risk-Reducing Strategies*
Short Title	*PRESCORES*
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1. Contents

2. Glossary

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
BRCA1	Breast Cancer Gene Type 1
BRCA2	Breast Cancer Gene Type 2
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
EPCAM	Epithelial cell adhesion molecule
EC	Endometrial Cancer
EQ-5D	EuroQol 5-dimensional questionnaire
GAFREC	Governance Arrange for NHS Research Ethics Committees
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRQL	Health-Related Quality of Life
HRUS	Health-Related Utility Scores
ICF	Informed Consent Form
LNG-IUS	Levonorgestrel Intrauterine System
LS	Lynch Syndrome
MLH1	MutL homolog 1
MSH2	MutS homolog 2
MSH6	MutS homolog 6
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
OC	Ovarian Cancer
PMS2	Post Meiotic Segregation increased 2
PI	Principle Investigator
PIS	Participant Information Sheet
QALY	Quality Adjusted Life Year
REC	Research Ethics Committee
RRS	Risk Reducing Surgery
RRH	Risk Reducing hysterectomy
RRHBSO	Risk Reducing hysterectomy and bilateral salpingo-oophorectomy
SAE	Serious Adverse Events
SDV	Source Document Verification
SOP	Standard Operating Procedure
SNP	Single Polynucleotide
SSA	Site Specific Assessment
TMG	Trial Management Group

3. Signature page

CI Agreement

The study, as detailed within this Research Protocol, will be conducted in accordance with the principles of Good Clinical Practice (GCP), the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I agree to take responsibility for the statistical analysis and oversight of this study.

CI Name:	**Professor Ranjit Manchanda**
Signature:	
Date:	**10/1/24**

4. Summary and synopsis

Short title	PRESCORES
Methodology	Cross-sectional cohort study, questionnaire-based
Objectives / aims	To determine who would benefit from preventive strategies for Endometrial Cancer: - To determine the health-related utility scores for risk reducing hysterectomy for endometrial cancer - To determine the lifetime risk thresholds of Endometrial Cancer for cost-effectiveness of preventive interventions - To determine the acceptability of preventive strategies for endometrial cancer in the general population
Number of participants	Not applicable
Inclusion and exclusion criteria	**Inclusion criteria:** Part 1: a) Female b) Age ≥18 years old c) Lynch Syndrome diagnosis - confirmed germline mutation in *MLH1*, *MSH2*, *MSH6*, *PSM2*, *ECPAM* d) UK Resident **Exclusion criteria:** Part 1: a) Unwilling or unable to provide informed consent b) Inability to understand written and verbal English c) Prior history of endometrial, ovarian or cervical cancer
Statistical methodology and analysis (if applicable)	Baseline characteristics will be calculated with descriptive statistics. Appropriate regression analysis & cohort matched analysis will be used to evaluate impact of covariates on categorical and linear variables. Decision analysis using Markov model for health-economic analysis.
Study duration	36 months

5. Introduction

5.1. Background

Endometrial cancer and prevention
Endometrial cancer (EC) is the fourth commonest women's cancer in the UK with ~9300 cases each year(1-3) This incidence is predicted to rise by 25.4% in the UK, and 52.7% globally by 2040(4). Reproductive and lifestyle factors which increase oestrogen exposure are acknowledged to influence carcinogenesis (5), including obesity, diabetes mellitus, early menarche, nulliparity and Tamoxifen use. However, 2-5% of EC arise in the context of a hereditary cancer syndrome(6-8).

Lynch Syndrome (LS) affects an estimated 1 in 280-370 people (9, 10), and is responsible for around 3% of EC cases (7, 8, 11). It is caused by an autosomal dominant inherited pathogenic variant (PV) or likely pathogenic variant (here forth called pathogenic variant or PV) in the DNA mismatch-repair (MMR) genes (*MLH1, MSH2, MSH6, PMS2, EPCAM*), and is the commonest inheritable cause of EC. This results in a lifetime risk of EC of 13-57% (12-14), depending on the mismatch repair gene involved. EC is often described as the 'sentinel' cancer in LS women (13, 15, 16). However, LS also results in an increased lifetime risk of ovarian cancer (OC) of up to 17% (14, 17), and predisposes to colorectal cancer as well as cancers of the stomach, hepatobiliary, urinary tract and brain (13).

Management of LS is primarily focused on reducing cancer risk. For LS associated gynaecological cancers, screening programmes are not yet nationally available as a clear impact on mortality remains to be demonstrated (18, 19). Therefore, access remains dependent on involvement in a research trial and/or geographical location.

Risk-reducing surgery is the most clinically effective intervention to prevent EC and OC in women with LS, with no cases of EC and only a few case reports of primary peritoneal cancer found following this.(18, 20) Risk reducing surgery involves risk-reducing hysterectomy (RRH) for endometrial cancer prevention, with bilateral salpingo-oophorectomy (BSO) to remove the fallopian tubes and ovaries, for OC prevention.

The decision making process for risk reducing surgery for LS is complex and dynamic, and changes with time. It may be affected by a number of factors including age, cancer history, fertility wishes, menopausal status and other considerations. Whilst the decision for surgery is often motivated by a desire to reduce cancer worry and risk (21), RRH results in a definitive end to fertility and can raise complex psychosocial concerns surrounding femininity (22). Any operation has risks of peri-operative complications, and a recovery period. Pre-menopausal bilateral oophorectomy, for women at increased risk of OC, leads to an abrupt oestrogen withdrawal and premature menopause. This is associated with significant sequelae such as vasomotor symptoms and an adverse impact on libido and sexual function (23, 24), as well as longer-term risks of osteoporosis, coronary heart disease, cognitive impairment and dementia, Parkinsonism, and detrimental impact on quality

of life (25-30). These effects are greater in women who have RRH-BSO under the age of 45-50 years and who don't take Hormone Replacement Therapy. Different women will have different priorities in choosing whether and when to have risk-reducing surgery (31).

Health Economic Disutility Analysis
The impact of RRH with or without BSO for EC prevention upon Health-Related Quality of Life (HRQoL) remains unknown. HRQoL is defined as a subjective perception of the impact of health status, including disease and treatment, on a person's physical, psychological and social functioning (32). Although this measure is primarily based on patient experiences, objectively quantifying these figures allows comparisons within disease cohorts and more broadly across different health-care interventions. Health-Related Utility Scores (HRUS) represent an objective measures of a health state, by assigning a value of between 0 (death) and 1 (perfect health) to each condition.

The UK's National Institute for Health and Care Excellence (NICE) recommends economic decision models should use HRUS to calculate quality-adjusted life years (QALYs) (33). In their guidance on the evaluation of health technologies, NICE recommends such models be based upon the "reference case", to ensure a consistent approach to health-economic modelling across multiple diseases and technologies (34-36). The preferred instrument is the EQ-5D; a generic patient-reported-outcome measure developed by the EuroQol Group, which assesses quality of life using five domains; mobility, self-care, usual activities, pain/ discomfort, anxiety/depression (37). This questionnaire was originally available with three levels of response for each domain (known as EQ-5D-3L), although a version with five-levels of response has been developed, allowing for finer discrepancy between health states (known as EQ-5D-5L, hereafter referred to as EQ-5D) (38). EQ-5D ratings are converted to HRUS using a country-specific formula, derived from a time-trade-off exercise conducted on a representative sample of the general population for each country (39). Thus the "reference case" provides for patient-reported outcomes to be converted to HRUS using the valuations of society.

Understanding the impact of RRH-BSO on HRQoL would enable clinicians to better support women with increased EC risk contemplating risk-reducing surgery in a complex decision making process. Additionally, the derivation of HRUS would enable more accurate health-economic and cost-effectiveness analysis of risk reducing surgery to prevent EC. Disutility is a key variable and driver which can affect the results of these analysis. It is currently unknown what level of lifetime EC risk would justify risk-reducing treatments, although such modelling has been undertaken for risk-reducing BSO in OC prevention (40, 41).

The aim of this research would be to obtain HRUS for pre and post-menopausal patients undergoing RRH for EC prevention. This can then be used to build decision analysis models to define the EC lifetime risk threshold at which to perform RRH.

5.2. Rationale

The major benefit of this modelling is that it would be relevant for any condition which raises EC lifetime risk, which includes not only LS, but any number of potential genetic or lifestyle risk factors. This includes women with mutations in *PTEN* tumour suppressor genes, who have a lifetime EC risk of 19-28% (42). This may also in the future include women with model based risk estimation or potentially women heterozygous for *BRCA1* PVs. While some studies suggest an increased risk of serous EC relative to the low-risk population (43) (44, 45) (46), in *BRCA1* women, the overall data on serous EC risk are inconsistent, with some studies showing no increase in risk,(47) and overall EC-risk is not increased. While not currently recommended in most guidelines, internationally and even within the UK, there is some inconsistency in international clinical practice with respect to offering a RRH in combination with risk reducing BSO in *BRCA1* women.

The need for multiple parts

This modelling requires accurate HRUS for risk-reducing surgery for EC. Ideally, the impact of EC prevention on quality-of-life would be considered in isolation, without additional disutility from screening or prevention of other cancers (such as ovarian or colorectal cancer), or of an early surgical menopause for pre-menopausal patients. Opportunistic bilateral salpingectomy is commonly performed with hysterectomy to provide some degree of OC risk reduction, even in a low-risk population (48). There is no evidence that bilateral salpingectomy with RRH reduces hormonal function or quality-of-life over that of RRH alone (49), and therefore no requirement to consider the impact of bilateral salpingectomy separately from RRH. Bilateral oophorectomy with RRH for post-menopausal women would not be expected to add to the disutility of RRH alone. The major distinction therefore lies in pre-menopausal patients, and whether bilateral oophorectomy is performed with RRH.

Our target population from which to obtain EQ-5D ratings would therefore be:

1) **Pre-menopausal** women undergoing RRH for EC risk-reduction, **with** bilateral oophorectomy.
2) **Pre-menopausal** women undergoing RRH for EC risk-reduction, **without** bilateral oophorectomy
3) **Post-menopausa**l women undergoing RRH for EC risk-reduction, with or without bilateral oophorectomy.

RRH without bilateral oophorectomy is not commonly performed, as national guidelines recommend that women with LS have RRH-BSO to protect them from their additional OC risk (50) (51). There may be a small number of LS women who have received RRH alone without bilateral oophorectomy outside of recommended practice. Whilst these women would be valuable in obtaining HRUS for this procedure, they would be expected to have some additional risk of anxiety from their remaining risk of ovarian and colorectal cancer. Whilst there are numerous risk factors for EC, few patients other than those with LS undergo RRH (52), and so there is no major cohort of patients who have received RRH alone (for cancer prevention) without bilateral oophorectomy, and who are now free from an elevated risk of any other cancer.

Due to the rarity of this target patient cohort, it is challenging to perform a prospective EQ-5D study for patients undergoing this procedure. Where EQ-5D ratings are not available for a specific treatment or condition, due to rarity or other factors, NICE recommends alternatives, including the use of the closest available "proxy conditions", and vignettes (36, 53). People with LS represent the best available target patient population for the development of HRUS for EC preventive surgery. However, it is necessary to use a separate methodology for pre-menopausal patients undergoing RRH without bilateral oophorectomy. A preferred study design is the development of vignettes describing the treatment and condition of interest, which is then rated using EQ-5D by the general population or patients with similarities to the condition. This provides the closest match to the NICE reference case (54).

This study will therefore obtain EQ-5D ratings of risk reducing surgery for endometrial cancer via two related approaches:

1) A cross-sectional EQ-5D study of women with LS, including those who have undergone RRH ± BSO and those who have not (controls). This will enable HRUS for RRH to be obtained, including for pre and post-menopausal patients undergoing RRH-BSO.
2) A vignette-based study of pre-menopausal RRH without bilateral oophorectomy (for a patient with no remaining cancer risk). This will be valued by members of the general population using EQ-5D ratings.

Acceptability of risk-reducing strategies

Prior to clinical utilisation, it is necessary to determine if risk-reducing surgery is acceptable to women in the target population.

Acceptability has been defined by Sekhon and colleagues as "the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention" (55). These authors described seven component constructs, which can be measured before (prospectively), during (concurrently), or after the delivery of the intervention (retrospectively) (56): Affective attitude (how the patient feels about the procedure), burden (the expected amount of effort required to undergo the procedure), intervention coherence (the extent to which the patient understands why the procedure is being done), ethicality (how the procedure fits with the patient's values or beliefs), opportunity costs (the costs involved in undergoing the procedure, and recovering), perceived effectiveness (the extent to which the patient believes the procedure will achieve its aims), and self-efficacy (the confidence a patient has in being able to complete the procedure).

The acceptability of an intervention is distinct from the experience of that service, which may be affected by factors such as the quality of facilities, waiting times, transport links and others (57).

A recent study highlights initial data on willingness of obese women at increased risk of EC to undergo non-surgical primary preventive interventions to reduce EC risk.(58) Data also exist on acceptability of diet and lifestyle interventions in EC survivors.(59)

However, to the best of our knowledge, no previous studies have examined the acceptability of risk-reducing hysterectomy for EC prevention (outside the context of women with LS) at various EC risk levels. For ovarian cancer prevention, risk reducing salpingo-oophorectomy has been shown to be acceptable to a large proportion of women in the general population at the 5% level of absolute lifetime risk (60). Other studies have demonstrated risk-reducing early-salpingectomy followed by delayed oophorectomy to be acceptable to women at high risk of ovarian cancer (61, 62). We intend to assess the prospective acceptability of RRH to the general population, for EC prevention at differing levels of lifetime absolute risk of EC.

This study has scope to influence clinical practice for all patients with elevated risk of EC by defining the risk threshold at which to offer RRH and determining the acceptability of preventive surgery at that risk level. This study conforms to the methodological considerations of NICE, and will be directly applicable to health-economic and cost-effectiveness analyses of preventive treatments for endometrial cancer.

This study will address a number of **knowledge gaps** regarding endometrial cancer prevention**:**

- EQ-5D ratings of risk-reducing hysterectomy for endometrial cancer prevention, with separate ratings for:
    - Pre-menopausal risk-reducing hysterectomy with bilateral salpingo-oophorectomy
    - Pre-menopausal risk-reducing hysterectomy without bilateral salpingo-oophorectomy
    - Post-menopausal risk-reducing hysterectomy with bilateral salpingo-oophorectomy
- The lifetime endometrial cancer risk-threshold at which risk reducing surgery and other strategies are cost-effective
- The prospective acceptability of risk-reducing strategies for endometrial cancer prevention for women in the general population

5.3. Risks / benefits

Benefits
Participants in this study are unlikely to gain immediate benefit from participation, except for the satisfaction of having contributed to this study on endometrial cancer prevention.

Participants in this study may benefit, along with women in the wider population, from the knowledge gained from this study, if they are at elevated endometrial cancer risk. If successful, this study will demonstrate the endometrial cancer lifetime risk at which prevention strategies could be adopted, which will pave the way for their consideration by national commissioning bodies such as NICE.

Risks
There are few risks to participants in this questionnaire-based study, involving the completion of only one questionnaire per participant at a single time point.

Potential participants may not wish to complete the study. All participants will have ample opportunity to read the relevant participant information sheet (PIS), before giving voluntary written informed consent, should they choose to participate. Participation in the study is entirely voluntary and will not in any way affect their medical care, and this will be emphasised during the consent process.

Some participants may find it difficult to complete the questionnaires, due to the sensitive or personal nature of some questions (focusing on cancer risk and prevention). Participants will be told that participation is entirely voluntary, and they are free to either not continue or withdraw from the study at any time, without giving a reason. Information about support from charities such as Lynch Syndrome UK will be provided in the PIS.

6. Study objectives

6.1. Primary objective

- To obtain health-related utility scores for risk-reducing hysterectomy for endometrial cancer prevention

6.2. Secondary objectives

- To determine variables predictive for risk reducing hysterectomy
- To determine separate health-related utility scores for pre and post-menopausal patients undergoing risk-reducing hysterectomy with and without ovarian conservation.
- To define the endometrial cancer risk threshold for undergoing risk-reducing hysterectomy
- To determine the cost-effectiveness of risk-reducing hysterectomy
- To establish whether risk-reducing hysterectomy and other preventive options are acceptable to women in the general population at differing levels of lifetime risk of endometrial cancer
- To determine variables predictive of acceptability of risk-reducing hysterectomy

6.3. Primary endpoint

- Utility Scores for risk-reducing hysterectomy

6.4. Secondary endpoints

- Variables predictive for risk-reducing hysterectomy
- Cost-effectiveness: incremental cost effectiveness ratio (ICER) per QALY (ICER/QALY) of risk reducing hysterectomy (with and without bilateral salpingo-oophorectomy)
- Endometrial cancer risk threshold for undergoing risk-reducing hysterectomy
- Acceptability of risk-reducing hysterectomy and other preventive options to women in the general population and different EC risk thresholds

7. Study design

This study will consist of 3 parts:

- **Part 1** will involve recruitment of women with LS, who will be sent questionnaire 1 to complete on paper/ online. This is a cross-sectional survey of women with LS, designed to determine the HRUS of pre and post-menopausal women undergoing RRH-BSO.

- **Part 2A** will consist of the development of questionnaire 2, which is designed to determine the HRUS of women at increased risk of EC (but not other cancers) undergoing RRH alone (without BSO). This will involve collaboration with patient and clinical experts to develop a vignette-based questionnaire.

  Following development and refinement of this questionnaire, a substantial amendment will be submitted for permission to use this questionnaire amongst a sample of the general population (part 2B).

Following results from parts 1 and 2, health economic modelling using cost-utility analysis will take place. This will determine the lifetime EC risk at which preventive interventions (including RRH and others) are clinically and cost-effective.

- **Part 3A** will consist of the development of questionnaire 3, which is a vignette-based study, designed to determine the prospective acceptability of RRH for EC prevention in women from the general population, at differing levels of EC risk (with exact levels to be determined by health economic modelling described above.

  Following development and refinement of this questionnaire, a substantial amendment will be submitted for permission to use this questionnaire amongst a sample of the general population (part 3B).

Recruitment to each part of the study would be separate, and is described for each part below. Each participant will only be asked to complete one questionnaire at one time point.
Study flow charts for all 3 parts are given in section 9.5. A flowchart for part 1 is given in section 9.5.1, for part 2 in section 9.5.2, and for part 3 in section 9.5.3.

7.1. Part 1

Design: Cross-sectional cohort survey study.

A study flow chart is shown in section 9.5.1.

Screening and recruitment
Please see section 8 for inclusion/ exclusion criteria.
Potential participants will be identified by their treating clinicians through established NHS clinics and databases. This will include Familial Cancer/ Family History/ Cancer genetics Clinics within relevant clinical departments like Gynaecological Oncology and NHS Regional genetics services. Potential participants with LS who meet inclusion criteria will be identified by their usual treating clinicians (the central PRESCORES research team will not have access to this information). Potential participants will also be identified through established relevant research cohorts e.g. the CAPP study and LS registries (e.g. St Marks registry). The researchers on these trials will identify patients who meet the inclusion criteria (the PRESCORES research team will not have access to this information).

Potential participants will also be informed of the study through patient and support groups and charities (for example Lynch Syndrome UK and the Eve Appeal). These organisations may advertise the study on websites or via established mailing lists, and may include electronic links to the PRESCORES website and the study.

Patients identified via treating clinicians or established research studies will be provided with a cover letter (cover letter 1) and the PIS (PIS-1), in either paper or electronic form. Paper and electronic versions will be identical in substance, except for minor differences in instructions relating to the format. This may in person in the clinic, or via post or electronic communication.

Individuals who have seen information about the study disseminated by charities will be able to follow a link to the study website. Individuals who receive the study information in paper form will also be able to follow a link to the study website if they prefer to complete the study electronically. Visitors to the study website will be required to complete a short screening questionnaire (screening questionnaire 1) to determine their eligibility. They will then be able to view PIS-1 and continue on to the consent form and questionnaire.

Consent
Participants are required to complete the study consent form (Study Consent Form Part 1) to participate (on paper/online).

An optional Consent form B is enclosed, which allows participants to provide their contact details if they would like to be informed by our team of any future opportunities to participate in research. Any future research would need separate ethical approval. Completing this form does not compel the participants to become involved in any other research. Completion of this form is not a requirement of the PRESCORES research project. It is stressed that this form is optional, and participants should not complete this if they do not want to be informed about future research. If they are willing to be informed, they may complete this form, and enclose it in the freepost self-addressed envelope with the study consent form and questionnaire 1.

Data collection
After completion of the study consent form, participants will be able to complete questionnaire 1, on paper/electronically. Questionnaire 1 is a survey of women with LS, designed to determine the HRUS of pre and post-menopausal women undergoing RRH-BSO. More information on questionnaire 1 is given in section 7.4.1.

Participants will be able to complete this at a time and place of their choosing. Those who receive the paper PIS-1 but prefer to complete the consent form and questionnaire electronically will be able to follow a link in PIS-1 to the survey website.

Participants will be asked to post completed paper Study Consent Form part 1 (required), consent form B (optional), and Questionnaire 1 (required) back to the study team via an enclosed freepost return envelope. This ends the participant's involvement in the PRESCORES study. Consent forms for those participants consented in clinic can be collected at that time. The participants will be able to complete the questionnaire 1 at a time of their choosing and return by freepost as appropriate.

The completed paper consent form(s) and questionnaire will be returned via enclosed freepost envelope to the central PRESCORES research team at Queen Mary University of London. The PRESCORES research team will retain the questionnaire and optional consent form B, and post consent form 1 to sites. Completed paper consent form 1 will be securely stored at participating sites. Completed paper questionnaires and optional consent form B will be securely stored at Queen Mary University of London.

Data from electronically completed consent forms and questionnaires will be held securely on servers hosted by Queen Mary University of London. Please see section 13 for further information on data collection, management and storage.

Duration of participation
The duration of participation in this study will consist of the time required to read the study information including the PIS-1 and consent form(s), and the completion and return of the consent form(s) and questionnaire 1. After this there will be no further involvement of these participants in this study.

7.2. Part 2

Design: Development of a vignette-based cohort survey study

This part of the study is designed to generate one or more vignettes which represent a **pre-menopausal patient undergoing risk-reducing hysterectomy without bilateral oophorectomy**, for raised endometrial cancer risk (without additional cancer risk at other sites). These vignettes are intended to be valued by participants using EQ-5D. The development process follows methodological recommendations from NICE and other authors (53, 54).

A flowchart for part 2 is given in section 9.5.2.

7.2.1. Part 2A: Development of Questionnaire 2

Vignette development will be informed by a review of published literature on quality-of-life following similar surgery (including quantitative and qualitative studies), and any other published sources of information such as from established medical organisations, or charities.

Individuals with insight into the health state will be recruited into the vignette development process. This will consist of several patient-representatives, who have experienced hysterectomy (for a variety of indications), and endometrial cancer. They will be recruited via established clinical networks, patient-public-involvement groups who work with Queen Mary University of London, and/or charities such as Lynch syndrome UK and others. We will also recruit several clinical experts with experience in managing patients after hysterectomy, who may be gynaecologists, or other clinicians including nurses. These will be recruited via established clinical/academic networks. These patient-representatives and clinical experts will be interviewed, individually or as one or more groups, to obtain evidence to inform vignette content.

The number of vignettes and the descriptions of health states within the vignette will be determined by evidence obtained from the literature review and clinical/patient experts, to match that required by the economic model. The length and level of detail of each vignette will be determined by this process. The vignette(s) will be formatted and worded in such a way as to be easily comprehensible. After initial development, the vignette(s) will be further reviewed by the patients and clinical experts, to ensure they clearly describe a typical experience with this health state, and refined accordingly.

The vignette(s) will then be piloted on a small number of individuals who were not previously involved in their development. These participants will be recruited via the above channels of patient and public involvement groups, charities, support groups, and/or via commercial polling companies. The aims of this pilot are to ensure vignettes are comprehensible, the task is understood, and the number of vignettes and time taken to complete the task is not too great. Following this process, the vignette(s) will be further refined as required.

7.2.2. Part 2B: Questionnaire 2: EQ-5D valuation of vignette(s)

Following the development of questionnaire 2, a substantial amendment will be submitted for permission to use this questionnaire for research purposes.

7.3. Part 3

Design: Development of an experimental survey study

This part of the study will develop a questionnaire which is designed to evaluate the **prospective acceptability of risk-reducing hysterectomy and other prevention strategies**, at varying levels of lifetime risk of endometrial cancer.

A flowchart for part 3 is given in section 9.5.3.

7.3.1. Part 3A: Development of Questionnaire 3

Questionnaire 3 will be developed in a process similar to that of previously published work. (62) We have previously undertaken research and published on acceptability of ovarian cancer prevention at different ovarian cancer risk thresholds (60).

A draft of questionnaire 3 will be developed following a literature review. This will then be reviewed by experts in the field of gynaecology/ gynaecological oncology/ gynaecological cancer prevention/ psychology, who will be recruited via established clinical/academic networks. This will also be reviewed by patient representatives, recruited in a similar manner to that described previously, via established clinical networks, patient-public-involvement groups who work with Queen Mary University of London, and/or charities such as Lynch syndrome UK and others.

The questionnaire will provide some background information on endometrial cancer, and management strategies for prevention (including lifestyle changes, hormonal treatments such as the levonorgestrel intrauterine system (LNG-IUS), and RRH). It will also contain one of a number of scenarios, describing the results of a hypothetical test, giving a certain lifetime risk of endometrial cancer.
The questionnaire will then ask questions around the acceptability of the different risk-reducing interventions (for that given risk level). Following this there will be background questions on socio-economic status and medical history. It will also contain a validated measure of anxiety and cancer worry, such as the Hospital Anxiety and Depression Scale, and the Cancer Worry Score respectively, as well as questions on perceived response efficacy. There may be other questions as deemed necessary by the development process.

The number of scenarios, and the lifetime risk levels within each scenario, will be determined following the economic modelling which takes place after parts 1 and 2. This economic modelling will determine at what level of lifetime endometrial cancer risk various interventions are effective and cost-effective. This study will then examine acceptability of those interventions at and around those risk levels. Questionnaire 3 will be developed in accordance with this process described above, with input from clinical and patient experts. This will then be piloted on a small number of individuals not previously involved in their development. These participants will be recruited via the above channels of patient and public involvement groups, charities, support groups, and/or via commercial polling companies. The aims of this pilot are to ensure that materials are comprehensible and easy to use. Following this process, there may be further refinement as necessary.

7.3.2. Part 3B: Questionnaire 3: Acceptability of risk-reducing hysterectomy

Following the development of questionnaire 3, a substantial amendment will be submitted for permission to use this questionnaire for research purposes.

7.4. Questionnaire structure

7.4.1. Study Part-1: Questionnaire 1 Structure

Paper/electronic questionnaires will be identical, and participants will be required to complete one format of the questionnaire of their choosing. The questionnaire will be completed at one-time point, to reflect the cross-sectional study design. Upon completion there will be no further responsibilities.

Questionnaires will contain the following sections;

- Lynch Syndrome and health
- EQ-5D-5L questionnaire (63, 64) for participants' current HRQoL
    - Consists of two sections: EQ-5D-5L descriptive system and the visual analogue scale. It has five dimensions: mobility, self-care, activities of daily living, pain and mood disturbance. Participants are asked to indicate their health state on a five-point Likert scale.
- EQ-5D-5L questionnaire (63, 64) for participants' HRQoL 4 months after their RRH (for participants who have undergone RRH)
- Cancer Worry Scale (65)
    - The 4 items of the CWS are rated on a 4-point Likert scale ranging from "never" to "almost always." Scores range from 4 to 16. Higher scores indicate more frequent worries about cancer (66). The Cancer

Worry Score has been validated for use in Hereditary Cancer Syndrome Context with a Cronbach-alpha from 0.88 to 0.89 (66).

- Medical and family history
- Demographic information

7.4.2. Study Part 2: Questionnaire 2 Structure

This questionnaire will be designed in order to be completed electronically, and at one-time point.

It will consist of one or more vignettes describing the quality-of-life of a person following RRH. Participants will be asked to complete the EQ-5D-5L for each vignette. They may also be asked to complete a self-EQ-5D-5L, and relevant demographic and personal medical information.

The exact structure of the questionnaire will be finalised following the process described in part 2A. A substantial amendment will be submitted following development of this questionnaire, for permission to use in generating research data.

7.4.3. Study Part 3: Questionnaire 3 Structure

This questionnaire will be designed in order to be completed electronically, and at one-time point.

It will consist of a hypothetical scenario, where participants are asked to imagine that that they have had personalised EC risk-prediction, with the results being expressed as a lifetime risk of developing EC. It will be stressed that this testing and results are fictional, and do not arise from real-world testing of participants.

They will then be given accurate, truthful information on EC risk-reducing management options, including lifestyle advice, the LNG-IUS, and RRH, and their benefits and risks. It will be stressed that this testing and results are fictional, and do not arise from real-world testing of participants.

They will then be presented with a number of scenarios, describing the hypothetical results of this test, and asked which risk-reduction management options they would be willing to consider if they were faced with such results in reality.

The exact structure of the questionnaire will be finalised following the process described in part 3A. A substantial amendment will be submitted following development of this questionnaire, for permission to use in generating research data.

8. Study population

8.1. Inclusion criteria

Part 1:

- Diagnosis of Lynch Syndrome (confirmed germline mutation in *MLH1*, *MSH2*, *MSH6*, *PSM2*, *EPCAM*)
- ≥18 years
- Female
- UK resident
- Able and willing to provide informed consent

For part 1, eligible participants will be adult women with LS living in the UK. This is to reflect the full range of views and experiences from this group, including from different age groups.

8.2. Exclusion criteria

Part 1:

- Unwilling or unable to provide informed consent
- Inability to understand written and verbal English
- Prior history of endometrial, ovarian or cervical cancer

Participants are excluded if they are unable to provide written informed consent in English, or if they have a prior history of gynaecological cancer for which the treatment is hysterectomy (which includes endometrial, ovarian and cervical cancer). This is because such cancer precludes them from having had or considering a risk-reducing hysterectomy.

9. Study procedures

9.1. Informed consent

Participating patients will need to provide written consent either on paper or online format. To do this they will complete the study consent form for their part - Study Consent Form Part 1. Please see section 7.1 for more information around consent.

For part 1, consent form B is optional, and provides an opportunity for participants to provide their contact details, should they wish to be informed of any future relevant research projects from our team. This is not a requirement for completion of this

research. It is stressed that completing this is entirely optional, and participants should not complete this page if they do not want to be contacted about future research. Completing this section does not commit the participants to be involved in future research. Any future research would need separate ethical approval.

9.2. Screening and recruitment

Screening and recruitment has been previously described in detail. Please see section 7.1 for more information.

9.3. Study interventions

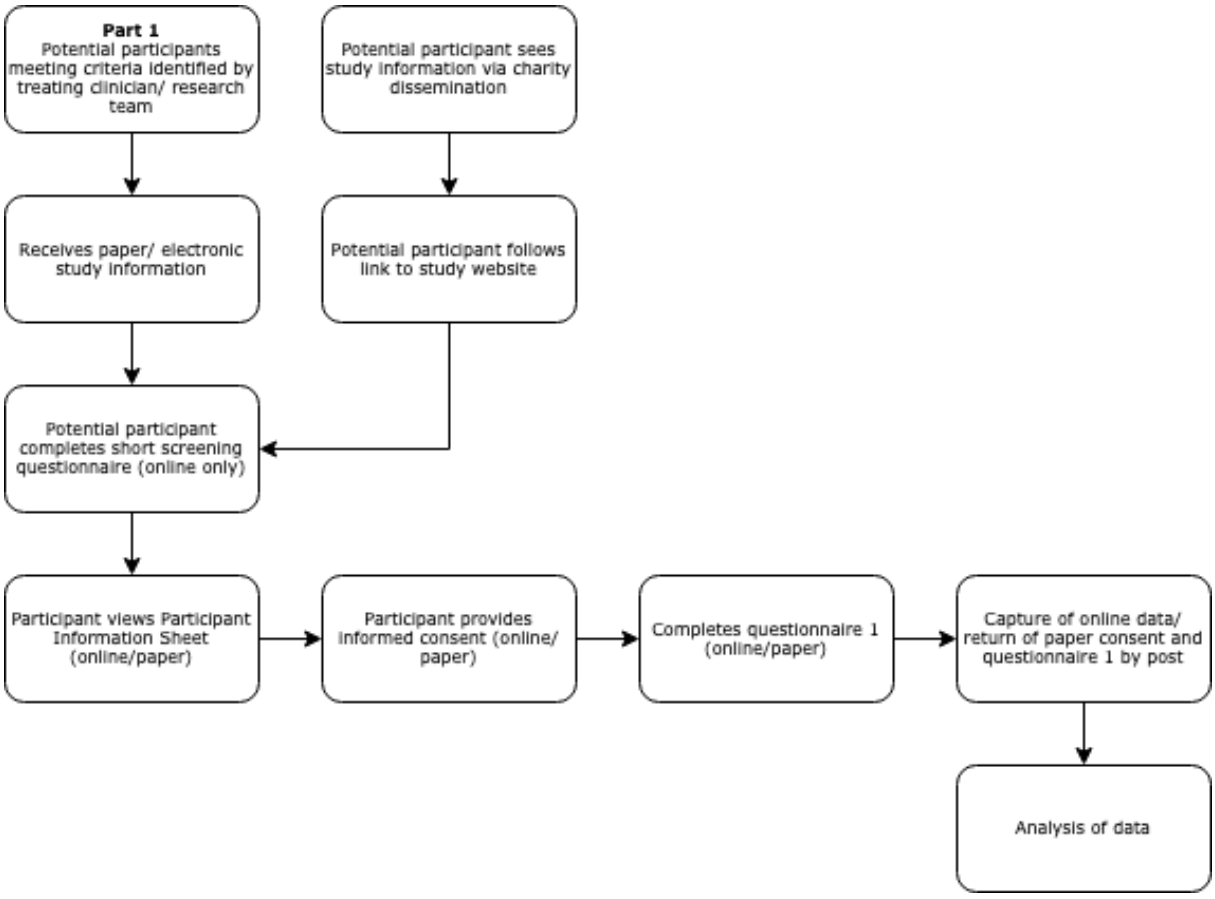
Questionnaire 1:
Eligible participants determined by the inclusion criteria will be asked to complete a specially developed questionnaire regarding their socio-demographics, personal and family medical history, HRQoL and cancer worries.

9.4. Schedule of Assessment

Assessment	**Part 1: Questionnaire 1**			**Part 2A: Development of Questionnaire 2**			**Part 3A: Development of Questionnaire 3**		
Eligibility confirmation	X								
Consent		X							
Complete questionnaire			X						
Interviews with patient representatives				X			X		
Interviews with clinical experts					X			X	
Piloting of questionnaire						X			X

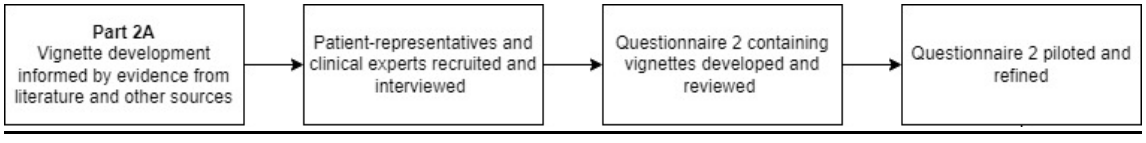
9.5. Study Flowchart

9.5.1. Part 1

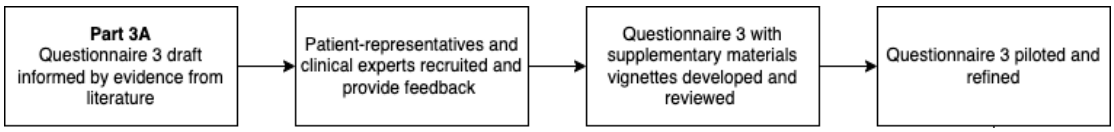


Note – the short online screening questionnaire is only for participants completing the study online. Participants who are sent a paper study and choose to complete this on paper do not have to complete this screening questionnaire, as they will have been screened by their treating clinician.

9.5.2. Part 2



9.5.3. Part 3



9.6. Data collection

A secure customised database will be created for the study, held securely at Queen Mary University of London. Electronic versions of questionnaires will be held on secure servers at Queen Mary University of London. Data entered into this electronic questionnaire will be held on this secure customised database. An electronic case report form (eCRF) will be used for each study participant.

Completed paper consent forms and questionnaires will be returned via a freepost self-addressed envelope to the PRESCORES research team at Queen Mary University of London. The PRESCORES research team will retain optional consent form B and the questionnaire, and post consent form 1 to sites. Completed paper consent form 1 will be securely stored at participating sites. Completed paper questionnaires and optional consent form B will be securely stored at Queen Mary University of London.

Consent forms will be stored at site, separately from identification logs. Researchers at QMUL will enter data from paper documentation onto eCRFs on the customised electronic database. Support from a data capture company/service may be used if required. These data are pseudo anonymised.

No data will be collected by any other sites. All source data will be handled, computerised and stored in accordance with QMUL Information Governance guidelines, GDPR and GCP. Please see section 13 for further information on data handling.

9.7. Follow-up Procedures

There will be no follow-up for any participant in any part of the study. Upon completion of the relevant questionnaire (and return of the consent form and questionnaire for those completing on paper), there will be no further involvement in the study.

9.8. Participant withdrawal

Volunteers are free to withdraw from the study at any time, through personal choice or without giving any reason for doing so. Information on how to do this is provided in each PIS, and on the consent forms. The co-ordinating centre team will be informed of all withdrawals.

9.9. End of Study Definition

The end of study is defined as 36 months after receipt of the last questionnaire. This time period is required for data collation, analysis and write up. In cases of early termination of the trial or temporary halt, the coordinating centre will notify the main REC within 15 days of the decision and detailed, written explanation for the termination/halt will be given.

10. Statistical considerations

10.1. Sample size

No formal sample size calculation has been undertaken for part 1 as our aim is to survey a large representative sample of women with LS, including those who have experienced RRH.

Given that the UK population is approximately 67,000,000 (67), the prevalence of LS is estimated as 1 in 280-370 (9, 10), and that an estimated 95% of individuals with pathogenic variants are unaware of this; there are therefore an estimated 9,054-11,964 people in the UK who are aware that they have LS, or 4527 – 5982 women. The proportion of women with LS who have undergone RRH is approximately 30% (68); an estimated 1358 – 1794 UK women.

A desirable sample size would include 250 women *who have undergone RRH*, with a lower limit of 100, and an upper limit of 400. This allows for sufficient post-hoc exploratory analysis. This translates to an overall desirable sample size of respondents of 750 women with LS (regardless of RRH history), with a lower limit of 300, and an upper limit of 1200. This sample size is in line with previous questionnaire studies in women at inheritable risk of gynaecological cancers (62). The number of people approached would therefore be dependent on the response rate. Assuming a response rate of 35%, the number of participants invited can vary from 1392, 557, 2229 to achieve 750, 300 and 1200 respondents respectively.

10.2. Method of analysis

Baseline characteristics will be calculated using descriptive statistics. Appropriate statistical tests will be used. Chi-square tests will be used to compare categorical

variables and t-Test (parametric) and Mann-Whitney (non-parametric) tests to compare continuous outcome variables between two groups. Appropriate Logistic/ Linear regression models will be used to evaluate impact of covariates on Linear outcome variables. The data set will be subject to two analysis formats to minimise the risk of bias during interpretation. Initially by cohort-matching, to reduce the influence of confounding variables. Secondly by regression analysis to analyse the impact of covariates of the categorical and linear variables. All analysis will be performed on R (R Core Team, Foundation for Statistical Computing, Vienna, Austria), or equivalent software package.

A Markov model built in TreeAge software (TreeAge, Williamstown, MA) will form the basis of an economic evaluation on the cost-effectiveness of RRH for endometrial cancer prevention. We will also build models to determine the endometrial cancer risk threshold at which to perform surgical prevention (hysterectomy) or other non-surgical preventive interventions (such as the levonorgestrel-intrauterine system, or other chemo-prevention) for endometrial cancer risk. Models will be built in order to evaluate lifetime costs as well as effects with undertaking 'risk reducing hysterectomy' in premenopausal and postmenopausal women by comparing it with 'no risk reducing hysterectomy' at varying levels of endometrial cancer risk. Additional modelling will also evaluate lifetime costs as well as effects with undertaking non-surgical preventive interventions in premenopausal and postmenopausal women by comparing it with 'no intervention' at varying levels of endometrial cancer risk. The analysis will be undertaken primarily within the UK National Health Service (NHS) context. We will also explore the impact of outcomes in other health systems.

Utility score data for the model will be obtained from this survey study. Additional model parameters will be obtained from the published literature. A lifetime time horizon will be used to capture all costs and benefits and the analysis will be conducted using a healthcare perspective. An appropriate discount rate will be applied to costs and outcomes. The ICER/QALY will be calculated, and compared with the NICE cost-effectiveness willingness-to-pay threshold to determine whether or not RRH±BSO is cost-effective and to determine the endometrial cancer risk thresholds for undertaking hysterectomy for prevention. To investigate the sensitivity of the results, both deterministic and probabilistic sensitivity analysis will be performed.

11. Ethics

The study will receive full ethical approval prior to commencing recruitment.

The Chief Investigator will ensure that the study is carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements.

The Principal Investigator will ensure that the study is carried out in accordance with ethical principles in the Research Governance Framework for Health and Social care legislation as well as any amendments.

In addition to this, the research team have considered multiple ethical issues:

1. Participants may feel obliged to take part: When participants are approached in person, especially during a visit to outpatient clinic, they may feel obliged to take part in the study. To address this issue, we emphasise that participation is voluntary, participants do not have to respond and are given the opportunity to take the information away and respond at a later date. We emphasise that declining to take part in the study will have no impact on their future care.
2. Participant burden: Participants will be contacted by email or during their attendance at outpatient clinic and they may feel burdened. To address this, we emphasise that there is no obligation to complete the questionnaire. Participants can withdraw from the study at any point.
3. Increased anxiety for the participants: Our target population may already be facing a heightened period of anxiety and may need to consider making difficult decisions which can have a significant impact on their health and their family. Invitation to participate in our study may potentially add to anxiety in some individuals. In order to address this, all study participants will have the contact details for the research team who they will be able to contact for reassurance/to ask questions. Additionally, we make clear that participation is completely optional.
4. Internet-based tasks: Some participants will be approached by email. It is possible some may not be familiar with the online survey tool, and this could lead to anxiety and frustration in some. Women who are approached this way will already be engaging in an online support group and are more likely to be familiar with internet based tasks. Women are also offered the option of completing a postal questionnaire if they feel that this will be a more acceptable method for them, for part 1.
5. Obtaining consent from participants invited to take part by support groups/charities: Informed consent will be obtained from the participant after reading the information leaflet online and completing the web-based consent form. This does not allow opportunity for the participant to ask questions, when compared to obtaining informed consent in person. To address this, we have clearly highlighted contact details of the research team and independent charity organisations in the patient information sheet, should the participant wish to discuss concerns prior to giving consent. We have also built in a facility for the participant to save their responses on the web-based survey tool and return to it at a later date.
6. Breach of confidentiality: Any breach of confidentiality can cause distress and inconvenience to the participants. Great care will be taken to ensure that the data collected will be strictly confidential and not released to anyone else outside the study without the volunteer's consent. Questionnaire results will be entered on a secure password protected customised database held at the coordinating centre on a server at the Wolfson Institute of Population Health, Queen Mary University of London. This will be accessible only to members of the research team through a username/password protected computer. Each team member

will have a unique password and each computer a separate certificate key. The computers will not be accessible to unauthorised personnel. Paper copies (consent forms, questionnaire results) will be stored in a secure filing area in the coordinating centre. Unauthorised persons will not have access to this data. There is a special dedicated team of IT specialists to ensure and monitor data security. The IT team and environment is IG tool kit compliant.

11.1. Annual Safety Reporting

The Annual Progress Report (APR) will be sent by the CI to the sponsor and REC, using the NRES template. The first APR will be submitted on the anniversary date of the "favourable opinion" letter from the REC. A copy of the APR and an associated correspondence with REC will also be sent to participating sites.

12. Public involvement

There will be significant Patient Public Involvement (PPI) in various stages of this study. Patients and representatives of patient-charities have been involved in contributing to and reviewing the initial design of this study, and materials for participants. They will help with recruitment to part 1, by the distribution of approved materials informing potential participants of the study. They will be closely involved in part 2A (the development of vignettes to be rated using EQ-5D), and part 3A (on the acceptability of risk-reducing interventions), and in the development of participant-facing materials for these. There will be patient representation on the study management and oversight teams. Patient groups and charities will also be involved in increasing awareness, and dissemination of research and research findings.

13. Data handling and record keeping

13.1. Data management

A secure customised database will be created for the study, held at the coordinating centre on a secure server at the Wolfson Institute of Population Health, Queen Mary University of London. This will be accessible only to members of the research team through a username/password protected computer. Each team member will have a unique password and each computer a separate certificate key. The computers will not be accessible to unauthorised personnel. There is a dedicated team of IT specialists led by Mr Jonathan Croft to ensure and monitor data security. The IT team

and environment is IG tool kit and GDPR compliant. Our Barts CTU has a data protection and management officer (Araripe Garboggini) with well established guidelines and protocols for data management which will be followed.

This study uses electronic case report forms (eCRFs). An eCRF will be used for each trial participant. Data entered into the electronic questionnaires will be entered directly onto this secure customised database and held. Completed paper consent form 1 will be returned via post from the PRESCORES co-ordinating centre to each site for secure storage. Completed paper questionnaires and optional consent form B will be returned via freepost to the co-ordinating centre at Queen Mary University of London. The research team at the coordinating centre will enter data from paper documentation onto eCRFs on the secure electronic database. Paper questionnaires and optional consent form B will be stored in a secure filing area (under lock and key with restricted access) in the coordinating centre. Unauthorised persons will not have access to this data.

Study data, whether in paper or electronic form, will be returned to the study co-ordinating team at Queen Mary University of London.

All trial related documents should be filed in the Investigator Site File (ISF). It should contain essential documents as per the contents page provided to the Investigator by the PRESCORES centre team. The clinical trials team at the Barts CTU will inform the PI, and their staff, of any updates and forward on any relevant documentation. It is the participating PI's responsibility to maintain this file and keep all records up to date.

The Trial Management Group reserves the right to amend or add to the CRFs as appropriate. Revised or additional forms should be used by centres in accordance with the guidelines provided by the sponsor.

13.2. Source Data

The source data consists of data from completed questionnaires, in paper and electronic form.

Participants will return the consent forms and source data either directly in clinic or using an enclosed freepost self-addressed envelope. These will be returned to the PRESCORES research team at Queen Mary University of London. Upon receiving completed paper questionnaires, or by participants completing an electronic questionnaire, data will be entered into a secure server at Queen Mary University of London.
All source data will be handled, computerised and stored in accordance with General Data Protection Regulations (GDPR) and Good Clinical Practice (GCP).

13.3. Confidentiality

All information which is generated in the study will be kept strictly confidential. The researchers conducting the trial will abide by the GDPR, and the rights the patient has under this. Parts of the data collected for the study will be looked at by authorised personnel from the Sponsor. This is clearly stated on the consent form.

All of the researchers have a duty of confidentiality to research participants. The personal identity of participants will not be disclosed outside of the research team without their consent. Written data will be stored in a locked and dedicated room only accessed by authorised personnel at Queen Mary University of London. Electronic data will be stored on secure databases held on servers at Queen Mary University of London.

13.4. Record retention and archiving

At the end of the study all documentation, as defined by GCP, should be stored by each individual site's archiving facility, until notification, for destruction, from the Sponsor. The location of the archiving facility must be provided to Barts Clinical Trials Unit (coordinating centre) team.

Barts CTU will arrange a 'close out' visit where appropriate, where all study documentation will be prepared for archiving by that site. Records will be retained at each individual site. All records relating to the study should be stored together, including the ISF. It is the responsibility of the Principal Investigator to ensure a full set of records is collated and documented.

In addition, source documentation should be retained, as per Sponsor request, for the duration of the archiving period. These will be stored for 5 years. Barts CTU should be contacted prior to destruction.

14. Safety reporting

This is a low risk study.
Due to the nature and design of this study, involving the completion of one questionnaire per participant at a single time point, adverse events are extremely unlikely to occur.

15. Monitoring and auditing

The Sponsor or delegate retains the right to audit any study, study site or central facility. In addition, any part of the study may be audited by the funders where applicable.

The study will be overseen by Barts CTU. Research will be conducted in line with Good Clinical Practice guidelines and NHS Research Governance Framework. Regular monitoring of recruitment, informed consent, data quality, and complaints will be carried out by the co−ordinating centre. 5% of the manually-entered questionnaire data will be checked for accuracy. Overall monitoring and auditing will be undertaken by the sponsor of this study, QMUL.

16. Study committees

The study will be run and centrally co-ordinated through the Women's Precision Prevention team at the 'Coordinating centre' at the Wolfson Institute of Population Health, Queen Mary University of London (QMUL). The staff at the coordinating centre will include the study CI, a study co-ordinator, research staff and statistician. The study co-ordinator will be responsible for the day to day management of the study.

The co-ordinating centre team will meet monthly, and be responsible for recruitment, data collection, electronic data entry and analysis.

Responsibilities include-

- Confirming eligibility of participants and registration with the study.
- Overall co-ordination and day to day management of the study
- Data management
- Liaison with collaborators for all aspects of study management
- Answering queries about the study
- Mailing and collection of questionnaires

Study Management Group
The study management group will consist of the study co-ordination team, CI, statistician, clinical research fellow/ study co-ordinator, PIs, and collaborators. The group will meet as required to review the study progress and safeguard the participants and the quality of the study.

17. Finance and funding

The study is funded through Rosetrees Trust and the internal resources of the Women's Precision Prevention team, Wolfson Institute of Population Health, QMUL.

18. Insurance and indemnity

QMUL has agreed to act as Research Governance Sponsor for this study and has indemnity arrangements in place. The insurance that Queen Mary has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

19. Dissemination of research findings

The results of this study will be presented at conferences, scientific meetings and made available using scientific and medical publications that anyone can access. Participants will not be personally identified in any such publications. Information will also be disseminated through supporting charities, patient group meetings, patient support groups, social media, and relevant stakeholder platforms and networks. It will also contribute to a post-graduate student thesis.

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