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Early removal of Fallopian tubes and delayed removal of ovaries in women at high risk of ovarian cancer

Submission date 04/06/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol
Registration date 14/06/2018	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 10/03/2021	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-to-prevent-ovarian-cancer-by-removing-the-fallopian-tubes-and-then-the-ovaries-protector (added 10/03/2021)

Background and study aims
Some women have an inheritable fault in their genetic code which increases their risk of developing ovarian cancer. Genes in which a fault may lie are BRCA1/ BRCA2/ RAD51C/ RAD51D/ BRIP1. Some women with a strong family history of ovarian cancer or breast and ovarian cancer may also be at increased risk. There is currently no screening programme for ovarian cancer available on the NHS. Therefore current practice is to offer women at increased risk, once they have completed their family, an operation to remove their fallopian tubes and ovaries. This procedure is called risk-reducing salpingo-oophorectomy. This is the best known way to prevent ovarian cancer in women at increased risk. However, in women who are premenopausal it leads to early menopause. Early menopause has serious health implications. It results in menopausal type symptoms (e.g. hot flushes, changes in mood, reduced sex drive), increased risk of osteoporosis (brittle bones), heart disease, stroke, dementia and sexual problems. Research suggests many ovarian cancers start in the fallopian tube. This has led to the proposal of an alternative strategy to prevent ovarian cancer. This involves having the operation in two stages. The first operation involves removing the fallopian tubes alone. This is called 'early salpingectomy'. The second operation removes the ovaries after natural menopause (average age 51 in the UK). This is called 'delayed oophorectomy'. The advantage of this two-stage alternative is that it offers some protection against ovarian cancer in young women whilst avoiding negative health consequences of early menopause.
The aim of the PROTECTOR study is to assess the impact of this two-stage alternative approach on sexual function. The study also evaluates the impact on quality of life, hormonal well-being, psychological well-being and overall satisfaction. Outcomes from this new approach are compared to the traditional approach of removal of both tubes and ovaries at the same operation. We also compare this to the well-being of women who do not have an operation.

Who can participate?
Women at increased risk of developing ovarian cance, who are aged 30 years and over and have not gone through the menopause.

What does the study involve?
Participants will be given the choice of which arm of the study they wish to be part of:
1. RRESDO (risk-reducing early salpingectomy and delayed oophorectomy): the new, two-stage operation (initial removal of tubes alone, followed by later removal of ovaries at a second operation after natural menopause or sooner if requested).
2. RRSO (risk-reducing salpingo-oophorectomy): removal of both tubes and ovaries at the same time. This is the current standard operation offered on the NHS to prevent ovarian cancer.
3. Controls: no operation involved.
Everyone will be required to complete questionnaires at the start of the study and annually. These ask about medical history, family history, quality of life, sexual function, cancer worry, psychological well-being and how satisfied individuals are with their decision.
All participants will also have a blood test at the start of the study and during follow up for a hormone called FSH. This will provide information on how the ovaries are functioning. Women who decide to have an operation to prevent ovarian cancer (either RRSO or RRESDO) will have a baseline ultrasound scan to look at the ovaries and a blood test for an ovarian cancer marker called CA125.
A small number of women from each study arm will be approached to take part in an optional interview. Interviews will explore views on acceptability, interest, factors influencing decision-making and willingness to undergo the new two-stage operation. Those who go on to have an operation (RRESDO/RRSO), will be contacted 1 year after their operation for a follow-up interview to discuss their satisfaction with the process and their general health and wellbeing.

What are the possible benefits and risks of participating?
Benefits include:
1. The opportunity of having a two staged operation (RRESDO) to prevent ovarian cancer. This is not currently routinely available outside the study. It involves removal of the tubes in the first step followed by removal of ovaries at a later date.
2. Removal of the tubes alone will provide some protection against developing ovarian cancer and also preserve ovarian function which will delay or avoid early menopause. This can prevent the adverse health consequences of early menopause.
3. Participants will be given the choice of deciding which arm of the study they wish to be a part of: RRESDO (new procedure), RRSO (current standard practice), or controls (no surgery).
4. Participants will be contributing to research into preventing ovarian cancer in women at increased risk. Results of this study will help us better understand the impact of the new two stage procedure. This will help develop future clinical care guidelines and plan future care pathways for women at increased risk of ovarian cancer.
Risks:
1. Although there is evidence to suggest removal of tubes alone provides some protection against developing ovarian cancer, the precise extent of this protection is unclear. There is the possibility of getting ovarian cancer despite removal of tubes.
2. It is unclear if a possible benefit of reduced breast cancer risk is lost by not removing ovaries before menopause.
3. The two-stage option (RRESDO) involves two operations instead of one (RRSO: removal of both tubes and ovaries). Each operation has potential complications. As there are two operations this may lead to more complications overall.
4. There is concern that not everyone having their tubes removed initially will go on to have their ovaries removed at a later date. This would mean that these women who don’t do so could still remain at an increased risk of developing ovarian cancer.

Where is the study run from?
Queen Mary University of London (UK)

When is the study starting and how long is it expected to run for?
July 2018 to July 2028

Who is funding the study?
Barts and the London Charity

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number

IRAS number
237992

ClinicalTrials.gov number

Secondary identifying numbers
IRAS project ID: 237992

Study information

Scientific Title
Preventing Ovarian Cancer through early Excision of Tubes and late Ovarian Removal

Acronym
PROTECTOR

Study objectives
1. Early salpingectomy is non-inferior for sexual function compared to no surgery.
2. Early salpingectomy is superior for sexual function and non-inferior in terms of quality of life compared to the standard risk-reducing salpingo-oophorectomy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Bloomsbury Research Ethics Committee, 18/04/2018, ref: 18/LO/0555

Study design
Multicentre prospective three-armed cohort study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Prevention of ovarian cancer

Interventions
Participants who meet the eligibility criteria and who have been identified through various NHS outpatient clinics, GP-surgeries or who have self-referred to the study team, self-select which of the three study arms they wish to participate in: risk-reducing early salpingectomy and delayed oophorectomy (RRESDO); risk-reducing salpingo-oophorectomy (RRSO); controls (no surgery).

Baseline investigations
Participants enrolled into the two surgical arms (RRESDO/RRSO) have a CA125 and transvaginal ultrasound of the pelvis. Participants in all three arms have a baseline FSH as a measure of ovarian function and are required to complete interventional questionnaires that collect data on medical and reproductive history, socio-demographics, family history of cancers, endocrine symptoms, quality of life, satisfaction, psychological health and cancer risk perception and worry.

RRSO arm
Participants who have completed their family undergo risk reducing salpingo-oophorectomy and peritoneal washings. A strict histopathological SEE-FIM based protocol is followed and pathology samples are sent for central pathology review..

RRESDO arm
Participants who have completed their family undergo surgery in two stages. The first stage involves salpingectomy and peritoneal washings. The second stage involves oophorectomy and peritoneal washings once natural menopause has been reached (or sooner if requested). A strict histopathological SEE-FIM based protocol is followed and pathology samples are sent for central pathology review.

Control arm
Participants do not undergo surgery but undergo a blood test measuring FSH levels and are required to complete the interventional questionnaires.

Qualitative in-depth interviews
A small number of women from each of the three study arms are invited to one-to-one semi-structured in depth interviews to explore acceptability, interest, factors influencing decision making and willingness to undergo RRESDO. Women who elected to have surgery are followed up with another interview one year post salpingectomy/RRSO to explore satisfaction with the counselling process and the effects of surgery on health and wellbeing.

Follow up
All participants are followed up with annual questionnaires and FSH levels (annually after salpingectomy/control arm; 3 months after RRSO/delayed oophorectomy).

Intervention Type
Procedure/Surgery

Primary outcome measure
Sexual function measured using the Sexual Activity Questionnaire and Sexual Quality of Life 3D (SQOL-3D) questionnaire completed at baseline, 3 months post surgery and annually.

Secondary outcome measures
1. Endocrine function and menopause is measured using the FACT-ES questionnaire completed at baseline, 3 months post surgery, annually and FSH levels measured 3 months after surgery and annually (ealry salpingectomy/control arm)
2. Quality of life measured using the EQ5D-5L questionnaire completed at baseline, 3 months post surgery and annually
3. Satisfaction/regret is measured using the 5-item Decision Regret Scale (O'Connor, Ottawa 1996) and 1-item ('I am satisfied with the decision I have made' on a 5-point Likert scale from Madalinska et al, 2005) completed at baseline, 3 months post surgery and annually
4. Surgical morbidity measured by recording complications experienced by the participant 4 weeks after surgery during the post-surgical clinic review
5. Psychological health measured using the Hospital Anxiety and Depression Scale (HADS), assessing cancer worry using the 4-item scale from Lerman et al and measuring intrusive thoughts using the Impact of Events Scale (7 intrusive items, Horowitz et al, 1997) completed at baseline, 3 months post surgery and annually
6. Number of serous-tubal-intraepithelial-carcinoma (STIC)/invasive (tubal/ovarian/peritoneal /non-ovarian) cancers will be recorded following histopathology review by a central pathology review committee using the SEE-FIM protocol
7. Utility scores for early salpingectomy will be derived using the Sexual Quality of Life 3D (SQOL-3D) questionnaire
8. Cost-effectiveness (incremental cost effectiveness ratio per quality adjusted life years (ICER /QALY)) of early salpingectomy/delayed oophorectomy will be established via a cost utility analysis performed using a Markov model
9. A national register of women undergoing early salpingectomy will be created by collating the details of all participants who have undergone early salpingectomy as part of the trial

Overall study start date
01/01/2017

Completion date
01/07/2028

Eligibility

Key inclusion criteria
1. Women at increased risk of ovarian cancer: BRCA1/BRCA2 mutation carriers; RAD51C/RAD51D /BRIP1 mutation carriers; strong family history of breast and ovarian cancer or ovarian cancer alone.
2. Premenopausal
3. Aged ≥30 years.
4. Completed family (for surgical arms)

Participant type(s)

Patient

Age group
Adult

Lower age limit
30 Years

Sex
Female

Target number of participants
1000

Key exclusion criteria
1. Previous bilateral-salpingectomy or bilateral-oophorectomy.
2. Postmenopausal (amenorrhoea ≥1year (uterus in situ) / FSH >40).
3. Previous tubal/ovarian/peritoneal malignancy
4. <12 months post cancer treatment
5. Pregnancy
6. Clinical suspicion of tubal/ovarian cancer at baseline
7. Inability to provide informed consent

Date of first enrolment
01/07/2018

Date of final enrolment
01/07/2025

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Barts Health NHS Trust
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Sponsor type
University/education

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ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Charity

Funder Name
Barts and the London Charity

Results and Publications

Publication and dissemination plan
Results of the research will be presented at scientific conferences and published in scientific journals. They will also be made available through cancer charities, patient support groups and the Queen Mary University of London website.

Intention to publish date
01/07/2029

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v4	16/04/2018	02/04/2019	No	Yes
Protocol article	protocol	01/02/2021	11/09/2020	Yes	No
HRA research summary			28/06/2023	No	No