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Avoiding late diagnosis of ovarian cancer

Submission date
27/01/2020

Recruitment status
No longer recruiting

Registration date
17/02/2020

Overall study status
Completed

Last Edited
18/08/2023

Condition category
Cancer

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Women with BRCA1 or BRCA2 mutation are at a high risk of developing Ovarian Cancer (OC). The only way to prevent OC is surgery to remove their ovaries and fallopian tubes. Having surgery is a major decision however as it causes infertility and early menopause, so many women choose to delay surgery until their families are complete or they have reached the natural menopause, leaving them at risk of developing OC in the meantime. Some women decline surgery even after the menopause. OCs diagnosed with symptoms are usually diagnosed at a late stage, which can result in more complex surgery, longer hospital stays and poorer survival. The ALDO project will offer a surveillance option to women declining surgery, using the ROCA blood test which has been shown to detect OC at earlier stages compared to women with symptoms. The ROCA test calculates the probability of someone having OC based on age, menopause status and changes in CA125 blood levels. The aim of this study is is to provide evidence to support widespread implementation of the ROCA Test within the NHS, by showing it can detect earlier-stage cancers, is cost-effective and is a positive experience for women at high risk of OC. This will be done by working with health economists, the National Institute for Health and Care Excellence (NICE) and NHS commissioners.

Who can participate?
Women aged 35 or over with the BRCA1 or BRCA2 mutation who have not yet had surgery to remove their ovaries and fallopian tubes

What does the study involve?
Participants have a routine blood sample for CA125 taken 4 monthly for one year. The CA125 is run through the ROCA test which gives a risk score for how likely it is they currently have OC. Women with a normal score continue with 4-monthly surveillance tests, and women with a high score have the test repeated sooner and may also require an ultrasound scan of their pelvis and referral to a ‘rapid-access’ gynaecology clinic. The number of OCs detected through the ROCA test and the stage and grade of these cancers are measured throughout the surveillance up until 18 months (after 6 months of follow up)

What are the possible benefits and risks of participating?
The ROCA Test has been tested successfully in several clinical trials over the past 15 years involving over 200,000 women. Women diagnosed with an ovarian cancer as a result of screening had less advanced cancers compared to those who presented with symptoms after screening

had ended. As a result, their surgery was less complex and the proportion of women who had all of their tumour removed was very high. Women will be closely monitored whilst taking part which they may find reassuring.
The ROCA Test will not prevent cancer from occurring and it may not detect all women with ovarian cancer. If the ROCA Test is elevated, then it will need to be repeated and in some circumstances other tests (such as ultrasound of ovaries, MRI or CT scan) may be needed to help the doctors decide if surgery is needed. This may create anxiety in some women even if there is no cancer present (other medical problems can cause an elevated ROCA result and some women have a naturally high level of CA125 which can cause a temporary elevated ROCA result until the algorithm learns what their natural level of CA125 is). Surveillance with the ROCA Test has not definitively been shown to save lives.

Where is the study run from?
1. University College Hospital London Familial Cancer Clinic (UK)
2. Barts Familial Cancer Clinic (UK)
3. Great Ormond Street Clinical Genetics (UK)
4. Guy's and St Thomas Cancer Genetics (UK)
5. North West Thames Cancer Genetics (UK)
6. South West Thames Regional Genetic Services at St Georges Hospital (UK)
7. Oxford University Hospital (UK)
8. Manchester Regional Genetics (UK)
9. Leeds Clinical Genetics (UK)
10. Liverpool Clinical Genetics (UK)
11. Princess Anne Hospital Southampton (UK)
12. North Tees and Hartlepool Hospitals NHS Foundation Trust (UK)
13. Birmingham Women and Children's Hospital (UK)
14. Birmingham City Hospital (UK)
15. University Hospital of Wales (UK)

When is the study starting and how long is it expected to run for?
June 2018 to June 2022

Who is funding the study?
Abcodia Ltd (UK)

Who is the main contact?
Dr Adam Rosenthal, adam.rosenthal@ucl.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-of-a-test-called-roca-for-women-who-have-a-high-risk-of-developing-ovarian-cancer-aldo

Contact information

Type(s)
Scientific

Contact name
Mr Adam Rosenthal

ORCID ID
http://orcid.org/0000-0001-6924-0721

Contact details
Gynaecological Research Centre
1st Floor Maple House (1b)
149 Tottenham Court Road
London
United Kingdom
W1T 7DN
+44 (0)20 3447 2112
adam.rosenthal@ucl.ac.uk

Type(s)
Scientific

Contact name
Ms Sue Philpott

Contact details
Gynaecological Research Centre
1st Floor Maple House (1b)
149 Tottenham Court Road
London
United Kingdom
W1T 7DN
+44 (0)7773572706
Sue.philpott1@nhs.net

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
245363

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 38151, IRAS 245363

Study information

Scientific Title
Avoiding Late Diagnosis of Ovarian Cancer (ALDO)

Acronym
ALDO

Study objectives

The ALDO project will offer a surveillance option to women declining surgery, using the ROCA blood test which has been shown to detect OC at earlier stages compared to women with symptoms. The ROCA Test calculates the probability of someone having OC based on age, menopause status and changes in CA125 blood levels. The primary objective is to provide evidence to support widespread implementation of the ROCA Test within the NHS, by showing it can detect earlier-stage cancers, is cost-effective and is a positive experience for women at high risk of OC. This will be done by working with health economists, the National Institute for Health and Care Excellence (NICE) and NHS commissioners.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/08/2018, South Birmingham Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; Tel: +44 (0)207 104 8107, +44 (0)207 104 8388; Email: NRESCommittee.westmidlands-southbirmingham@nhs.net), REC ref: 18/WM/0144

Study design
Non-randomised; Both; Design type: Screening, Surgery, Active Monitoring, Cohort study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Ovarian cancer

Interventions
This is a pilot implementation of the ROCA Test into the NHS in women with BRCA1 or BRCA2 who are at high risk of developing ovarian cancer.

Participants will be under surveillance using the ROCA Test for one year and will have 3 routine blood samples taken during that year (the blood test will be scheduled 4 monthly). The participants will be sent a letter telling them when their blood sample is due, along with a pack containing everything they need to have the blood sample taken which they will need to take to their GP to have the blood sample taken.

The participant will then post the blood sample back to the laboratory using the pre-paid pre-addressed envelope enclosed.

The blood pack will include a GP notification letter explaining the project, as well as an instruction form and a ROCA Test form. The GP or participant will need to write the date and time that the blood sample was taken (blood samples are stable for 7 days in ambient temperatures and so any sample received by the lab after 7 days will need to be repeated), and answer some menopause questions to determine if the participant is pre or post-menopausal. Women classified as post-menopausal will only need to answer these questions at the first blood sample; premenopausal women will need to answer them at each routine sample.

The blood sample is then analysed for the blood chemical CA125, with the result being sent back to the project manager via secure NHS mail.

The CA125 is then run through the ROCA Test. The ROCA Test looks at the CA125 value, previous CA125 levels if available, age and menopause status and calculates a risk score for how likely it is that the participant currently has ovarian cancer (OC). The risk scores are then classified as below:
<1 in 1000: Normal
1 in 1000 to 1 in 501: Mildly Elevated
1 in 500 to 1:34: Moderately Elevated
>1 in 33: Significantly Elevated

Participants with a 'Normal' ROCA result will continue on routine surveillance with 4-monthly CA125 tests.

Participants with a 'Mildly Elevated' ROCA result will be scheduled for a repeat blood test in 6 weeks. The blood pack for this will be sent out to the participant with the result letter.
Participants with a 'Moderately Elevated' ROCA result will be scheduled for a repeat blood in 6 weeks plus a transvaginal ultrasound scan (TVUS). The TVUS will be arranged by the patient's named referral hospital. The project manager will contact the named gynaecologist at the referral hospital to arrange the TVUS for as soon as possible.
Participants with a 'Significantly Elevated' ROCA result will be referred to the 2-week wait rapid access clinic (RAC) with their named gynaecologist for a TVUS and clinical assessment. The referral will be made by the project manager who will contact the named gynaecologist by email and post.

At the RAC, the clinical assessment should include ruling out other causes of CA125 elevation which include: colitis, chronic active hepatitis, cirrhosis, renal disease with serum creatinine >2.0 mg/dL, systemic lupus erythematosus, sarcoidosis, acute pancreatitis, diverticulitis, endometriosis, polyarteritis nodosa, Sjögren's syndrome, pericarditis, rheumatoid arthritis, osteoarthritis, breast cancer or other cancers. A clinical assessment form will be provided for the assessing Consultant to complete and return to the Project Manager.
The project manager will maintain regular contact with the gynaecologist whilst the participant is under their care.

At the end of the year, the researchers will write to the participants telling them that the surveillance has ended and that their care has been handed back over to their clinical team or gynaecologist. They will send the results of the surveillance to their GPs.

The project design has been based on the UKFOCSS protocol which successfully screened 4348 high-risk women, with 7 important modifications:
1. The researchers will be using the term 'surveillance' rather than 'screening' as this is in keeping with NICE guidelines for surveillance for early detection of breast cancer in high-risk women.

2. The researchers will not be performing an annual TVUS. In UKFOCSS all women had an annual TVUS, the date of which was pulled-forward if the ROCA score was 'intermediate'. However, the annual scans overloaded centres with requests, causing delays (75% of scans on UKFOCSS were annual scans), and more importantly annual scans were not responsible for the detection of any BRCA-positive cancers in UKFCOSS (although scans were abnormal in a proportion BRCA-positive cancers with abnormal ROCA scores). This modification to the UKFOCSS protocol was agreed at the ALDO project inaugural steering committee meeting on 29/11/2017.
3. Based on the results from UKFOCSS, the researchers have adjusted the ROCA cut-offs for determining the categories for repeating surveillance tests. In UKFOCSS, cut-offs varied between 1 in 460 and 1 in 1640 according to blood draw numbers and menopausal status (to return a fixed proportion of women to repeat testing at each blood draw). Now that it is known from UKFOCSS that there would not have been any delay in detecting any of the BRCA-positive cancers had the threshold for repeat testing been as high as 1 in 500, it was agreed at the ALDO project inaugural steering committee meeting on 29/11/2017 that the previous levels had been far more conservative than was necessary, and a level of 1 in 500 was appropriate for clinical implementation.
4. The risk level at which women will be referred directly to gynaecology rapid access clinics (RAC) (without waiting for a repeat blood test or scan) has been set at 1 in 33 i.e. the NICE risk threshold for automatic 2-week wait (WW) referral for suspected cancer. This modification to the UKFOCSS protocol was agreed at the ALDO project inaugural steering committee meeting on 29/11/2017.
5. Following discussions with BRCA carriers, the researchers have changed the terminology for classifying non-normal results. In UKFOCSS the terms used were 'Normal', 'Low Intermediate', 'High Intermediate' and 'Elevated'. The researchers have reclassified them as 'Normal', 'Mildly Elevated', 'Moderately Elevated' and 'Significantly Elevated' which they and BRCA-carriers feel is easier to understand.
6. In UKFOCSS, the CA125 had to be analysed within 56 hours of the blood being drawn. Any sample received after this time was discarded and a repeat sample was requested. Abcodia and The Doctors Lab (TDL) have conducted a 7-day stability study to see if the CA125 sample remains stable in whole blood for a longer period in order for the samples to be posted back safely using Royal Mail. This study found that CA125 was stable post venepuncture, with only a 2% variability over a 7 day period, which did not impact ROCA scores.
7. The algorithm to determine menopause status has been improved to include women with the Mirena coil.

The researchers will also be sending 2 questionnaires out to the participants, one at the beginning (pre-surveillance) and one at the end (post-surveillance). The purpose of the first questionnaire is to find out why they have delayed surgery so far and to see what they feel surveillance will offer them, and the second questionnaire is to see if they found the surveillance a positive experience. Each questionnaire should take no longer than 30 minutes to complete and can be posted back to us using the pre-paid, pre-addressed envelopes provided.

Based on the results from UKFOCSS, surveillance in 2000 BRCA carriers should result in between 8 to 10 OC's being diagnosed during the year. Surveillance is for one year in line with the NHS Cancer Vanguard support.

The surveillance testing will last for one year, after which the women will be followed up for a further 18 months (study schedule below). During the 18 months, the researchers may contact the women with details of other (ethically approved) research they may be interested in.

Activity: Month
Patient Consent: 1

Pre-Surveillance Questionnaire: 1
1st Routine ROCA Test: 1
2nd Routine ROCA Test: 5
3rd Routine ROCA Test: 9
Post-surveillance Questionnaire: 12
End of Surveillance: 12
Surveillance results sent to GP: 12-13
Data preparation: 13-15
Economic analysis: 15-18
Final Report: 18
Continuing Follow up: 12-30

Intervention Type
Other

Primary outcome measure
The number of ovarian cancers (OC) detected through the ROCA Test and the stage and grade of these cancers, measured using surgery and histopathology reports, reviewed by a pathologist throughout the surveillance and for 6 months of follow up. OC specifically refers to 'invasive epithelial ovarian cancer' and does not include 'borderline ovarian tumour'

Secondary outcome measures
1. Number of women presenting to A&E with ovarian cancer symptoms, determined by the route of diagnosis (picked up by the surveillance or through emergency admission with symptoms). This will be assessed through all clinic letters and surgery and histopathology results in women diagnosed with OC throughout the project and for 6 months of follow up
2. The cost of surveillance in terms of treatment and surgery measured using a Markov model at 1 year
3. Participants experience of participating, measured using questionnaire data at baseline and at withdrawal (for those that withdraw during the trial) or at end of surveillance

Overall study start date
13/06/2018

Completion date
30/06/2022

Eligibility

Key inclusion criteria
1. Women who have tested postive for a pathogenic BRCA1 or BRCA2 mutation
2. Women aged 35 years or over
3. Women who still have at least one ovary or fallopian tube in situ
4. Women who are able and willing to travel to one of the named referral centres

Participant type(s)
Patient

Age group
Adult

Sex
Female

Target number of participants
Planned Sample Size: 2000; UK Sample Size: 2000

Total final enrolment
875

Key exclusion criteria
1. Women who have tested negative for pathogenic BRCA1 or BRCA2 gene mutation
2. Women who have not been tested for a pathogenic BRCA1 or BRCA2 gene mutation
3. Women who are less than 35 years of age
4. Women who are pregnant are not eligible for the ROCA® Test until 6 weeks after the end of their pregnancy. Neither CA125 nor ultrasound scanning can be used reliably to screen for OC during pregnancy
5. Women with a past history of bilateral salpingo-oophorectomy (Note: Women who still have one or more fallopian tube or ovary in situ are still eligible as they remain at increased risk of ovarian/tubal cancer)
6. Women previously treated for an ovarian malignancy
7. Women who are under investigation for suspected OC
8. Women currently being treated or within 6 weeks of treatment for any other malignancy

Date of first enrolment
02/08/2018

Date of final enrolment
31/03/2019

Locations

Countries of recruitment
England

United Kingdom

Wales

Study participating centre
UCLH Familial Cancer Clinic
Gynaecology Cancer Research Centre
1st Floor Maple House
149 Tottenham Court Road
London
United Kingdom
W1T 7DN

Study participating centre
Barts Familial Cancer Clinic
St Bartholomew's Hospital
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
Great Ormond Street Clinical Genetics
Clinical Genetics Unit
Great Ormond Street Hospital
Great Ormond Street
London
United Kingdom
WC1N 3JH

Study participating centre
Guy's and St Thomas Cancer Genetics
Genetics clinic
7th floor, Borough Wing
Guy's Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
North West Thames Cancer Genetics
Level 8V
Northwick Park and St Mark's Hospitals
Watford Road
Harrow
United Kingdom
HA1 3UJ

Study participating centre
South West Thames Regional Genetic Services at St Georges Hospital
Department Of Clinical Genetics
St George's University Of London
Cranmer Terrace

London
United Kingdom
SW17 0RE

Study participating centre
Oxford University Hospital
Clinical Genetics Research
Oxford University Hospitals NHS Foundation Trust
Block 8
Nuffield Orthopaedic Centre
Oxford
United Kingdom
OX3 7LD

Study participating centre
Manchester Regional Genetics
Manchester Centre for Genomic Medicine
6th Floor
St Mary’s Hospital
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Leeds Clinical Genetics
Cancer Genetics
Department of Clinical Genetics
Third Floor
Chapel Allerton Hospital
Chapeltown Road
Leeds
United Kingdom
LS7 4SA

Study participating centre
Liverpool Clinical Genetics
Research and Development Team
Liverpool Women's NHS Foundation Trust
Crown Street
Liverpool
United Kingdom
L8 7SS

Study participating centre
Princess Anne Hospital Southampton
Wessex Clinical Genetics
University Hospital Southampton NHS Foundation Trust
Princess Anne Hospital
Coxford Road
Southampton
United Kingdom
SO16 5YA

Study participating centre
North Tees and Hartlepool Hospitals NHS Foundation Trust
Neonate Research Office
Second floor, Tower block
University Hospital of North Tees
Hardwick
Stockton-on-tees
United Kingdom
TS19 8PE

Study participating centre
Birmingham Women and Children's Hospital
Clinical Genetics
Norton Court
Birmingham Women's Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2TG

Study participating centre
Birmingham City Hospital
Pan-Birmingham Gynaecological Cancer Centre
City Hospital Birmingham
Dudley Road
Birmingham
United Kingdom
B18 7QH

Study participating centre
University Hospital of Wales
Clinical Genetics
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

Sponsor information

Organisation
University College London

Sponsor details
c/o Tabitha Kavoi
1st Floor Maple House (suite B)
149 Tottenham Court Road
London
England
United Kingdom
W1T 7DN
+44 (0)20 3447 5557
randd@uclh.nhs.uk

Sponsor type
University/education

Website
http://www.ucl.ac.uk/

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Industry

Funder Name
Abcodia Ltd

Results and Publications

Publication and dissemination plan
The economic analysis will be published in the second half of 2020. The final report will be published in 2021.

Intention to publish date
31/12/2021

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Adam Rosenthal (adam.rosenthal@ucl.ac.uk). Any data shared outside of the project team will be anonymised and this is stated in the Patient Information Sheet and Consent Form. Anonymised data will only be shared if the participant has consented to this. We will be holding patient identifiable data (kept in a secure database within the UCLH server). This data includes name, DOB, address, telephone, email, GP details etc, as well BRCA status, CA125 results, ROCA results and results of any investigations they may have (including surgery and histopathology). Participants will be completing 2 questionnaires during the project asking how they feel about the surveillance. Data will be available once FU is complete and for 18 months post surveillance (end of 2020). The data will be held by UCLH for at least 10 years after that as per their requirements. Participants will be asked for consent to share their anonymised data with Professor Ali McGuire for the economic analysis and with Abcodia to support future developments in ovarian cancer surveillance. Future requests by other groups to access the anonymised data will be reviewed by the Project Steering Group. The study is under ethical review and we are confident there will be no ethical barriers to this project. This project was selected by the NHS Cancer Vanguard in their Early Diagnosis Industry Challenge, the aim of which was to select high impact projects which will ultimately lead to a tangible improvement in the earlier diagnosis of cancer in the NHS. It has undergone peer reviews, which were positive and acknowledged the importance of this work.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v1	03/10/2018	17/02/2020	No	Yes
Protocol file	version 1.5	22/02/2021	06/01/2022	No	No
HRA research summary			28/06/2023	No	No
Results article		01/11/2022	18/08/2023	Yes	No