Avoiding Late Diagnosis of Ovarian Cancer

ALDO

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UCLHCC
Cancer Vanguard
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R&D / Sponsor Reference Number(s): 17/0841

Study Registration Number:

PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Old	1	13-March-2018	Sue Philpott, Project Manager	
Old	1.1	04-October-2018	Sue Philpott, Project Manager	Additional information added about sending an invitation letter out to the women and additional recruiting sites added
Old	1.2	November 2018	Sue Philpott, Project Manager	Page 18 amended (Patient initials and DOB only being added to blood sample tube)
Old	1.3	25 June 2019	Sue Philpott, Project Manager	Additional sites and PIs added into the document and surveillance extended into March 2020; Failsafe measure introduced (section 3.5)
Old	1.4	09 March 2020	Sue Philpott, Project Manager	Project extension until 31st March 2021
Current	1.5	22 February 2021	Sue Philpott, Project Manager	Additional letter sent to the participants regarding surveillance post ALDO and follow up.

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

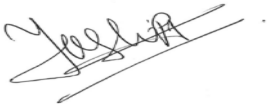
Chief Investigator:

Signature:  **Date** 22/02/2021

Print Name(in full): Adam Rosenthal

Position: Consultant Gynaecologist

On behalf of the Study Sponsor:

Signature:  **Date** 22/02/2021

Print Name(in full): Pushpsen Joshi

Position: Research Governance Manager

STUDY SUMMARY

Identifiers	
IRAS Number	245363
REC Reference No	
Sponsor Reference No	17/0841
Other research reference number(s) (if applicable)	N/A
Full (Scientific) title	Avoiding Late Diagnosis of Ovarian Cancer
Health condition(s) or problem(s) studied	Women with BRCA1 or BRCA2 will be screened for ovarian cancer using the ROCA test
Study Type i.e. Cohort etc	Cohort
Target sample size	2000
STUDY TIMELINES	
Study Duration/length	Surveillance will last until March 30th 2020, with up to 18 months for follow-up.
Expected Start Date	June 2018
End of Study definition and anticipated date	18 months after last surveillance test, October 2021
Key Study milestones	First patient recruited Recruitment completed First surveillance detected cancer Final surveillance test Engagement with NICE and Clinical Commissioning Data collation Completion of final analysis Completion of economic analysis
FUNDING & Other	
Funding	Funded by Abcodia Ltd. Dr Julie Barnes is the founding CEO and Chief Scientific Officer. julie.barnes@abcodia.com
Other support	The North Central and East London Cancer Alliance (formerly the National Cancer Vanguard (through the UCLH Cancer Collaborative)) is supporting this project through the Early Diagnosis Industry Challenge. Hlega Laszlo is the Senior Project Manager: helga.laszlo@nhs.net Naser Turabi is the Programme Director: n.turabi@nhs.net
STORAGE of SAMPLES (if applicable)	
Human tissue samples	Blood serum samples for analysis of CA125 will be sent via Royal Mail (using approved Royal Mail packaging) to The Doctors Lab (TDL), part

	of the Health Services Lab in London. Mike Gandy is the Translational Research Manager: michael.gandy@tdlpathology.com The Health Services Lab already provide diagnostic services to the NHS and provides all the pathology services for UCLH.
Data collected / Storage	The samples will not be transferred outside the NHS. Where consent has been provided, the samples will be stored for future ethically approved research at TDL (details above). Where there is no consent to store the samples for future research, the samples are stored for 3 months before being destroyed (as per TDLs protocol). The CA125 results will be sent password protected by NHS mail to the Project Manager at UCLH. At the end of the study, de-identified CA125 results will be shared with Abcodia.
KEY STUDY CONTACTS	Full contact details including phone, email and fax numbers
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Principle Investigator UCLH Familial Cancer Clinic	*Professor Usha Menon: u.menon@ucl.ac.uk
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Co –Investigator Guy's and St St Thomas' NHS	Dr Vishakha Tripathi

Foundation Trust	
Principle Investigator Liverpool Women's Hospital	Dr Dorothy Halliday
Principle Investigator Leeds Teach Hospitals NHS Trust	Dr Julian Adlard
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Principle Investigator Oxford University Hospital	Dr Joyce Solomons
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Principle Investigator Birmingham Women's Hospital	Dr Jonathan Hoffman
Principle Investigator Birmingham City Hospital	Mr Janos Belago
Principle Investigator North Tees and Hartlepool Hospitals NHS Foundation Trust	Dr Mary George
HSL Transitional Research Manager	Mike Gandy: michael.gandy@tdlpathology.com
Steering Committee Members	Members are indicated by an * before their names above. Additional members are: Caroline Presho (Patient representative): caroline.presho@gmail.com Athena Laminos (Charity representative) - Eve Appeal Mr Richard Edmondson (Consultant Gynaecological Oncologist), St Mary's Hospital Manchester)

KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the RE of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

PRINCIPLE INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

OTHER: The ALDO project is supported by the NHS Cancer Vanguard as part of their Early Diagnosis Industry Challenge. The NHS Cancer Vanguard will be providing support through clinical expertise and will help to develop a clearer route to consideration of the ROCA Test being commissioned in the future.

KEY WORDS

Ovarian Cancer, Surveillance, ROCA Test, BRCA1, BRCA2, Mutation, BRCA Carriers, Women, Blood Test, CA125, Risk Reducing Salpingo-Oophorectomy, Transvaginal Ultrasound Scan

LIST OF ABBREVIATIONS

A	Abnormal
A&E	Accident and Emergency
ALDO	Avoiding Late Diagnosis of Ovarian Cancer
BRCA	BReast CAncer susceptibility gene
CD	Clinical Decision
CI	Chief Investigator
CRO	Contract Research Organisation
CRUK	Cancer Research UK
DOB	Date of Birth
EDIC	Early Diagnosis Industry Challenge
FCC	Familial Cancer Clinic
FTC	Fallopian Tube Cancer
GAfREC	Governance Arrangement for NHS Research Ethics
GP	General Practitioner
HSL	Health Services Laboratory
HRA	Health Research Authority
HRT	Hormone Replacement Therapy
HTA	Human Tissue Authority
ICERs	Incremental Cost-Effectiveness Ratios
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Studies Number
MMS	Multi Modal Screening
N	Normal
NICE	The National Institute for Health and Care Excellence
OC	Ovarian Cancer
PI	Principle Investigator
PIS	Participant Information Sheet
PM	Project Manager
POD	Pouch of Douglas
QA	Quality Assurance
QC	Quality Control
RAC	Rapid Access Clinic
REC	Research Ethics committee
ROCA	Risk of Ovarian Cancer Algorithm
RRSO	Risk Reducing Salpingo-oophorectomy
SOP	Standard Operating Procedure
SSI	Site Specific Information
TDL	The Doctors Lab
TMF	Trial Master File
TVUS	Transvaginal Ultrasound Scan
U	Unsatisfactory
UCLH	University College Hospital London
UKCTOCS	UK Collaborative Trial of Ovarian Cancer Screening
UKFOCSS	UK Familial Ovarian Cancer Screening Study

CONTENTS

1 INTRODUCTION

7300 women develop ovarian cancer (OC) in the UK every year, with only 2500 surviving more than 5 years. Up to 10% of these cases occur in women who have inherited a faulty gene (e.g. BRCA1 or BRCA2), and women with these genes can have up to a 60% lifetime risk of developing OC. Currently, the only option for these women are either to 'watch and wait' for OC symptoms, or to undergo surgery to remove both ovaries and fallopian tubes, which will prevent OC developing. For women who have not yet reached the menopause, undergoing this surgery is a major decision because it causes infertility and early menopause. Having a surveillance test as an additional choice for such women, alongside ongoing discussions about having preventative surgery would be a welcome option.

The ROCA (Risk of Ovarian Cancer Algorithm) Test is a surveillance strategy that has proven to be beneficial in the UK Familial Ovarian Cancer Screening Study (UK FOCSS)[1], in which high risk women were screened using the ROCA test. In UKFOCSS, 9 out of 10 OCs were detected before any symptoms were apparent, the cancers were more likely to be a lower stage cancer when compared to cancers detected in women no longer on the trial and the cancers were less likely to have spread macroscopically beyond the pelvis.

The Avoiding Late Diagnosis in Ovarian cancer (ALDO) project will build on this evidence to demonstrate that surveillance in high risk women is a valid alternative until they are ready for surgery.

We will invite up to 2000 women who carry the BRCA1 or BRCA2 gene and have decided to defer or decline RRSO to take part in this surveillance project. Participants will be identified through Cancer Genetic Centres and Familial Cancer Centres in the first instance. If required we will advertise the project via on-line BRCA-carrier forums and relevant cancer charities.

The surveillance will consist of a 4 monthly blood test for CA125 which is then analysed using the ROCA Test. The ROCA Test monitors changes in the CA125, which typically rises in OC. Depending on the levels, the test may indicate the need for a repeat test and possibly an ultrasound scan of the pelvis to examine the ovaries. In participants with concerning scans or worsening ROCA results, surgical investigation to rule out OC will be recommended.

The ROCA test is CE marked by Abcodia Ltd. In June 2017, Abcodia and Dr Adam Rosenthal were successful in their bid to collaborate on the ALDO project with the NHS Cancer Vanguard as part of its Early Diagnosis Industry Challenge. This is a unique and innovative opportunity to work with the Vanguard's knowledge and resources in order to implement the ROCA test into the NHS and achieve the following aims:

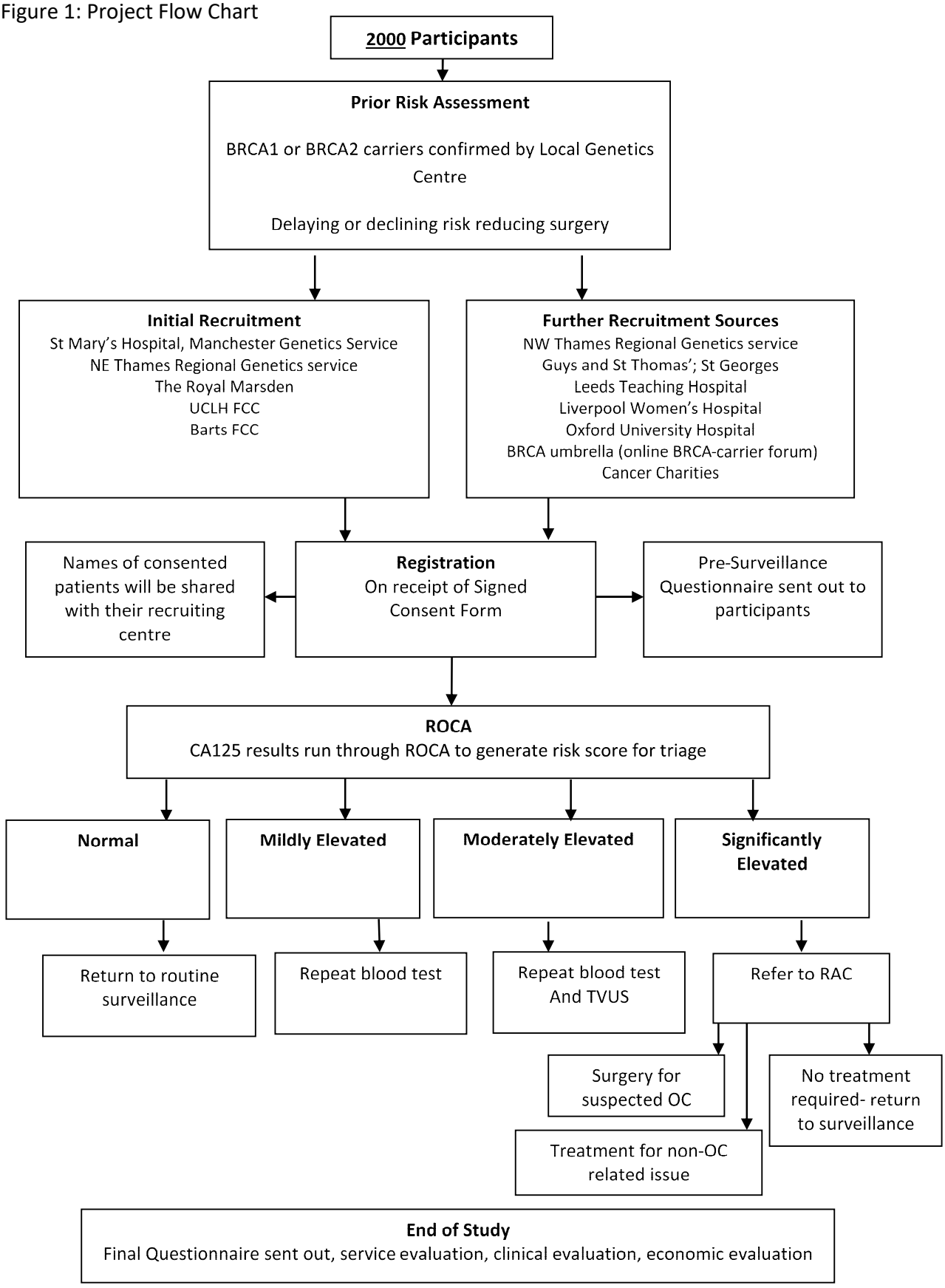
1. To demonstrate that surveillance using the ROCA test in this cohort can improve the care pathway for women at high risk of OC, resulting in a higher proportion of cancers diagnosed at earlier stages (≤ stage 3a) in these high risk women and as a consequence; less extensive surgery, a reduced length of hospital stay and overall a lower cost of treatment in those diagnosed with OC.

2. To demonstrate a reduction in emergency first OC presentations to Accident and Emergency departments (A&E). Currently 29% of all OCs diagnosed between 2006-2013 were through admission to A&E (source: London Cancer).[2]

3. To demonstrate that women found the experience of being under surveillance a positive one because of increased contact with the NHS (via invitation letters, provision of detailed information about surveillance and surgery, 4-monthly results letters, and where required, support from an expert doctor).

4. To provide economic evidence to allow NICE/commissioners to determine whether ROCA-based surveillance is cost-effective and should be recommended as standard NHS practice for eligible women.

Figure 1: Project Flow Chart



FCC = Familial Cancer Clinic; ROCA = Risk Of Cancer Algorithm; TVUS = Transvaginal Ultrasound Scan; RAC = Rapid Access Clinic; RRSO = Risk Reducing Salpingo-oophorectomy

BACKGROUND AND RATIONALE

Ovarian cancer is the sixth most common cancer in females in the UK; in 2013, there were 7,284 new cases of ovarian cancer and 4,271 deaths from it[3]. The prognosis for patients with OC depends on the pathological stage at time of detection. The earlier the detection the longer their survival times are. The 5 year survival rate for someone with stage 1 OC is 90%, compared to 19% for someone with stage 3 and 3% for someone with stage 4[3]. However, only 35% of OC's are diagnosed at the earlier stages of 1 and 2[3].

Approximately 10-20% of ovarian cancer cases occur in women with inherited mutations in the BRCA1 or BRCA2 genes[4]. Women inheriting these mutations have a high lifetime risk for OC: 11% to 37% by age 70 years in BRCA2 carriers and 39% to 65% in BRCA1 carriers[5,6].

Mutations in these genes occur in an estimated 1 in 325-500 women across the population, and in 1 in 50 women of Ashkenazi Jewish descent[7].

The only prevention strategy for women with the BRCA1 or BRCA2 mutation is to undergo prophylactic risk reducing surgery (RRSO) where the ovaries and fallopian tubes are removed. For women who have not yet reached the menopause, undergoing this surgery is a major decision because it causes infertility and early menopause. This can increase the chances of heart and bone disease, along with stroke and dementia in later life, unless they take hormone replacement therapy for many years. As a result, many women decline such a procedure, or delay having the surgery until after their menopause (which leaves them at risk of developing OC in the meantime). Additionally, a smaller number of post-menopausal women continue to decline the surgery, leaving them at risk of developing OC.

Currently 29% of all OCs diagnosed between the years 2006-2013 were through admission to A&E, presenting with symptoms[2]. Women diagnosed with OC after presenting with symptoms are usually diagnosed at a late stage when the cancer has spread, resulting in more complex surgery, longer hospital stays and poorer survival. Early stages of OC often cause no symptoms or if they do cause symptoms they are often symptoms that are commonly caused by other conditions. Symptoms include abdominal swelling, feeling full quickly when eating, needing to pass urine more frequently amongst others. It is not surprising therefore that nearly 60% of all OCs are diagnosed at a late stage[3].

Women who defer or decline risk reducing surgery are therefore at a higher risk of developing late stage cancer compared to those undergoing risk-reducing surgery. Having regular surveillance as an additional choice for such women would be a welcome option until they are ready to undergo surgery, if such surveillance would detect OC before any symptoms develop, resulting in a lower stage at diagnosis and a better prognosis.

The ROCA (Risk of Ovarian Cancer Algorithm) Test is a surveillance tool that has been validated in 2 large UK Clinical Trials, UKCTOCS[8,9] and UKFOCSS[1]. It is a computer algorithm that can be used to calculate the probability of a woman having ovarian cancer. It was co-invented by Professor Ian Jacobs and Dr Steve Skates[10,11] and was developed by studying serial serum Cancer Antigen 125

(CA125) profiles generated over several years from a population of more than 27,000 women, some of whom developed ovarian cancer. CA125 is found in the serum of a high percentage of women with non-mucinous ovarian tumours of epithelial origin[12]. Based on understanding the differences and changes in CA125 levels in women developing ovarian cancer compared to those in women who do not have ovarian cancer, the ROCA Test can accurately calculate the probability of a woman having ovarian cancer [1, 8, 9, 13,] . The ROCA Test works by using an initial risk of a woman having ovarian cancer based on her age, family history of ovarian/breast cancer and/or known genetic pre-disposition to ovarian cancer, e.g. BRCA1/2 status, and menopausal status. This risk is modified based on how closely her CA125 profile matches the profiles seen in healthy women and women with ovarian cancer; the more her profile resembles the profile seen in previous ovarian cancer cases, the greater is her estimated risk. By using a woman's first CA125 result and any subsequent changes in CA125 over time, the ROCA Test is proven to have a high performance for predicting the likelihood of a woman having ovarian cancer, and a higher specificity (i.e. lower false-positive rate), than using a single threshold rule e.g. 35 U/ml [5].

In the UKCTOCS trial 202,638 postmenopausal women aged between 50 and 74 were randomly assigned in a 2:1:1 ratio to three groups: no treatment (control; n=101,359); annual CA125 screening interpreted using the ROCA with transvaginal ultrasound scan (TVUS) as a second line test (so called Multimodal Screening - MMS, n=50,640); or annual screening with TVUS alone (n=50,639). Women with abnormal ROCA or TVUS results had repeat tests. Women with persistent abnormality on repeat screens underwent clinical evaluation and, where appropriate, surgery.

Results from the prevalence (first) screen (published in 2009)[8] showed a sensitivity of 89.4%, specificity of 99.8% and a positive predictive value of 43.3% for detecting all primary ovarian and fallopian tube cancers in the MMS group. Overall 8.7% of the women in the MMS group required a repeat test and 0.3% women required clinical evaluation. Surgery was performed on 0.2% women in the MMS group and 45 primary ovarian and tubal cancers were detected.

The results from the incidence screening were published in 2015. There were 296,911 incidence screens performed for 46,237 volunteers from the start of the trial in June 2002 until the last screen in December 2011 [5]. The sensitivity, specificity, and positive-predictive values for detection of primary invasive ovarian and tubal cancers were 85.8%, 99.8% and 20.8% respectively. 0.2% of screens resulted in women having screen positive surgery. Primary ovarian/tubal malignancies were detected in 154 of the 640 women having surgery (24.1%) and 411 had normal or benign pathology, with the remaining 45 having non-ovarian malignant neoplasms. Of the screen detected invasive epithelial ovarian/tubal cancers 82% were Type II (poor prognosis histological subtype).

The UKCTOCS data was also used to compare the performance of ROCA with what would have been achieved with using a fixed cut off value for CA125. Using fixed CA125 cut-offs at last annual screen of >35, >30 and >22U/mL would have identified 41.3%, 48.4% and 66.5% of invasive epithelial ovarian/tubal cancers respectively, compared to the 85.8% detected using ROCA in conjunction with MMS with TVUS and clinical assessment[9]. The sensitivity and specificity of ROCA alone (i.e. not in combination with TVUS and clinical assessment) was analysed and was found to be 87.1% and 87.6% respectively.

In Phase 2 of the UKFOCSS trial, the ROCA was evaluated as an approach for women at high risk of OC who wanted to defer or decline risk-reducing surgery e.g. to complete their family or delay

surgical menopause. The women were estimated to have a ≥10% lifetime risk of developing ovarian cancer, due to a family history of ovarian and/or breast cancer or a genetic risk such as BRCA1 or BRCA2 gene mutations, Lynch syndrome or women of Ashkenazi (Eastern European) Jewish descent with specific familial cancer histories [1, 13, 14]. UKFOCSS Phase 2 recruited 4,351 women between 2007 and 2012. The women were screened at 42 UK centres for 13,728 women screen years with an average of 3.3 years per woman. The median age was 45.5 years (range 34 - 85 years with a third aged over 50 years). Screening comprised 4-monthly CA125 tests analysed by the ROCA. TVUS was annual in those with 'Normal' algorithm results, but was triggered sooner if results were not 'Normal'. Women with suspicious scan and/or algorithm results were referred for consideration of surgical intervention. The median follow-up time was 4.8 years. Nineteen patients were diagnosed with invasive OC/fallopian tube cancer (FTC) within 1 year of prior screening (13 diagnoses were screen-detected and six were occult at RRSO). No symptomatic interval cancers occurred. Ten (52.6%) of the total 19 diagnoses were stage I to II OC/FTC (CI, 28.9%to 75.6%). Of the 13 screen-detected cancers, five (38.5%) were stage I to II (CI, 13.9% to 68.4%). Of the six occult cancers, five (83.3%) were stage I to II (CI, 35.9% to 99.6%). Modeled sensitivity, positive predictive value, and negative predictive value for OC/FTC detection within 1 year were 94.7% (CI, 74.0% to 99.9%), 10.8% (6.5% to 16.5%), and 100% (CI, 100% to 100%), respectively. Seven (36.8%) of the 19 cancers diagnosed <1 year after prior screen were stage IIIb to IV (CI, 16.3%to 61.6%) compared with 17 (94.4%) of 18 cancers diagnosed 1 year after screening ended (CI, 72.7% to 99.9%; P < .001). Eighteen (94.8%) of 19 cancers diagnosed <1 year after prior screen had zero residual disease (with lower surgical complexity, P = .16) (CI, 74.0% to 99.9%) compared with 13 (72.2%) of 18 cancers subsequently diagnosed (CI, 46.5% to 90.3%; P = .09). 92% of incident screen-detected cancers were completely cytoreduced and no woman was sub-optimally cytoreduced during UKFOCSS Phase 2.

The ROCA Test is CE marked by Abcodia Ltd. In June 2017, Abcodia in collaboration with Dr Adam Rosenthal (Co-Investigator on UKFOCSS) were successful in their bid to work with the NHS Cancer Vanguard as part of their their Early Diagnosis Industry Challenge (EDIC) through the ALDO project. The aim of the EDIC is to engage expertise from outside the NHS to undertake a small number of high impact projects which will ultimately lead to a tangible improvement in the earlier diagnosis of cancer in the NHS. The EDIC focuses on 2 outcomes:

1. Increasing the proportion of cancers detected at stages 1 and 2
2. Reducing the proportion of cancers detected through accident and emergency departments

This is a unique and innovative opportunity to work with the Vanguard's expert knowledge and resources in order to implement the ROCA Test into the NHS and help develop a much clearer route to consideration of the ROCA Test being commissioned in the future.

We aim to implement surveillance using the ROCA into the NHS for women with BRCA1 or BRCA2 who have chosen to delay or decline risk reducing surgery.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of the ALDO project is to implement the ROCA Surveillance Test into the NHS and to show that it can:

- Support the results from UKFOCSS that reported the detection of more early stage cancers, resulting in a better outcome after surgery (shorter hospital stays, less extensive surgery).
- Result in fewer women presenting to accident and emergency with OC symptoms (a Cancer Vanguard aim); London Cancer reported 29% OC cases presented as emergencies between 2006-2013)[2]. Based on published evidence, we expect 0% of women under surveillance with the ROCA test will present as emergencies, assuming full compliance with surveillance.
- Have an economic benefit on the NHS due to the above points.

2.2 Secondary Objective

- To be a positive experience for the women under surveillance, because of increased contact with the NHS (via invitation letters, provision of detailed information about surveillance and surgery, 4-monthly results letters, and where required, support from an expert doctor).

3 PROJECT DESIGN

This is a pilot implementation of the ROCA Test (Risk of Ovarian Cancer Algorithm) into the NHS in order to aid with early detection of OC in women at high risk of developing OC, supported by the North Central and East London Cancer Alliance, (formally the NHS Cancer Vanguard). Up to 2000 women with a BRCA1 or BRCA2 mutation and who have not yet had surgery to remove their ovaries and fallopian tubes will be invited to take part.

This project design is based on the UKFOCSS protocol with 7 important modifications:

1. We 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[15].
2. We 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 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, we 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 we know 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 direct 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, we have changed the terminology for classifying non normal results. In UKFOCSS the terms used were 'Normal', 'Low Intermediate', 'High Intermediate' and 'Elevated'. We have reclassified them as 'Normal', 'Mildly Elevated', 'Moderately Elevated' and 'Significantly Elevated' which we 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 (Appendix 1) 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 project will run until the 31st March 2021. Surveillance will consist of a 4 monthly blood test for CA125 measurement which is then run through the ROCA Test to give a risk score for how likely it is that the woman has OC. The frequency of CA125 testing is set at once every 4 months for two primary reasons. The first reason is that it is known that OC can grow rapidly and four monthly intervals will give a high likelihood of detecting the cancer at an early stage. Secondly, the higher frequency of serum samples will provide a detailed estimate of the natural history of OC in this high risk cohort.

3.1 Surveillance Strategy

A letter will be sent out to participants telling them when their blood sample is due, along with a blood taking pack (Appendix 2 and 3). The blood pack will contain everything needed for the blood to be taken: 8 ml red-top serum blood tube, needle, vacutainer with protective sheath, Royal Mail approved protective packaging for posting the sample back; ROCA Instruction Form (Appendix 4) and a ROCA Test Request Form (Appendix 5). Participants will need to take this to their GP to have the blood sample taken. The person taking the blood will need to complete the date and the time that the sample was taken on the blood request form. Participants can then send this straight to Health Services Laboratories (HSL) using the packaging and pre-paid pre-addressed envelope provided. HSL is the collaborating laboratory and provides all pathology services for UCLH. It is already set up to analyse the blood samples in the private ROCA service that Abcodia offer.

Participants will be asked to post the samples back on the day the blood was drawn. The samples will be returned by first class post. CA125 can remain stable for up to 7 days at ambient temperature and so should not be spoiled by any postal delays should they occur.

As HSL is an NHS lab, the samples received will be identified by the woman's initials, project ID number, date of birth (DOB) and unique ROCA ID. Serial CA125 results will be analysed by the ROCA algorithm.

3.2 The ROCA Test

CA125 is a protein that can rise in cases of ovarian cancer. The ROCA Test calculates the probability of someone having OC at a certain point in time, depending on their age, menopause status and change in the level of CA125 over time in serial blood samples up to that point. The probability is reported as a score for the risk for OC e.g. 1 in 2000 which is used as an aid to define the next intervention. The smaller the number the greater the risk, for example 1 in 500 is a higher risk than 1 in 1,000.

The ROCA® Test is the trade name of the Risk of Ovarian Cancer Algorithm (ROCA) that has been assessed in the UKFOCSS and UKCTOCS clinical trials in the UK. The ROCA® Test was developed as medical device software under the EC IVD Directive (98/79/EC) and in accordance with quality system standards EN ISO 13485 (Medical devices — Quality Management Systems — Requirements for Regulatory Purposes), and IEC 62304 (Medical Device Software – software life cycle processes). Abcodia secured a CE mark for the ROCA® Test in 2015 and currently offers a service for its use by select clinicians operating through private clinics in the UK.

3.3 ROCA Categories

The ROCA Test scores fall into four categories of risk for ovarian cancer; 'Normal', 'Mildly Elevated', 'Moderately Elevated' and 'Significantly Elevated'. These categories define the next surveillance action for that woman.

Table 1: ROCA Categories

ROCA Score	Category
<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

Following a routine blood sample the ROCA score will be categorised as above and the next action will follow the protocols shown in figures 2-5.

The specific letters sent for each outcome are shown in the appendices as per table 2 below.

3.3.1 Normal ROCA

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

3.3.2 Mildly Elevated

Participants with a 'Mildly Elevated' ROCA result will be scheduled for a repeat blood test in 6 weeks. The recommended actions from the results of the repeat test are shown in Chart A (Figure 3).

3.3.3 Moderately Elevated

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 patients named referral hospital. The project manager will contact the named gynaecologist at the referral hospital to arrange the TVUS for as soon as possible. The recommended actions from the results of the repeat tests are shown in chart B (Figure 4).

If the participant continues to get mildly or moderately elevated ROCA results, they will require a clinical decision by the Chief Investigator (CI) to determine the next action. This may result in her being returned to routine surveillance, needing further repeat tests or needing to be referred to her named gynaecologist for further clinical assessment.

3.3.4 Significantly Elevated

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.

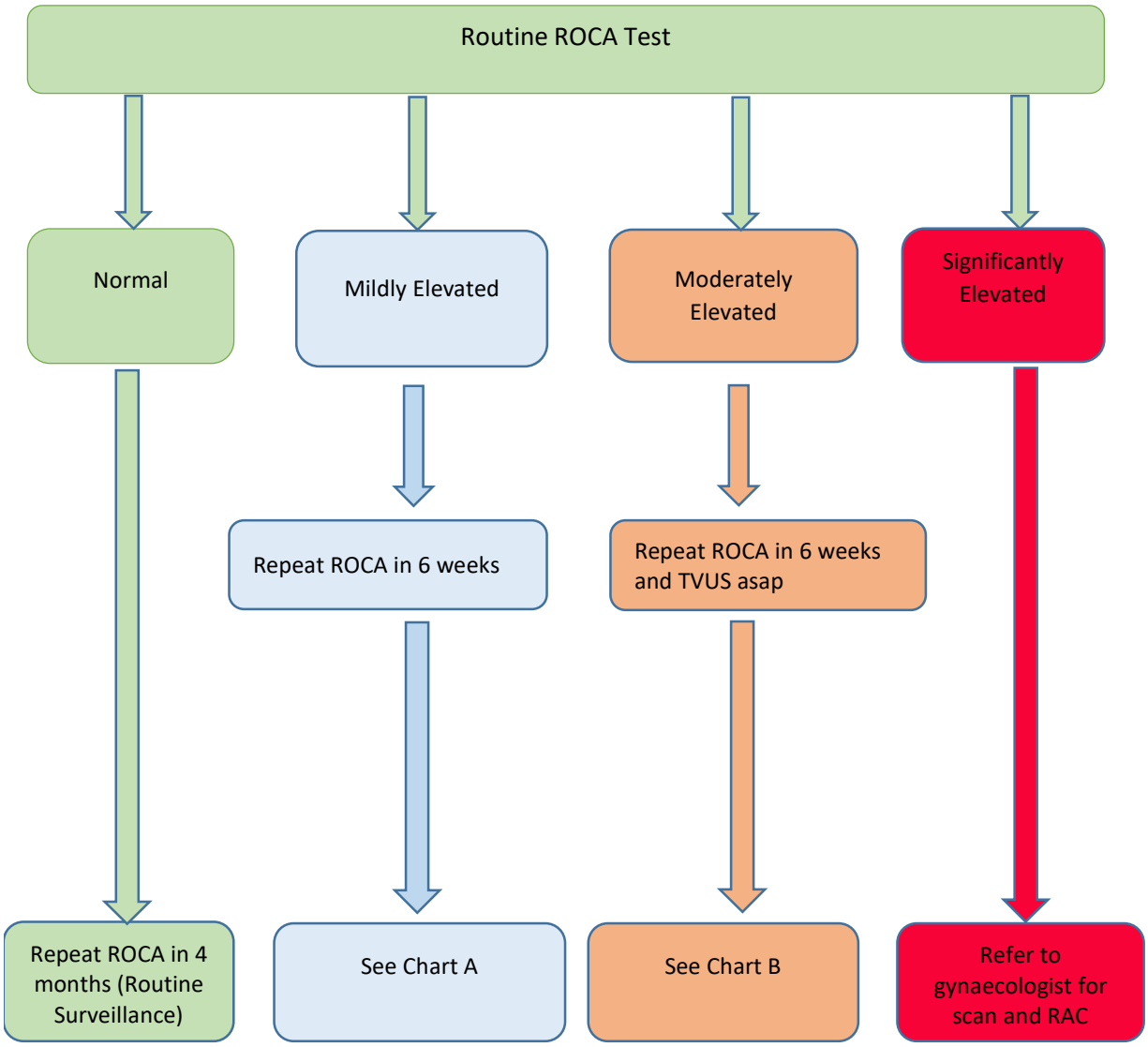
At the RAC, the clinical assessment should include ruling out other causes of CA125 elevation which include: colitis, chronic active hepatitis, cirrhosis, renal disease with serum creatinine >2.0 mg/dL, systemic lupus erythematosus, sarcoidosis, acute pancreatitis, diverticulitis, endometriosis, polyarteritis nodosa, Sjögren's syndrome, pericarditis, rheumatoid arthritis, osteoarthritis, breast cancer or other cancers. A clinical assessment form (Appendix 6) 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.

Table 2: Actions and letters following ROCA and TVUS Results

Test	Results	Next action	Letters in Appendix No.
Routine Sample	Normal ROCA	Continue with routine surveillance	7
	Mildly Elevated ROCA	Repeat ROCA in 6 weeks	8
	Moderately Elevated ROCA	Repeat ROCA in 6 weeks and TVUS asap	9
	Significantly Elevated ROCA	Refer for 2 week Rapid Access Clinic with TVUS first	10, 11
Repeat ROCA following Mildly Elevated ROCA	As above	As above	As above
Repeat ROCA and TVUS following Moderately Elevated ROCA	Normal ROCA and Normal Scan	Continue with routine surveillance	12
	Normal ROCA and Unsatisfactory Scan	Continue with routine surveillance	13
	Mildly Elevated ROCA and Normal Scan	Repeat ROCA in 6 weeks	14
	Mildly Elevated ROCA and Unsatisfactory Scan	Repeat ROCA in 6 weeks	15
	Moderately Elevated ROCA and Normal Scan	Clinical decision by CI	16
	Moderately Elevated ROCA and Unsatisfactory Scan	Clinical decision by CI	16
	Significantly Elevated ROCA **and/or** Abnormal Scan	Refer for 2 week Rapid Access Clinic with TVUS first	10, 11

Figure 2: Flow Chart 1: Surveillance Protocol Following a Routine ROCA Test



TVUS = Transvaginal Ultrasound Scan; RAC = Rapid Access Clinic; CD = Clinical Decision

Figure 3: Flow chart A. Surveillance Protocol Following a Mildly Elevated ROCA Score

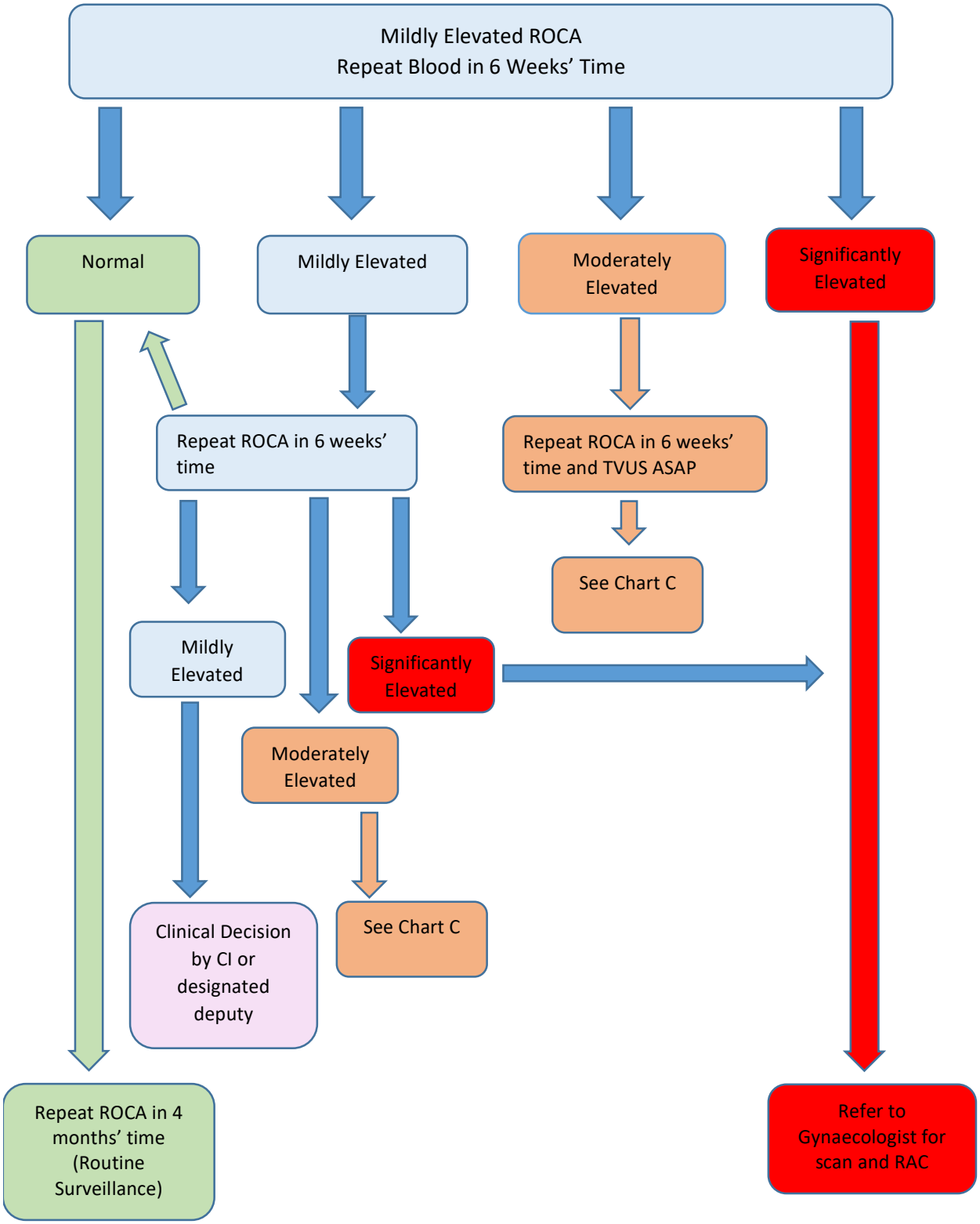


Figure 4: Flow chart B. Surveillance Protocol Following a Moderately Elevated ROCA Score

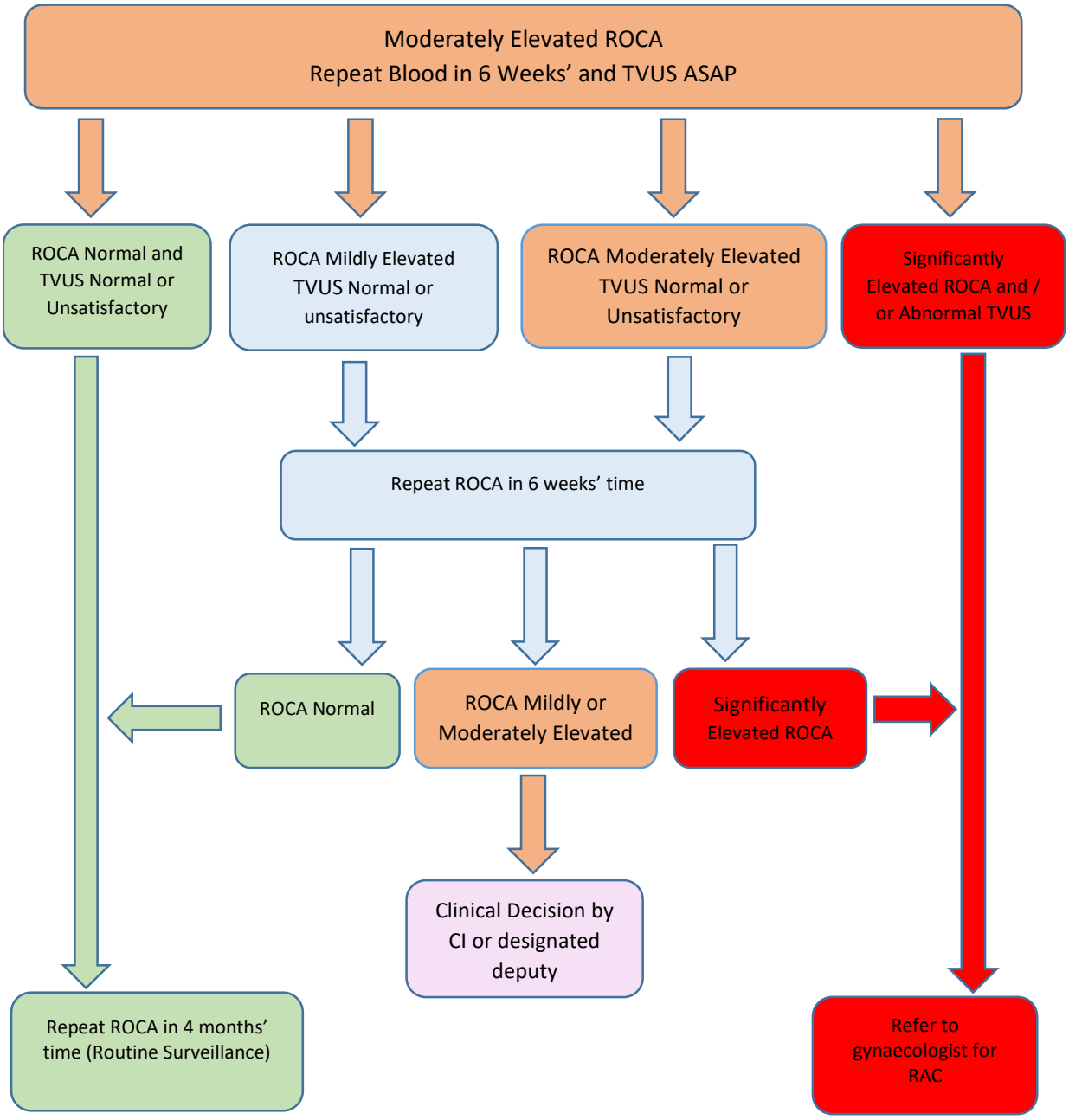
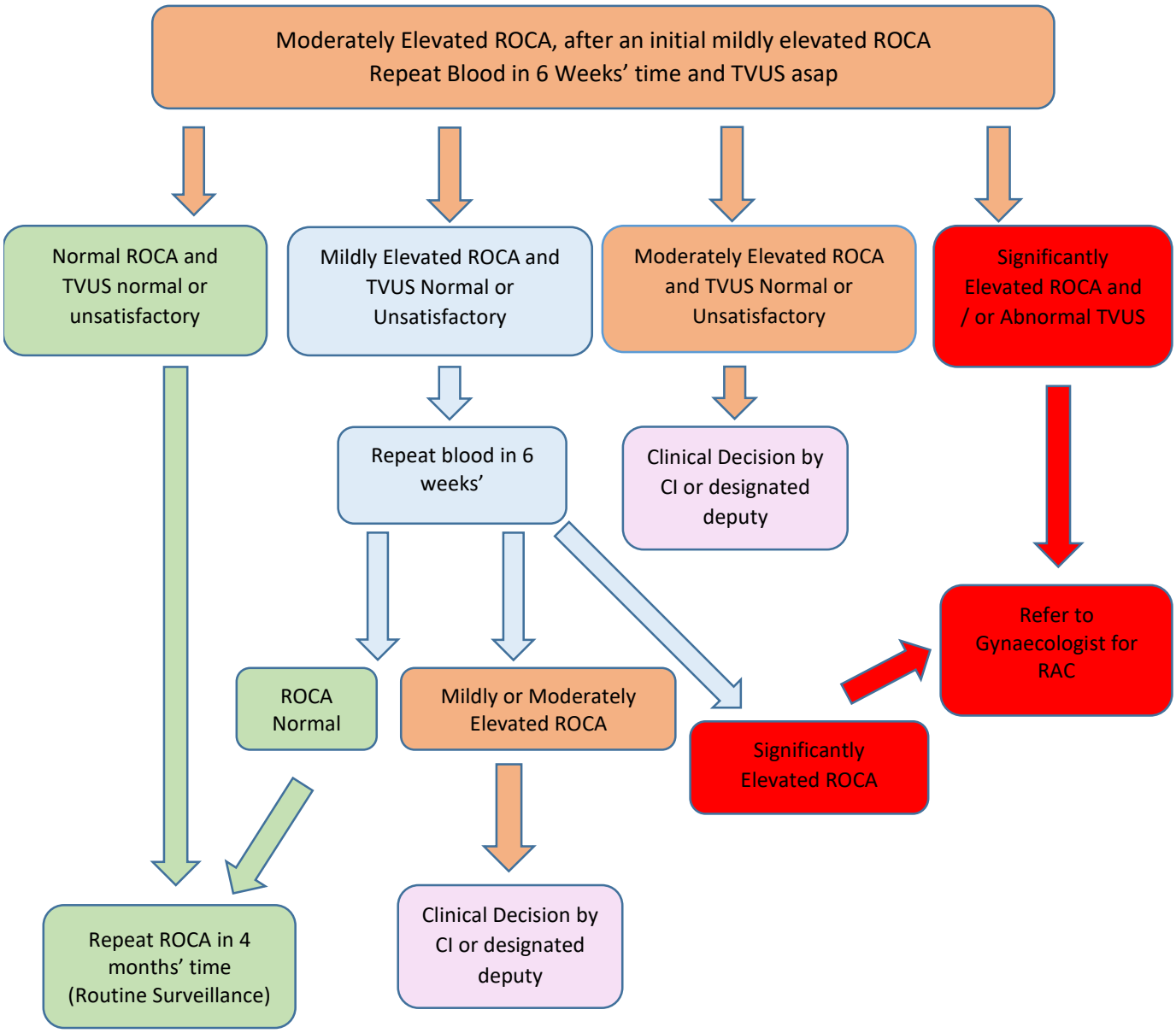


Figure 5: Flow chart C. Surveillance Protocol Following a Moderately Elevated ROCA Score after a Mildly Elevated score.



3.4 Transvaginal Ultrasound Scan of the Ovaries

If the ROCA Test is categorised as Moderately Elevated, a TVUS will be required which will be arranged and performed by one of four sites as outlined in section 4.5. The project manager will inform the site when a scan is required. Once done, the site will send a copy of the scan report to the project manager. The result of the scan will be classified as either Normal, Unsatisfactory or Abnormal as per table 3 below.

Table 3: Transvaginal Scan Classification Algorithm

Ovary 1	Ovary 2	Result
Not visualised, poor view	Not visualised, poor view	U
Not visualised, poor view	Normal morphology	U
Not visualised, poor view	Simple cyst of ≤60cc or mean diameter ≤5cms	U
Not visualised, poor view	Not visualised, good view of iliac vessels	U
Abnormal morphology	Normal morphology	A
Abnormal morphology	Not visualised, good view of iliac vessels	A
Abnormal morphology	Not visualised, poor view	A
Abnormal morphology	Simple cyst of any size	A
Simple cyst >60cc or mean diameter >5cms	Normal morphology	A
Simple cyst >60cc or mean diameter >5cms	Not visualised, poor view	A
Simple cyst >60cc or mean diameter >5cms	Simple cyst >60cc or mean diameter >5cms	A
Simple cyst >60cc or mean diameter >5cms	Not visualised, good view of iliac vessels	A
Ascites or fluid in POD >10mm, irrespective of ovarian findings		A
Normal morphology	Normal morphology	N
Normal morphology	Simple cyst of ≤60cc or mean diameter ≤ 5cms	N
Normal morphology	Not visualised, good view of iliac vessels	N
Not visualised, good view of iliac vessels	Not visualised, good view of iliac vessels	N

POD = Pouch of Douglas, N = Normal, U = Unsatisfactory, A = Abnormal

An abnormal scan will always result in a referral to the gynaecologist at the Rapid Access Clinic, regardless of the ROCA score. If the scan is normal or unsatisfactory, the next action will be dependent upon the ROCA score as per figures 2 – 5. It is recognised that simple cysts >60cc are highly unlikely to represent cancer, but as such cysts may be at risk of a 'cyst accident' (torsion, rupture/haemorrhage/infection) the woman should undergo a clinical assessment by her named Consultant.

Table 4. Expected percentage of results in each category for the ROCA® Test based on the UKFOCSS Trial

Category	% of ROCA tests in this category*
Normal	83%
Mildly Elevated	10%
Moderately Elevated	6%
Significantly Elevated	1%

*Assumes same proportion of premenopausal vs. postmenopausal women as were in UKFCOSS (approx. 2/3 premenopausal).

3.5 Off Protocol Samples

As a 'failsafe' measure, any 'Normal' ROCA result where the CA125 level is ≥ 50 U/mL or has increased by at least 50% since the last measurement will be reviewed by the Chief Investigator to decide if the participant is to continue on routine surveillance or whether they should be taken off protocol and have their test repeated after 6 weeks.

3.6 Referral Centres

Participants will be seen at one of 9 hospitals depending on where they are recruited from or where they live. The 9 referring sites will be:

- University College London Hospitals
- Barts Health NHS Trust, London
- St Mary's Hospital, Manchester
- St George's Hospital, London
- Leeds Teaching Hospitals NHS Trust
- Southampton University Hospital
- Birmingham City Hospital
- Liverpool Womens' Hospital
  North Tees and Hartlepool Hospitals NHS Foundation Trust

At the discretion of the CI, it is acceptable for participants to be assessed at other sites offering a high-level of gynaecological oncology care.

The participants will be told at the start of the project which of these hospitals they will be seen at if the ROCA score recommends a scan or referral. This is explained in the invitation letter, the patient information sheet and the consent form.

3.7 Menopause Status

CA125 is more variable in premenopausal women due to their menstrual cycle. The ROCA Test takes this extra variability into account so when the participants have their first routine blood sample taken, they will be required to answer some menopause questions on the blood request form which will be used to ascertain menopause status.

3.7.1 Menopause questions

1. Have you had a period in the past year?
    a. If yes, date of last period
2. Have you had a hysterectomy (an operation to remove your womb)?
3. Have you had surgery to remove both your ovaries?
4. Do you have a mirena coil fitted?
    a. If yes, is this part of HRT?
5. Have you ever had hot flushes and/or night sweats for more than 1 month?
6. Are you taking hormone replacement therapy (HRT)?

If a participant is postmenopausal, then she will not need to answer these questions again. If premenopausal, she will need to answer these questions at each routine blood drawer until she is classified as postmenopausal. The flow charts for determining menopause status based on hysterectomy status are shown below in figure 6 and 6a.

Figure 6: Flow Chart to Determine Menopausal Status for someone who has not had a hysterectomy

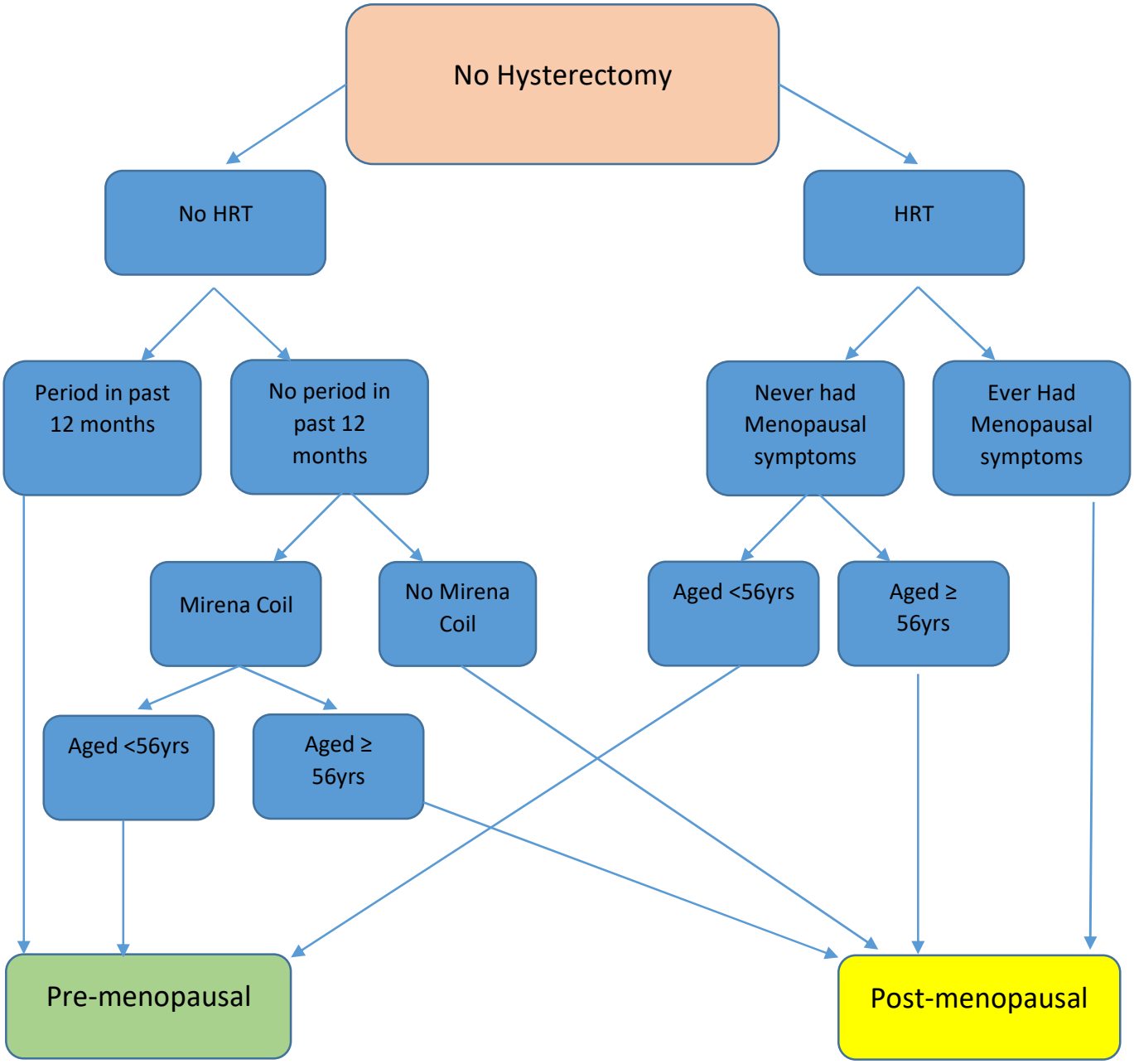
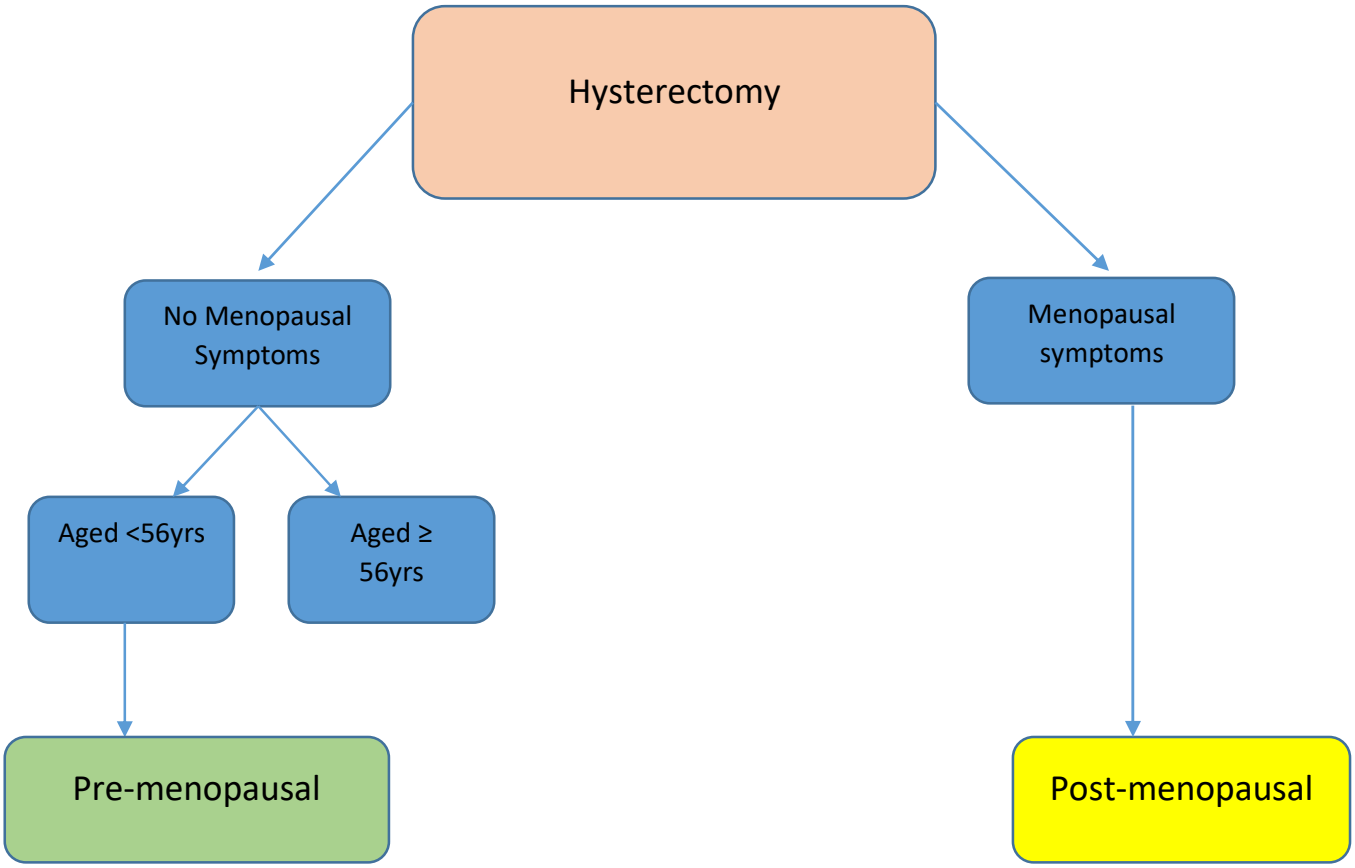


Figure 6a: Flow Chart to Determine Menopausal Status for someone who has had a hysterectomy



3.8 Surveillance Questionnaire

Participants will be asked to complete 2 questionnaires (Appendix 17 and 18) during the course of their surveillance: the first will be at the beginning of their surveillance and the other once it has ended. The purpose of the pre-surveillance questionnaire will be to find out why they have delayed having surgery to remove their ovaries and what they feel surveillance can offer them. The post surveillance questionnaire at the end will be to ascertain their views on the service and to find out if they have had surgery which we were unaware of.

4 STUDY SCHEDULE

The Project schedule is shown in table 5 below.

Table 5: Schedule of activities per participant

Activity	When
Patient Consent	August 2018 – April 2019
Pre-Surveillance Questionnaire	August 2018 – April 2019
1st Routine ROCA Test	August 2018 – June 2019
Subsequent Routine ROCA Test	Every 4 months until the end of March 2020
Post-surveillance Questionnaire	After their last routine ROCA Test
End of Surveillance	March 2021
Surveillance results sent to GP	March – May 2021
Data preparation for economic analysis	January 2020 – May 2020
Economic analysis	May 2020-July 2020
Economic Report	August 2020
Continuing Follow up	Until December 2021

Recruitment will begin as soon as Ethics, HRA and site approval has been received. Patients will be recruited over a 9 month period. The recruiting sites will send out the invitation letter, PIS and consent form to all potential eligible women. A reminder letter will be sent out by the sites if there has been no response after 6 weeks to the original invitation letter. If a woman wishes to participate she will send the completed consent form back to the project manager at UCLH. This consent form will include the woman's name and address which will be entered onto the project database. Once this has been entered, the woman will be sent her blood taking pack for the first routine blood sample. We will stagger sending out the first blood packs over a 3 month period to ensure the lab is not overwhelmed with too many samples coming in at the same time. This will result in approximately 166 blood packs being sent and samples received each week.

For participants whose ROCA Test results remain normal, they will continue with 4 monthly routine ROCA tests until the end of March 2021. For participants with Elevated ROCA Test results, their tests will be repeated sooner.

If any of the participants have elevated results at their final surveillance test, they will be followed up as per the flow charts until their results return to normal or they are referred for a clinical assessment. Women will be followed up for 18 months after the surveillance has ended to see if they undergo surgery to remove their ovaries or if they are diagnosed with OC.

After their final surveillance test, we will write to all participants informing them that surveillance has ended and that their care has been handed back over to their clinical team or gynaecologist (Appendix 19). We will send the results of the surveillance to their GPs.

4.1 Withdrawal Criteria and Procedures

Participants can withdraw from the project at any time, for e.g. if they have risk reducing surgery or through personal choice. Reasons for withdrawal will be:

- risk reducing surgery to remove both fallopian tubes and ovaries
- surgery to remove both fallopian tubes and ovaries for other reasons
- diagnoses of OC (including fallopian tube cancer)
- pregnancy
- personal choice
- ill health or
- death

If a participant withdraws during the project for a reason other than death, we will write to them confirming their withdrawal, as well as informing their recruiting centre, GP and referral centre if applicable.

4.2 End of Surveillance

31st March 2021, unless they withdraw earlier for one of the above reasons. If a participant withdraws before the project has ended, we will determine the reason for withdrawal. If they have had surgery or been diagnosed with OC we will request all clinical letters relating to the surgery, the surgical notes and histopathology results so that we can ascertain the reason for surgery and diagnosis (OC or not).

4.2.1 Reason for Surgery

Reason for surgery will be defined as:

- Risk reducing surgery – patient decided to have surgery with normal prior surveillance results
- Surveillance prompted surgery – patient was anxious about results and so decided to have surgery but OC was not suspected clinically
- True positive surgery – surveillance suggested OC and histology confirmed this
- False positive surgery – surveillance suggested OC but histology was anything other than invasive epithelial cancer.

Reason for surgery will be classified by both the project manager and the CI (Dr Adam Rosenthal). Histology will be reviewed by a pathologist for confirmation of OC or not. OC specifically refers to ‘invasive epithelial ovarian cancer’ and does not include ‘borderline ovarian tumour’.

4.2.2 End of Surveillance Communication

At the end of the surveillance we will write to the participants to: 1) let them know how they can access surveillance privately (based on enquiries received), and 2) to say that in the future we may want to look at long term benefits of surveillance by looking at their GP records or using NHS Cancer Registry Data. We will attach 2 consent forms with this letter.

The first (Abcodia Consent), will be asking their permission to allow the Private Consultant and Abcodia ltd access to their ALDO ROCA results if they decide to use the private service. The second (ALDO FU) will be asking their permission to allow the ALDO team access to GP records and NHS Cancer Registry Data in the future.

5 CONSENT

Potential women will be identified and invited to participate by the following clinical genetics centres or familial cancer clinics:

UCLH Familial Cancer Clinic
Barts Familial Cancer Clinic
Great Ormond Street Clinical Genetics
Guy's and St Thomas Cancer Genetics
North West Thames Cancer Genetics
South West Thames Regional Genetic Services at St Georges Hospital
Oxford University Hospital
Manchester Regional Genetics
Leeds Clinical Genetics
Liverpool Clinical Genetics
Princess Anne Hospital Southampton
North Tees and Hartlepool Hospitals NHS Foundation Trust
Birmingham Women and Children's Hospital
University Hospital of Wales

Very few of these centres know how many of their BRCA positive women will be eligible (i.e. who has not yet had surgery to remove their ovaries) and due to the short recruitment period, they will not have time to see each of these women in clinic in order to find out who is eligible or not. They will therefore need to send the project information (invitation letter, PIS and consent form) to the women by post. Additionally, women responding to the advert will be sent the invitation letter and patient information sheet by post or by email.

As very few of the women are likely to be seen in clinic, it is not possible for a researcher or clinician to witness the signature and countersign the consent form. The invitation letter and PIS provides a contact number for the women to talk to someone about the project if they do have any questions. All women will also have the opportunity to discuss the project with their genetics team if they wish.

Participants will be asked to print their name, sign and date the consent form, provide their personal details (name, DOB, contact details, NHS number, GP) and return it to us in the pre-paid pre-addressed envelope provide.

Women who do consent to participate, will need to attend their GP practice to have their blood samples taken. By making this appointment and taking the blood taking pack to their GP, the women are confirming their consent. It is not possible for the GP's to consent the women, as they will not have the time and resources to do this and many will refer the women to the practice nurse of phlebotomy clinic to take the blood sample.

A copy of the consent form will be sent back to the participant and the original copy will be filed in the Project Master File (PMF).

The genetics centres will be informed which of their patients have consented and details of all consented participants will be entered into the project database.

6 ELIGIBILITY CRITERIA

Participants will be eligible if they are aged 35 years and over, have a documented pathogenic BRCA1 or BRCA2 mutation, have not yet had surgery to have their ovaries and fallopian tubes removed and are willing and able to travel to one of the 4 named hospitals if they require a TVUS or a Gynaecological referral.

7.1 Inclusion Criteria (all 4 criteria must be satisfied for eligibility)

- Women who have tested positive for a pathogenic BRCA1 or BRCA2 gene mutation
- Women aged ≥35 years
- Women who still have at least one ovary or fallopian tube in situ
- Women who are able and willing to travel to one of the named referral centres

7.2 Exclusion Criteria (any of following will exclude woman from recruitment)

- Women who have tested negative for pathogenic BRCA1 or BRCA2 gene mutation
- Women who have not been tested for a pathogenic BRCA1 or BRCA2 gene mutation
- Women who are less than 35 years of age
- 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
- 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).
- Women previously treated for an ovarian malignancy
- Women who are under investigation for suspected OC
- Women currently being treated or within 6 weeks of treatment for any other malignancy

7 RECRUITMENT

Women with a BRCA1 or BRCA2 mutation will be identified through one of the 3 NHS Cancer Genetics centres which are part of the NHS Cancer Vanguard (NE Thames Genetics Service, the Royal Marsden Hospital Cancer Genetics Unit and Manchester Centre for Genomic Medicine), as well as other NHS Familial Cancer Clinics and Cancer Genetic Centres. Additionally we may advertise the project through BRCA online forums and patient forums attached to cancer charities if recruitment numbers are lower than expected.

For women recruited from Cancer Genetic Services and Familial Cancer Clinics, the recruiting centre will either see the women in clinic to give them the project information or will post the information out to them. The project information consists of an invitation letter (Appendix 20), Patient Information Sheet (PIS) (Appendix 21) and Consent Form (Appendix 22). The recruiting centres may not know if the woman has had risk reducing surgery (RRSO) and so the letter will explain that they

will not be eligible if they have had RRSO. A pre-paid addressed envelope will be included for the women to return the consent and patient details form to the project manager based at UCLH. The project manager will inform the sites which of their patients have consented by sending a regular spreadsheet. If there has been no response from a patient after approximately 6 weeks, then a reminder letter will be sent to the patient by the recruiting site.

If the numbers of women recruited through the NHS centres are low, then we will advertise the project through BRCA online forums and cancer charities. The advert is shown in Appendix 23 and will direct women to a website page (content shown in Appendix 24) with further information. This webpage will be hosted on the UCLH website.

On receipt of the signed consent form, the participant details will be entered into the study database and they will be scheduled for the first ROCA surveillance test. A copy of the signed consent form will be sent back to the participant for their own records along with the first blood pack. The blood pack includes a pre-paid addressed envelope for the samples to be returned in.

The recruiting centre will be provided with the names of women from their centres who have consented to take part (along with a copy of the signed consent form) and these centres will be required to send a copy of the participants BRCA test result to the project team at UCLH.

An information sheet (Appendix 25) will be provided for the GPs, which will be included in the blood taking pack. We will also enclose instructions on taking the blood (Appendix 4), and packaging the blood sample safely. The instructions are part of the blood taking pack and so if the woman is referred to the nurse or phlebotomist to take the blood, they will have all the information they require.

If a woman has consented but does not meet the eligibility criteria, we will write to them explaining the reason why they are not eligible. We will also inform their Clinical Genetics Team of this outcome.

8 STATISTICAL METHODS

Based on the results from UKFOCSS, surveillance in 2000 BRCA carriers should result in between 10 to 20 OC's being diagnosed during the year. Surveillance is for one year in line with the NHS Cancer Vanguard support.

Baseline data will be collected on BRCA status (BRCA1 or BRCA2), age and menopause status. All participants will be sent a pre-surveillance questionnaire. The purpose of this questionnaire is to understand their reason for delaying or declining risk reducing surgery and to try and understand what they feel the surveillance will offer them.

During the surveillance, we will collect data on the CA125 levels and results from the ROCA Test. If any of the participants needs a TVUS or other investigations, or undergoes surgery, we will collect data relating to those tests and surgery (date of surgery, reason for the surgery, type of surgery and

histopathology results). If anyone withdraws for a reason other than surgery, then we will try and ascertain the reason why.

Clinical data will be reported as descriptive only, with comparisons made with published/publicly available data on clinically-presenting BRCA-carriers.

At the end of the surveillance we will send the Post-Surveillance questionnaire.

An economic analysis will be conducted at the end of the project to calculate incremental cost-effectiveness ratios (ICERs) to provide information on the cost-effectiveness of ovarian cancer surveillance using the ROCA Test from a public health perspective for the high-risk populations of BRCA1 and the BRCA2 gene-carrying populations who have declined RRSO.
This along with engagement from NICE will be used to put forward the ROCA Test for incorporation into NICE guidelines for managing OC risk status in women who are BRCA1 and BRCA2 carriers.

9 PATIENT AND PUBLIC INVOLVEMENT (PPI)

The design of this project is based on the success of the UK FOCSS trial in which over 4000 participants were screened with the ROCA test. A qualitative study of the participants experience published in 2013 found that overall, screening was an acceptable risk management strategy[16]. They suggested that some improvements could be made in helping the participants understand the limitations of screening in order to avoid false reassurance. In this project we have listed the limitations very clearly on the Patient Information Sheet and again in the Consent Form. All result letters will also explain that symptoms should not be ignored as well as emphasising that surgery to remove your ovaries is the only way to prevent OC.

The ALDO project was successful in its bid to work with the NHS Cancer Vanguard Early Diagnosis Industry Challenge. The NHS Cancer Vanguard committee consisted of people working with the National Cancer Vanguard centres, the Cancer Research UK (CRUK) Director of Early Diagnosis & Cancer Intelligence, the Chief Medical Officer for London Cancer and Programme Director of the Academic Health Science Network Integrated Cancer programme as well as a person affected by cancer. The project was presented to this group during the final round of the bid (Appendix 26).

We are working closely with Caroline Presho who is a BRCA carrier and is the founder and director of BRCA Umbrella (http://brcaumbrella.ning.com), an online forum specifically for people with a BRCA1 or BRCA2 mutation to share their thoughts and experiences. Caroline was a participant in the UK FOCSS trial before she had risk reducing surgery to remove her ovaries and now works closely with a number of charities and healthcare professionals to raise awareness of hereditary cancers and support those affected. Caroline is a member of the project Steering Committee and will be advising us on the literature we send to the participants.

We will also be working closely with the relevant cancer charities: The Eve Appeal, CRUK, Ovacome, Ovarian Cancer Action and Target Ovarian Cancer. A charity representative from CRUK is sitting on

the project Steering Committee. Both the Eve Appeal and CRUK contributed to the funding of the UK FOCSS trial, and the then CEO of Ovacome sat on the Trial Steering Committee of UKFOCSS.

The Steering Committee (consisting of geneticists, gynaecologists, a charity representative and a lay person) will meet at regular intervals during the project to ensure smooth running and compliance.

We will be working closely with the Communications Lead from the UCLH Cancer Collaborative Cancer in publicising this project as well as disseminating the results. The Communications Lead will liaise with Caroline Presho and the cancer charities prior to any publications.

10 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the UCL/UCLH Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the relevant Local Clinical Research Network at other sites.

The research costs for this non-commercial project have been supported by Abcodia Ltd, the biotech company who own the rights to the ROCA Test. Abcodia will support all of the costs of this project including the project manager's salary, the cost of CA125 analysis, cost of the database design, postage, stationery etc (Funding Letter shown in Appendix 27). The costs of the project are detailed in table 6.

Table 6: Project costs

Item	Description	Cost
Staff	Project manager salary July 2017 – March 2020 (0.6 FTE)	£96,650
	Clinical Lead - Consultancy	£32,000
Surveillance Tests	Blood tests (CA125 analysis)	£34937.22
Invitation material, test packs and questionnaires	Stationery (paper and printing) and blood taking packs	£2,511.36
Postage	Postage for all study material – letters, questionnaires and blood taking packs	£10,780.92
IT costs	Amendment of an existing database used, IT consultancy	£13,640
Excess Treatment Costs*	Transvaginal Ultrasound (TVUS)	£13,425.78
Economic analysis and NICE Engagement	Collaboration with Prof Ali McGuire from the London School of Economics	£35,000
Total		£238,945.28

The UCLH Cancer Collaborative is also providing Senior Programme Manager support through its Early Diagnosis Industry Challenge programme.

*Any further investigations such as TVUS are classified as NHS treatment costs as per NHS England guidelines (https://www.england.nhs.uk/wp-content/uploads/2015/11/etc-guidance.pdf). Detail on the expected value of Excess Treatment Costs is included in Appendix 28.

11 DATA HANDLING AND MANAGEMENT

The project database will be housed securely within UCLH's server and will be backed up each night in accordance with UCLH IT procedures. UCLH will act as the Lead Data Controller for this project. A Data Processing Agreement is in place between UCLH and Abcodia, and between UCLH and HSL to govern the appropriate management of all personal data. A Privacy Impact Assessment has been carried out and approved through the UCLH Information Governance structures.

All data will be entered into the database by the project manager. The data will consist of the details provide by the participant on the Consent form (name, address, NHS number, contact details), along with the CA125 results, menopause status, the ROCA Test result and where applicable, TVUS results and surgery and histology results. Hard copies of consent forms, BRCA test results, TVUS reports and outcome data (surgery information) and any other identifiable outcome data will be filed and kept in a locked cupboard at UCLH as per data protection requirements.

TVUS scan reports will be requested from the hospital in which the scan was carried out. This will be either one of the 4 referral hospitals mentioned in section 4.5. The reports can be emailed via NHS.net or faxed to a secure NHS fax number. The date and result of the scan (Normal, Unsatisfactory, Abnormal) will be recorded in the database. If a patient has surgery, then we will request the surgical and histology notes from the hospital where they are treated and the date of surgery, reason for surgery and outcome (cancer or no cancer) will be recorded in the database.

All blood samples for CA125 will be sent to and tested at HSL, which is a progressive partnership between The Doctors Laboratory, Royal Free London NHS Foundation Trust (The Royal Free London) and University College London Hospitals Foundation Trust (UCLH). HSL currently provides diagnostic services to the NHS and is already set up to access and transfer patient data safely and securely within the NHS firewall.

The blood sample and blood request form for CA125 testing, will be sent to HSL with the following information: the woman's name, her Study ID number, her date of birth, and date and time the sample was taken. Once the sample has been processed, the blood request form will be sent to the project manager and an excel form containing this information, along with the CA125 result will be emailed via NHS.net to the project manager. This data will then be uploaded to the project database.

The following de-identified data fields will be shared with Abcodia: DOB; Menopause status; CA125 dates and results; ROCA results (Score and Category); fields relating to clinical intervention (e.g. scans, attendance at rapid access appointments, surgical procedures etc.). Participants will be asked to consent to this at the start of the project and data will only be shared for those participants who have provided consent.

12 MATERIAL/SAMPLE STORAGE

Blood samples will be collected from the participants in accordance with the patient consent form and patient information sheet and shall include all tissue samples or other biological materials and any derivatives, portions, progeny or improvements as well as all patient information and documentation supplied in relation to them. Samples will be processed, stored and disposed in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereafter.

Blood samples for CA125 testing will be sent via Royal Mail to HSL, London (using the secure packaging and pre-paid envelope provided) where the samples will be analysed. Samples can be kept at ambient temperature and remain stable for 7 days. Samples will be packaged to comply with current regulations on the transport and postage of biological samples. The primary blood serum tube will be packed in secondary hard packaging with gauze, in a leak proof plastic bag and then sealed in a biohazard envelope which is clearly marked with the characters UN3373 and 'Diagnostic Specimen'

Where consent has been provided, the samples will be stored at HSL for future ethically approved research projects. Where consent has not been given, the samples will stored for 3 months as frozen before being destroyed as per TDLs protocol. Samples will be identifiable by name, date of birth and ROCA ID number. Each week, HSL will send a password protected excel sheet containing the patients name, date of birth, date of CA125 test, CA125 result to the project manager via the secure NHS.net.

13 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by UCLH.

- This study has been peer reviewed within UCLH, by an independent and relevant peer committee on 26 April 2017. The Sponsor has accepted these reviews as adequate evidence of peer review.

The study was deemed to require regulatory approval from the following bodies:
Ethics
HRA
R&D
Each approval will be obtained before the study commences.

14 ASSESMENT AND MANAGEMENT OF RISK

All potential risks and how they will be managed have been included in the attached Risk Assessment Form (Appendix 29).

Throughout the project a number of quality checks will be conducted to ensure the ROCA Test is working, ensure the surveillance tests are being scheduled at the right time and that the participants are being followed up appropriately. After 6 months, the data will be reviewed, specifically comparing the ROCA cut off values with the corresponding CA125 levels to ensure the ROCA is working correctly.

15 TRAINING

No staff training is required as all those working on the project were involved in UKFOCSS and/or are already familiar with the clinical management of BRCA-carriers, TVUS results and interpretation of ROCA test results. Clinicians seeing patients on the project in rapid access clinics will receive additional support from the CI where necessary e.g. when deciding if a patient should undergo surgical investigation on the basis of a rising ROCA score only.

16 INTELLECTUAL PROPERTY

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCLH. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCLH and to disclose all such know-how to UCLH with the understanding that they may use knowledge gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of UCLH confidential information or infringement of UCLH IPR.

17 INDEMNITY ARRANGEMENTS

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

18 ARCHIVING

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at UCLH for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents for [insert duration] and in line with all relevant legal and statutory requirements.

19 PUBLICATION AND DISSEMINATION POLICY

The final project report and any publications arising from the project will be drafted by the CL and edited by the Steering Committee members, who are representatives from all the recruiting Cancer Vanguard sites. All steering committee members will be listed as co-authors. The CL will ensure that all reasonable comments made by the parties in relation to a proposed publication are incorporated into the publication. Should sites outside the Vanguard also be involved in recruitment, representatives from each site will be asked to edit and put their name to the above project outputs.

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21 APPENDICES

Appendix 1 - Assessment of 7 day stability of CA125

The ROCA has been evaluated in clinical trials using a 56 hour limit on the receipt of whole blood for CA125 testing by the central processing facility. As the ROCA Test develops into a commercial product, Abcodia has evaluated the possibility of extending that limit to allow use of the postal service nationally. This would avoid the use of costly courier services, and negate the need for re-sampling of patients when samples return outside that 56hour window (Up to 20% of samples send via Royal mail can be delayed). Reliable ROCA testing relies on consistency in the CA125 data which is particularly important because of the use of all historic serial CA125 data by ROCA.

In order to assess whether CA125 was sufficiently stable in whole blood at ambient temperature for up to 7 days, Abcodia has conducted a stability study using blood taken from 100 post-menopausal healthy women. Blood was taken from the volunteers, shipped to its central processing and testing laboratory, divided into 6 sub-samples, each then left for 2-7 days in the lab, and tested for CA125 at the appropriate times daily. Using that data, ROCA scores were calculated (assuming women were both normal risk and high risk for ovarian cancer i.e. 2 ROCA calculations run twice per woman per time point) All scores were categorised according to the clinical utility of the test. Variability was assessed.

Analysis of results by linear regression showed that the effect of 'day' i.e. time from sampling to CA125 testing, on CA125 levels was not significant.

Computation of ROCA scores from the 700 CA125 data points (computed 2, once assuming women were normal risk and once assuming women as high risk) revealed very few women (5 as normal risk; 3 as high risk) would have been categorised differently using the >56hour sample time limit.

Our conclusion is that this is an acceptable impact of the 7day max limit, given that all but one of the category changes were normal to intermediate and would have led to a repeat ROCA test only.

Appendix 2 – 1st Routine sample request letter

Cancer Vanguard NHS

[Title Name]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear xxx

Welcome to the ALDO surveillance project (Avoiding Late Diagnosis of Ovarian Cancer).

We have enclosed everything you need to have your first blood sample taken: a blood taking pack, a notification letter for your GP and a blood request form. You need to take these to your GP to do the blood test.

Please note the following:

- The blood sample should be taken within the next 2 weeks.
- The blood request form must be completed with the date and time the blood was taken.
- You must answer all menopause-related questions on the blood request form.
- The blood request form needs to be returned with the blood sample.
- The blood must be posted back the day it was taken using the freepost envelope

We have also enclosed a copy of your signed consent form for your records plus a questionnaire. Please complete the questionnaire and return it to us using the pre-paid envelope provided.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery.

If at any point you decide to have surgery, rather than continuing with this surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team

ALDO Project Manager Tel: Email:

ALDO_1R_20180109 v1.0

ROCA Test

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Appendix 3 – 2nd and 3rd routine sample request letter

Cancer Vanguard

NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Title Surname]

Your routine blood sample for the ALDO surveillance project is now due.

We have enclosed everything you need to have this sample taken: a blood taking pack and a blood request form. You need to take these to your GP to do the blood test.

Please note the following:

- Your blood sample is due on **[blood due date]**. Please have it taken as close to this date as possible (the sample can be taken up to one week before the due date or one week after it).
- The blood request form must be completed with the date and time the blood was taken.
- You must answer all menopause-related questions on the blood request form.
- The blood request form needs to be returned with the blood sample.
- The blood must be posted back the day it was taken using the freepost envelope provided.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery.

If at any point you decide to have surgery, rather than continuing with this surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team

ALDO Project Manager Tel: Email:

ROCA Test

ALDO_2R_20180208 v1.0

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Appendix 4 - ROCA Test Instruction Form

The Cancer Alliance for north and eas

Your Patient is taking part in an NHS Surveillance programme for women at high risk of developing ovarian cancer and we would be very grateful if you would take her blood sample using the equipment provided.

Instructions for Taking the Blood Sample for the ROCA Test

- Use the blood taking equipment and packaging that we have provided.
- A full tube of blood should be collected.
- Clearly complete the label on the blood collection tube with a ball point pen with:
  patient initials and **patient date of birth**.
- The date and time of blood collection must be added to the ROCA Test Request Form **at time of venepuncture.**
- Place the blood tube in Specimen Transport Bag and close securely. Insert the Test Request Form in the back pouch of the Specimen Bag and return in the pre-paid addressed envelope provided.

Do not centrifuge, refrigerate or freeze the blood tube.

It is critical that the blood is processed within **7 days** of venepuncture and therefore the accurate time and date of blood collection must be added to the Test Request Form. Samples received after 7 days will need to be repeated.

Your patient must post the sample back to us on the day the sample was taken.

Appendix 5 - ROCA Test Request Form

Cancer Vanguard

NHS

ROCA Test

Test Request Form

Patient Details	
First Name	[auto fill]
Last Name	[auto fill]
Date of Birth	[auto fill]
Project ID	[auto fill]
ROCA ID	[auto fill]

Sample Collection Details			
Date of sample	DD	MM	YY
Time of sample	HH	MM	

Menopause Questions (patient to complete)	circle yes or no	
Have you had a period in the past 12 months?	Yes	No
If yes, date of last period		
Have you had a hysterectomy?	Yes	No
Have you had surgery to remove both your ovaries?	Yes	No
Do you have a mirena coil fitted?	Yes	No
Have you had hot flushes or night sweats lasting for more than 1 month	Yes	No
Are you taking HRT for menopausal symptoms?	Yes	No

Please complete and return this form with your blood sample

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ROCA Test Request Form_v1_20180124 19-Dec-17

Appendix 6: Clinical Assessment Form

Cancer Vanguard

NHS

ALDO Clinical Assessment Form

Please complete and return to [insert ALDO email address / fax number]

First Name_____**Surname**_____**ALDO ID** _____

Date seen _____/_____/_____

Hospital_____

Consultant _____**Name of Person seeing the patient**_____

Does the patient have any symptoms YES NO (Please circle which symptoms)

General health	Lethargy	Malaise				
Breasts	Lump	Pain	Discharge	Skin problem		
Gastro-intestinal tract	Poor appetite	Constipation	Nausea	Bloating	Rectal bleeding	
	Diarrhoea	Malena	Vomiting	Dyspepsia	Pain	
Urinary tract	Urgency	Frequency	Dysuria	Nocturia	Haematuria	Incontinence
Genital tract	Abnormal vaginal bleeding		Dyspareunia	Post-coital bleeding		PV Discharge
Other symptoms						
Overall duration of symptoms (Months)						

Does the patient have any other illness that may contribute to her symptoms/findings? YES NO If yes please provide details

Does the patient have any of the following conditions that may account for an elevated CA125 level?

Polyarteritis nodosa	**Rheumatoid arthritis**	**Osteoarthritis**	**Sjorgren's syndrome**	**Other arthritis**	**Hepatitis**	**Colitis**
Cirrhosis	**Pancreatitis**	**Sarcoid**	**SLE**	**Renal disease**	**Endometriosis**	**Diverticulitis**
Pericarditis	**Other -**					

Examination

SITE	**NOT DONE**	**NORMAL**	**ABNORMAL**	**If abnormal, please specify abnormality**
BREAST				
ABDOMEN				
PV				
RECTAL				

Cancer Vanguard

NHS

ALDO Clinical Assessment Form

Clinical Impression (please tick)

				Date	Abnormal
Probably ovarian malignancy			Repeat CA125		
Uncertain			TVUS / Doppler		
Other gynaecological malignancy			CT Scan		
Non gynaecological malignancy			MRI		
Other (give details)			Radio–immune- scan		
			Other		

Further Investigations (tick if any tests were abnormal)

Details of any abnormal results from further investigations

Management Decision (please tick)

Surgery	
Conservative management and follow up	
Return to routine surveillance	
Other (give details)	

If surgery

Date booked for surgery _____/_____/_____ Placed on W/L for surgery Yes No

Proposed surgery

If follow up plan, please give rationale and details of follow up

Date of next appointment _____/_____/_____

Appendix 7 – ROCA Normal Result Letter

Cancer Vanguard

NHS

[Title Name]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear xxx

The result of your recent blood test taken on [date] is now available.

We are pleased to advise you that your ROCA result is 'Normal'. Your next routine blood sample is due in 4 months' time and we will send you a blood pack nearer the due date.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery at this time.

If at any point you decide to have surgery, rather than continuing with this surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team
ALDO Project Manager Tel: Email:

ALDO_RN_20180208 v1.0

ROCA Test

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Appendix 8 – ROCA Mildly Elevated Result Letter

Cancer Vanguard

NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Title Surname]

The result of your recent ROCA test taken on [date] has been classified as 'Mildly Elevated'. Please be reassured that this does happen on occasion and does not mean you have anything wrong with your ovaries. In view of this result you need to have a repeat blood test in 6 weeks.

We have enclosed a blood pack for you to take to your GP to have the repeat sample taken.

Please note the following:

- Your blood sample is due on **[blood due date]**. Please have it taken as close to this date as possible (the sample can be taken up to one week before the due date or one week after it).
- The blood request form must be completed with the date and time the blood was taken.
- The blood request form needs to be returned with the blood sample.
- The blood must be posted back the day it was taken using the freepost envelope provided.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery.

If at any point you decide to have your ovaries and fallopian tubes removed rather than continuing with surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important you see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team

ALDO Project Manager Tel: Email:

ROCA test

ALDO_MILD_20180208 v1.0

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Appendix 9 – ROCA Moderately Elevated Result Letter

Cancer Vanguard NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Title Surname]

The result of your recent ROCA Test taken on [date] has been classified as 'Moderately Elevated'. Please be reassured that this does happen on occasion and in most cases, it does not mean you have anything wrong with your ovaries. In view of this result you will need to have an ultrasound scan of your ovaries and a repeat blood test in 6 weeks.

Ultrasound Scan

xxxx Hospital will contact you to arrange a date and time for your scan appointment.

Blood Test

We have enclosed a blood pack for you to take to your GP to have the repeat sample taken.

Please note the following:

- Your blood sample is due on **[blood due date]**. Please have it taken as close to this date as possible (the sample can be taken up to one week before the due date or one week after it).
- The blood request form must be completed with the date and time the blood was taken.
- The blood request form needs to be returned with the blood sample.
- The blood must be posted back the day it was taken using the freepost envelope provided.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery.

If at any point you decide to have your ovaries and fallopian tubes removed rather than continuing with surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important you see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team

ALDO Project Manager Tel: Email:

ROCA Test

ALDO_MOD_20180208 v1.0

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Appendix 10 – ROCA Significantly Elevated Result Letter to Participant

Cancer Vanguard

NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Title Surname]

The result of your recent surveillance test(s) is now available. We have reviewed these results and recommend you are seen in clinic by a consultant gynaecologist who can advise if any further investigation or treatment is required. Please be reassured that this does happen on occasion and does not necessarily mean you have anything wrong with your ovaries, as various conditions (not related to cancer) can cause similar results.

[name of hospital] will contact you to arrange the appointment. If you do not hear from them within 1 weeks, please contact us via the telephone number or email below.

We have forwarded your results to the consultant to review and discuss with you.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA Surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery.

If at any point you decide to have your ovaries and fallopian tubes removed rather than continuing with surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important you see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project programme, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team

ALDO Project Manager Tel: Email:

ROCA Test

ALDO_SE_20160208 v1.0

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Appendix 11 – ROCA Significantly Elevated Result Letter to Gynaecologist

Cancer Vanguard NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Gynae]

[Participants Name, DOB, Address, NHS number if known, Mobile number]

[Title FirstName Surname] is participating in the ALDO ROCA Surveillance project for BRCA1 and BRCA2 carriers. I have reviewed her latest surveillance results and recommend that she is seen in your 2 week wait rapid access clinic with a view to undergoing further investigation and/or surgery. Her results are shown below.

[Insert results]

We have informed [Title Surname] that you will be contacting her within a week with an appointment date.

I would be grateful if you would let us know when her appointment is and keep us informed of the outcome by completing the enclosed Clinical Assessment Form, so we can continue her surveillance if she does not have her tubes and ovaries removed.

Many thanks for your help with her management.

With best wishes

Yours sincerely

Adam Rosenthal PhD FRCOG
Consultant Gynaecologist and Clinical Lead on the ALDO project

Cc GP

ALDO Project Manager Tel: Email:

ROCA Test

ALDO_SE_G_20180208 v1.0

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Appendix 12 – Post Moderately Elevated Normal ROCA and Scan

Cancer Vanguard NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Title Surname]

The results of your recent ROCA Test on {date} and ultrasound scan on [date] are now available.

We are pleased to advise you that they have both been classified as 'Normal'. You can therefore continue with routine surveillance and your next blood test will be in 4 months'.

We will send out a blood pack when your next sample is due.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery at this time.

If at any point you decide to have your ovaries and fallopian tubes removed rather than continuing with surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important you see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team

ALDO Project Manager Tel: Email:

ROCA Test

ALDO_MODN_20160208 v1.0

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Greater Manchester Cancer Vanguard Innovation, RM Partners and UCLH Cancer Collaborative

Appendix 13 - Post Moderately Elevated Normal ROCA and Unsatisfactory Scan

Cancer Vanguard NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Title Surname]

The results of your recent ROCA test on [date] and ultrasound scan on [date] are now available. Your ultrasound scan was Normal. Your ROCA Test has been classified as 'Moderately Elevated'. Please be reassured that this does happen on occasion and does not mean you have anything wrong with your ovaries. In view of these results you need to have a repeat blood test in 6 weeks.

Blood Test

We have enclosed a blood pack for you to take to your GP to have the repeat sample taken.

Please note the following:

- Your blood sample is due on **[blood due date]**. Please have it taken as close to this date as possible (the sample can be taken up to one week before the due date or one week after it).
- The blood request form must be completed with the date and time the blood was taken.
- The blood request form needs to be returned with the blood sample.
- The blood must be posted back the day it was taken using the freepost envelope provided.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery at this time.

If at any point you decide to have your ovaries and fallopian tubes removed rather than continuing with surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important you see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team

ALDO Project Manager Tel: Email: ROCA Test

ALDO_MOD2_20180208 v1.0

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Appendix 14 - Post Moderately Elevated – Mildly Elevated ROCA and Normal Scan

Cancer Vanguard NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Title Surname]

The results of your recent ROCA test on [date] and ultrasound scan on [date] are now available. The ROCA Test is classified as 'Mildly Elevated' which means you need to have a repeat blood test in 6 weeks. Your ultrasound scan was Normal.

Please be reassured that this does happen on occasion and does not mean you have anything wrong with your ovaries.

Blood Test

We have enclosed a blood pack for you to take to your GP to have the repeat sample taken.

Please note the following:

- Your blood sample is due on **[blood due date]**. Please have it taken as close to this date as possible (the sample can be taken up to one week before the due date or one week after it).
- The blood request form must be completed with the date and time the blood was taken.
- The blood request form needs to be returned with the blood sample.
- The blood must be posted back the day it was taken using the freepost envelope provided.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery at this time.

If at any point you decide to have your ovaries and fallopian tubes removed rather than continuing with surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important you see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team

ALDO Project Manager Tel: Email:

ROCA Test

ALDO_MODMILD_20160208 v1.0

The Cancer Vanguard is a partnership between
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Appendix 15 - Post Moderately Elevated – Mildly Elevated ROCA and Unsatisfactory Scan

Cancer Vanguard

NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Title Surname]

The results of your recent ROCA test on [date] and ultrasound scan on [date] are now available. The ROCA Test is classified as 'Mildly Elevated'. Your ovaries could not be seen on the scan. Please be reassured that this does happen on occasion and does not mean you have anything wrong with your ovaries. In view of these results you need to have a repeat blood test in 6 weeks.

Blood Test

We have enclosed a blood pack for you to take to your GP to have the repeat sample taken.

Please note the following:

- Your blood sample is due on **[blood due date]**. Please have it taken as close to this date as possible (the sample can be taken up to one week before the due date or one week after it).
- The blood request form must be completed with the date and time the blood was taken.
- The blood request form needs to be returned with the blood sample.
- The blood must be posted back the day it was taken using the freepost envelope provided.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery at this time.

If at any point you decide to have your ovaries and fallopian tubes removed rather than continuing with surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important you see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team

ALDO Project Manager Tel: Email:

ROCA Test

ALDO_MODMILDU_20180208 v1.0

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Appendix 16 – Clinical Decision Letter

Cancer Vanguard

NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Title Surname]

Your most recent ROCA Test on [date] was 'Moderately Elevated'. As this is your second such result it has been reviewed by the project Clinical Lead. The recommended next action is to [insert next action – repeat the ROCA Test again in 6 weeks *or* refer to RAC *delete as necessary*].

If needed Blood Test

We have enclosed a blood pack for you to take to your GP to have the repeat sample taken.

Please note the following:

- Your blood sample is due on **[blood due date]**. Please have it taken as close to this date as possible (the sample can be taken up to one week before the due date or one week after it).
- The blood request form must be completed with the date and time the blood was taken.
- The blood request form needs to be returned with the blood sample.
- The blood must be posted back the day it was taken using the freepost envelope provided.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery at this time.

If at any point you decide to have your ovaries and fallopian tubes removed rather than continuing with surveillance, please let us know. You can continue being tested up until your surgery date.

If you have any worrying symptoms, it is important you see your GP as soon as possible. Do not wait for the results of the surveillance.

If you have any questions about this project, please telephone or email us on the contact details below.

Yours sincerely

ALDO Team

ALDO Project Manager Tel: Email:

ROCA Test

ALDO_CD_20180208 v1.0

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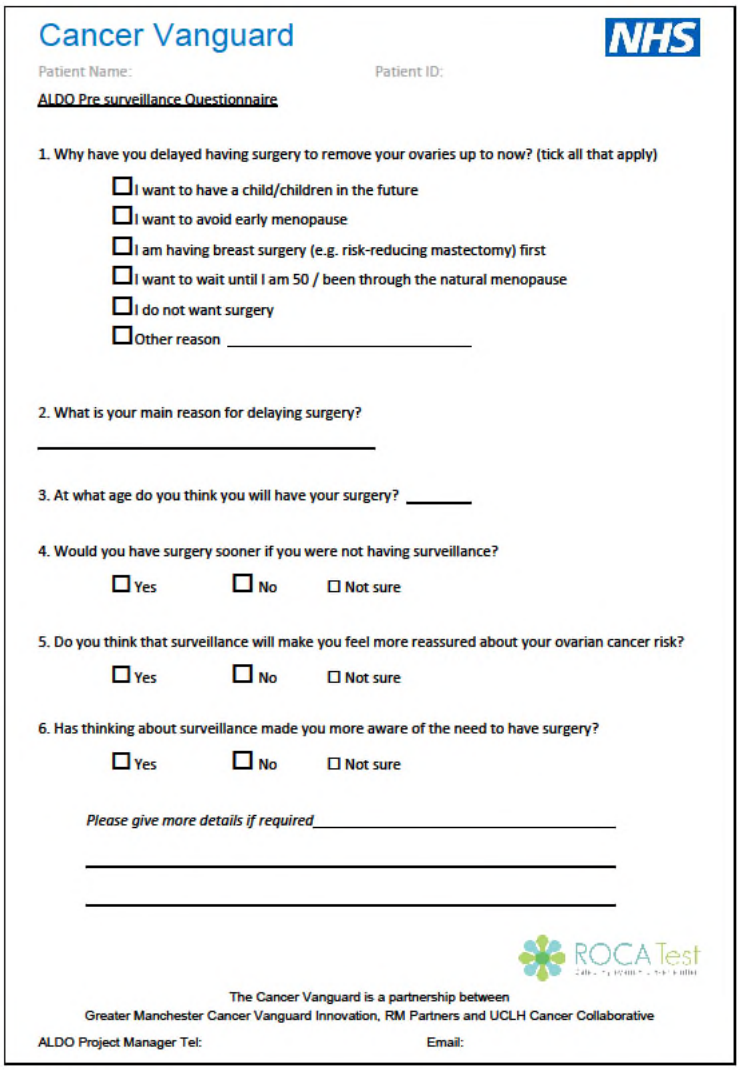
Greater Manchester Cancer Vanguard Innovation, RM Partners and UCLH Cancer Collaborative

Appendix 17 – Pre-Surveillance Questionnaire



Cancer Vanguard

NHS

Patient Name: Patient ID:

ALDO Pre surveillance Questionnaire

1. Why have you delayed having surgery to remove your ovaries up to now? (tick all that apply)

- ☐ I want to have a child/children in the future
- ☐ I want to avoid early menopause
- ☐ I am having breast surgery (e.g. risk-reducing mastectomy) first
- ☐ I want to wait until I am 50 / been through the natural menopause
- ☐ I do not want surgery
- ☐ Other reason _____

2. What is your main reason for delaying surgery?

_____

3. At what age do you think you will have your surgery? _____

4. Would you have surgery sooner if you were not having surveillance?

☐ Yes ☐ No ☐ Not sure

5. Do you think that surveillance will make you feel more reassured about your ovarian cancer risk?

☐ Yes ☐ No ☐ Not sure

6. Has thinking about surveillance made you more aware of the need to have surgery?

☐ Yes ☐ No ☐ Not sure

*Please give more details if required*_____

_____

_____

ROCA Test

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ALDO Project Manager Tel: Email:

Patient Name: Patient ID:

7. Have you had any previous surveillance for ovarian cancer (blood tests or ultrasound scans of your ovaries?

☐ Yes ☐ No ☐ Not sure

If you answered yes, who arranged this:

☐ GP ☐ NHS Gynaecologist ☐ Private gynaecologist

☐ Other _____

8. How proactively do you feel your ovarian cancer risk has been managed up until now?

☐ Very proactively
☐ Proactively
☐ Unsure
☐ Not very proactively
☐ Not at all proactively

9. How much do you agree with the following statements?

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
Surveillance will reassure me that everything is OK	☐	☐	☐	☐	☐
Surveillance is an effective way of detecting cancer before symptoms develop	☐	☐	☐	☐	☐
Surveillance will lead to an early diagnosis	☐	☐	☐	☐	☐
Surveillance will not take too much of my time	☐	☐	☐	☐	☐
Surveillance will detect all ovarian cancers	☐	☐	☐	☐	☐

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ALDO Project Manager Tel: Email: 2

Patient Name: Patient ID:

10. What do you think is the purpose of ovarian cancer surveillance? (tick all that apply)

- ☐ To allow early detection of ovarian cancer
- ☐ To prevent ovarian cancer developing
- ☐ To provide reassurance
- ☐ To prevent ovarian cancer deaths

11. Which of the above would you say is the main purpose of surveillance?

_____

12. What would you do if you developed some persistent symptoms of ovarian cancer (listed on the Patient Information Sheet) after you have had a normal ROCA test result?

- ☐ Go to see your GP immediately
- ☐ Leave it a month to see if the symptoms go away
- ☐ Wait for the next screening test
- ☐ Unsure

Thank you for taking the time to complete this questionnaire
Please return it using the pre-paid envelope provided

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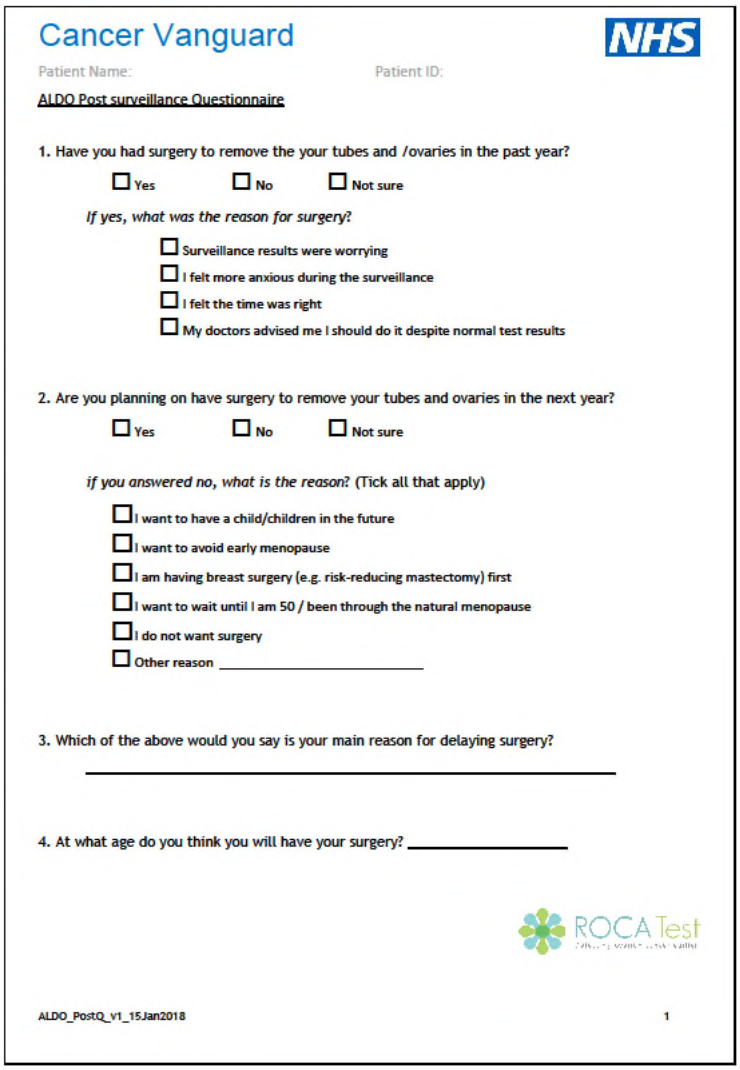
ALDO Project Manager Tel: Email: 3

Appendix 18 – Post Surveillance Questionnaire



Cancer Vanguard

NHS

Patient Name: Patient ID:

ALDO Post surveillance Questionnaire

1. Have you had surgery to remove the your tubes and /ovaries in the past year?

☐ Yes ☐ No ☐ Not sure

If yes, what was the reason for surgery?

☐ Surveillance results were worrying
☐ I felt more anxious during the surveillance
☐ I felt the time was right
☐ My doctors advised me I should do it despite normal test results

2. Are you planning on have surgery to remove your tubes and ovaries in the next year?

☐ Yes ☐ No ☐ Not sure

if you answered no, what is the reason? (Tick all that apply)

☐ I want to have a child/children in the future
☐ I want to avoid early menopause
☐ I am having breast surgery (e.g. risk-reducing mastectomy) first
☐ I want to wait until I am 50 / been through the natural menopause
☐ I do not want surgery
☐ Other reason _____

3. Which of the above would you say is your main reason for delaying surgery?

_____

4. At what age do you think you will have your surgery? _____

ROCA Test

ALDO_PostQ_v1_15Jan2018 1

Cancer Vanguard NHS

Patient Name: Patient ID:

5. Did this surveillance make you feel more reassured about your risk of ovarian cancer?

☐ Yes ☐ No ☐ Not sure

What is the reason for your answer?

_____

6. Please state if you agree with the following statements:

	Strongly Agree	Agree	Don't know	Disagree	Strongly Disagree
If surveillance had not been available during this past year, I would have had surgery sooner	☐	☐	☐	☐	☐
Participating in the surveillance project has made me think more about having surgery	☐	☐	☐	☐	☐
I feel my BRCA risk was managed better by participating in this surveillance project	☐	☐	☐	☐	☐
I found surveillance a positive experience	☐	☐	☐	☐	☐
I found it easy to find time to get my blood samples taken	☐	☐	☐	☐	☐

7. Did we give you enough time to make the appointment and get the sample taken?

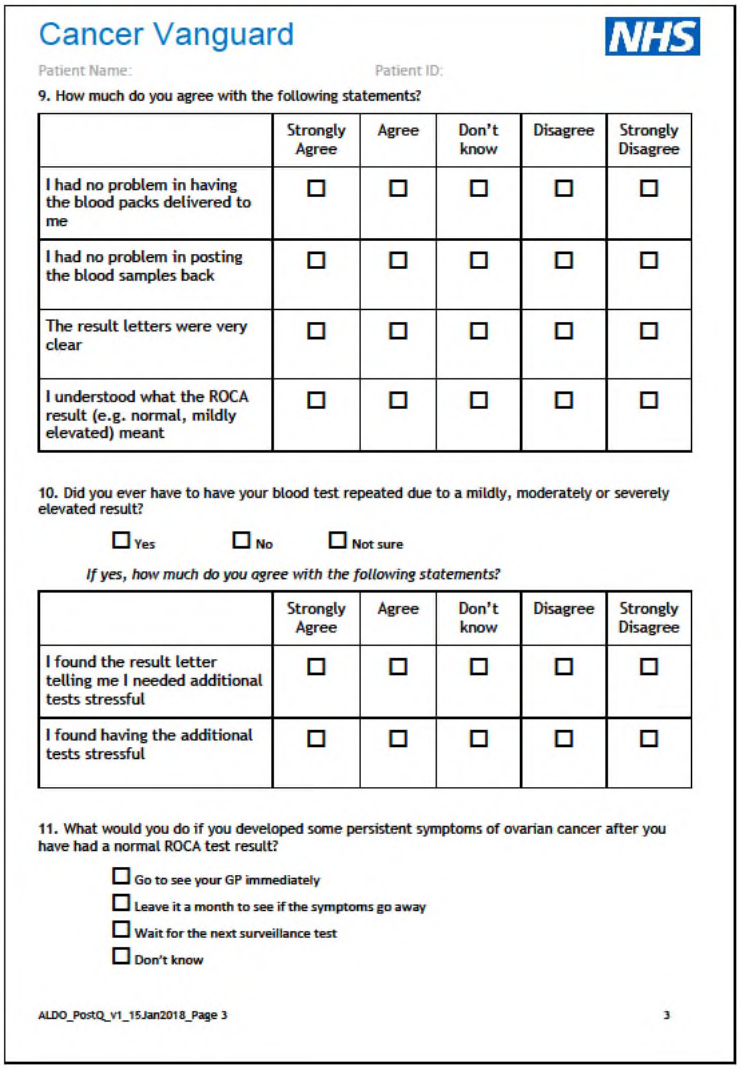
☐ Yes ☐ No ☐ Not sure

8. Did you have any problems in having your blood sample taken? (For example, your GP not happy to do it)

☐ Yes ☐ No ☐ Not sure

*If yes please give provide details*_____

ALDO_PostQ_v1_15Jan2018_Page 2 2



Cancer Vanguard

NHS

Patient Name: Patient ID:

9. How much do you agree with the following statements?

	Strongly Agree	Agree	Don't know	Disagree	Strongly Disagree
I had no problem in having the blood packs delivered to me	☐	☐	☐	☐	☐
I had no problem in posting the blood samples back	☐	☐	☐	☐	☐
The result letters were very clear	☐	☐	☐	☐	☐
I understood what the ROCA result (e.g. normal, mildly elevated) meant	☐	☐	☐	☐	☐

10. Did you ever have to have your blood test repeated due to a mildly, moderately or severely elevated result?

☐ Yes ☐ No ☐ Not sure

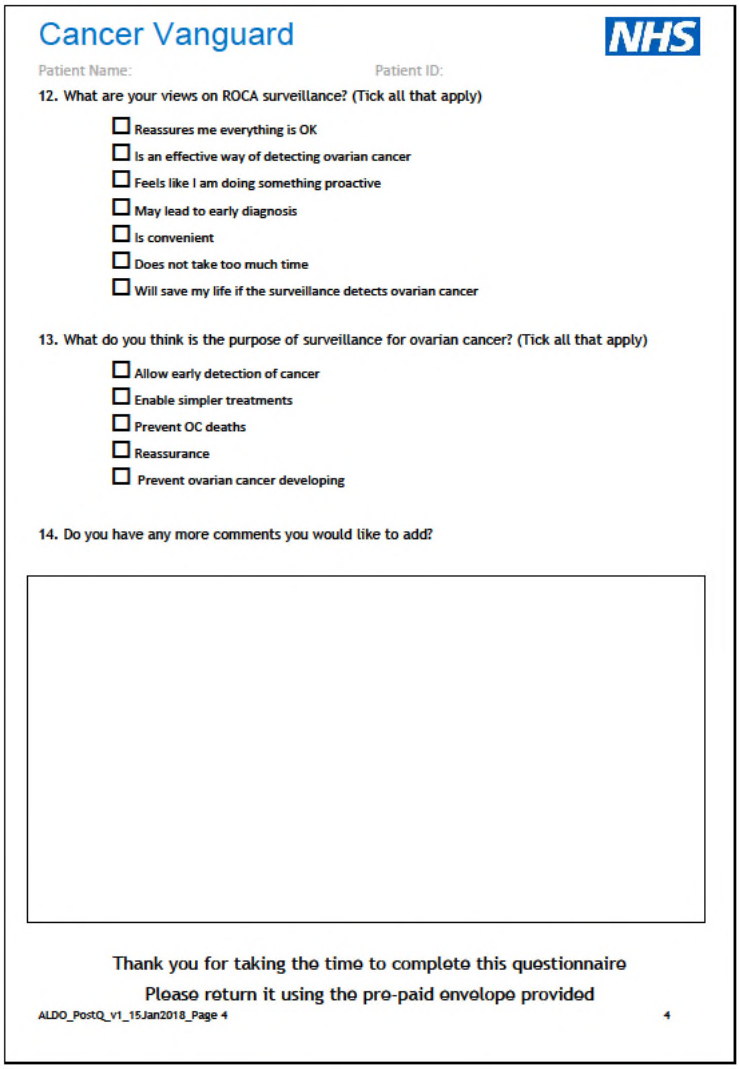
If yes, how much do you agree with the following statements?

	Strongly Agree	Agree	Don't know	Disagree	Strongly Disagree
I found the result letter telling me I needed additional tests stressful	☐	☐	☐	☐	☐
I found having the additional tests stressful	☐	☐	☐	☐	☐

11. What would you do if you developed some persistent symptoms of ovarian cancer after you have had a normal ROCA test result?

☐ Go to see your GP immediately
☐ Leave it a month to see if the symptoms go away
☐ Wait for the next surveillance test
☐ Don't know

ALDO_PostQ_v1_15Jan2018_Page 3 3



Cancer Vanguard

NHS

Patient Name: Patient ID:

12. What are your views on ROCA surveillance? (Tick all that apply)

- ☐ Reassures me everything is OK
- ☐ Is an effective way of detecting ovarian cancer
- ☐ Feels like I am doing something proactive
- ☐ May lead to early diagnosis
- ☐ Is convenient
- ☐ Does not take too much time
- ☐ Will save my life if the surveillance detects ovarian cancer

13. What do you think is the purpose of surveillance for ovarian cancer? (Tick all that apply)

- ☐ Allow early detection of cancer
- ☐ Enable simpler treatments
- ☐ Prevent OC deaths
- ☐ Reassurance
- ☐ Prevent ovarian cancer developing

14. Do you have any more comments you would like to add?

Thank you for taking the time to complete this questionnaire

Please return it using the pre-paid envelope provided

ALDO_PostQ_v1_15Jan2018_Page 4 4

Appendix 19 – End of Surveillance Letter to Participant

Cancer Vanguard NHS

[Title FirstName Surname]
[Address 1]
[Address 2]
[Town]
[County Postcode]

[Date]

Dear [Title Surname]

The result of your recent blood test taken on [date] is now available. We are pleased to advise you that your ROCA result is 'Normal'.

This surveillance project was for one year only which means this was your last ROCA test. We would like to thank you for your valued participation.

We will forward all of your results to your GP for their records.

We are very keen to find out your thoughts on participating and have enclosed a questionnaire for you to complete. Please return this in the pre-paid envelope provided.

The Next Step

We will be looking at all the data and carrying out an economic analysis which we will present to the NHS with the aim of establishing/offering the ROCA Test as a standard surveillance test for women with the BRCA1 or BRCA2 gene mutation until they are ready to have surgery to remove their ovaries and fallopian tubes.

In the meantime we are unable to offer any further surveillance and you will need to discuss your options with your local genetics team or gynaecologist.

Please note that surgery to remove the ovaries and fallopian tubes is the only proven way of reducing your risk of ovarian cancer and is the current recommendation for high risk women such as yourself. ROCA surveillance cannot prevent ovarian cancer. Please ask your local Clinical Genetics Department or contact the ALDO project team to request a referral to a suitable Consultant Gynaecologist if you would like to discuss preventative surgery.

If you have any worrying symptoms (see attached sheet), it is important see your GP as soon as possible.

Once again, thank you for your participation.

Yours sincerely

ALDO Team
ALDO Project Manager Tel:
Email:

ROCA Test

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Appendix 20 – Invitation Letter

Hospital Headed paper

Name
Address1
Address2
County
Postcode

[Date]

Dear [patient name]

We are writing to invite you to take part in the ALDO project (Avoiding Late Diagnosis of Ovarian cancer), an NHS pilot scheme offering ovarian cancer surveillance using the ROCA Test©. This surveillance is available for women like you, who are at high risk of developing ovarian cancer because you carry a known BRCA1 or BRCA2 gene mutation. You will only be eligible to take part if you have not as yet had surgery to remove your ovaries and fallopian tubes.

If you have had surgery to remove your ovaries and fallopian tubes, then please disregard this letter.

Surveillance will last for 1 year and involves having a blood test taken every 4 months. The blood test will look at your CA125 level which can rise in ovarian cancer. Unlike standard CA125 testing, the ALDO project will analyse CA125 using the ROCA Test, which looks at changes in your CA125 levels over time and tells us how likely it is that you have ovarian cancer.

In order to take part, if at any point during the year, the test result recommends an ultrasound scan or clinic appointment with a specialist gynaecologist, you must be able to travel to one of the following hospitals:

University College London Hospital, Euston Road, London NW1 2BU
Barts Hospital, West Smithfield, London EC1A 7BE
St George's Hospital, Blackshaw Road, London SW17 0QT
St Mary's Hospital, Oxford Road, Manchester M13 9WL

Please take your time to read the Patient Information Sheet enclosed with this letter. If you have any questions, please contact the ALDO Project Manager [insert PM name] by email [inset email] or by phone [xxxxxxx]. You can also contact us by ringing the telephone number at the top of this page.

If you would like to take part in this surveillance project, please complete, sign and date the enclosed consent form, enter your personal details and return it to the project team using the pre-paid envelope provided. We will contact you within 2 months of returning the consent form.

Yours sincerely

Clinical genetics name / consultant, Qualifications

ALDO_Pt Invitation letter_v1_19-Dec-2017
19-Dec-17

Appendix 21 – Patient Information Sheet

ALDO PIS v1.0 13 March 2018.doc

Appendix 22 – Consent Form

ALDO Consent v1.0
13-March 2018.doc

Appendix 23 – ALDO Advert

Cancer Vanguard

NHS

Avoiding Late Diagnosis in Ovarian Cancer – the 'ALDO' project: opportunity to participate

The national Cancer Vanguard is running an important project for women in London and Manchester who have a BRCA 1 or 2 genetic mutation. The project is focused on avoiding late diagnosis of ovarian cancer amongst BRCA carriers who have decided not to have their ovaries and fallopian tubes removed at present.

The project will last for a year and involve participants having a blood test at their local GP surgery every four months. Some women may require further investigations, such as an ultrasound scan, in Manchester or London, and would need to travel for these.

To date, we have been working with specific genetics centres and familial cancer clinics to contact women who might be interested in participating. We are now able to open the project more widely.

If you haven't yet been contacted about the project and are interested in participating or finding out more, please visit our webpage [www.xxx] for more information and details of how to contact the project team.

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Appendix 24 – Consent for webpage

Website copy for ALDO project recruitment

The ALDO project - Avoiding Late Diagnosis of Ovarian Cancer

This ALDO (Avoiding Late Diagnosis of Ovarian Cancer) project is a partnership between the national Cancer Vanguard [link to www.cancervanguard.nhs.uk] and Abcodia Ltd. The Cancer Vanguard is a partnership between UCLH Cancer Collaborative, Greater Manchester Cancer Vanguard Innovation and RM Partners, working to change the way cancer care is provided through NHS England's new care models programme. The ALDO project is hosted by University College London Hospitals NHS Foundation Trust (UCLH), on behalf of the Cancer Vanguard. Abcodia is a private company dedicated to improving early cancer diagnosis who are funding this project.

What is the purpose of the project?

Women who carry a mutation in the BRCA1 and or BRCA2 gene are at a high risk of developing ovarian cancer. The only way to prevent ovarian cancer is to have risk-reducing surgery (having the ovaries and fallopian tubes removed). However, many women delay having surgery for a number of reasons such as wanting to complete their family, avoiding early menopause and associated symptoms, or because they have other significant health problems which make surgery too risky.

There is currently no standard surveillance or monitoring recommended or in place for this group of high risk women who do delay having surgery. The aim of this project is to test a method of surveillance within the NHS and gather evidence to help the NHS decide whether this should be adopted as standard practice.

What will the project involve?

The project will run for a year and will recruit 2,000 eligible women to take part. To be eligible, women must carry a mutation in the BRCA1 or BRCA2 gene and have chosen not to undergo risk reducing surgery to remove their ovaries and fallopian tubes at the present time.

Participants will be required to have a blood sample taken at their local GP surgery every four months. This will be sent off and tested for CA-125, a protein which increases in cases of ovarian cancer. The result of the CA-125 will then be analysed by the ROCA Test, which tells us how likely it is that a woman currently has ovarian cancer.

Website copy for ALDO project recruitment

The ROCA Test calculates an individual's risk by looking at their age, their menopause status and previous CA-125 levels - if any are available. Some women whose risk score is elevated, may then need to have further investigations, such as an ultrasound scan. These will be carried out in one of the project centres in London or Manchester, and participants in the project would need to travel for these tests.

Routine surveillance with the ROCA Test does not prevent ovarian cancer, but it can detect the cancer at an earlier stage than if no surveillance is done. The ROCA Test has been tested successfully in several clinical trials over the past 15 years involving over 200,000 women.

At the end of the project, the data collected will be independently evaluated. The results of the evaluation will be shared with NICE and NHS Clinical Commissioners so that they can assess whether this service is beneficial to NHS patients. We hope also to publish the results of the evaluation so that a wider audience can benefit from this project.

Can I take part in the project?

The project team have been working with specific genetics centres and familial cancer clinics to contact women who might be interested in participating. We are now able to open the project more widely to women across England who meet the following criteria:

- Have a known BRCA1 or BRCA2 mutation
- Are aged 35 or over
- Have not had both ovaries removed at surgery. Women can still take part if only one ovary has been removed or if they have one or both of fallopian tubes
- Are willing to travel to London or Manchester for any follow up investigations, should these be necessary.

If you would like to take part in the project, then please contact the project team [LINK]. They will send you a full information pack which details the project, what is required of you as a participant, and the risks and limitations of the project, so that you can consider whether you would like to take part.

2

Appendix 25 – GP Notification Letter

Cancer Vanguard

NHS

GP Notification letter

ALDO Project: Avoiding Late Detection of Ovarian Cancer

Dear Dr.

Your patient XXXXXXXXX DOB xxxxx, with a BRCA1 or BRCA2 mutation, has agreed to participate in the ALDO project.

As a BRCA carrier, your patient has an 11-65% lifetime risk of developing Ovarian Cancer (OC). The only proven method to prevent OC is to have a risk reducing salpingooophrectomy (RRSO). However, many women chose to defer the surgery until they have completed their family or until they have reached the natural menopause, whilst some decline altogether.

The objective of the ALDO project is to pilot the implementation of a surveillance test into the NHS and improve the care pathway for women at high risk of OC who have deferred or declined RRSO.

Your patient is eligible because she is aged 35 years or older and has not yet undergone RRSO. The project is being coordinated by University College London Hospitals NHS Foundation Trust, with support from the NHS Cancer Vanguard. Your patient has been provided with a patient information sheet and has signed a consent form agreeing to take part.

The project utilises the ROCA Test®*, an algorithmic analysis that accurately assesses the rate of change of the tumour marker CA125. This test has been evaluated through prospective trials using an intensive surveillance protocol (4-monthly in UK, 3-monthly in US) in high-risk women and results[1,2] have indicated successful down-staging of OC diagnoses in these women.

This project will last for one year and your patient will be required to have a routine blood test taken for CA125 every 4 months. We will send the blood packs out to your patient and we ask that your practice please takes the sample, which your patient can then post back to us in the packaging provided. If you do not have venepuncture facilities on site, then we ask that you kindly refer your patient to your local phlebotomy service in order to have the blood taken.

The results of the ROCA Test will be provided as a category (Normal, Mildly Elevated, Moderately Elevated or Significantly Elevated) and women with an elevated score will need their blood test repeating after 6 weeks and may require a transvaginal ultrasound scan (TVS) or a rapid access referral. The project team will arrange all TVS and rapid access referrals with the relevant hospital. We will copy you in to any referral letters.

Should you have any questions or require further information about this project, please do not hesitate to contact the project manager [insert name] on [insert tel number] or by email [insert email address].

GP Notification letter_20180122v1.0

Appendix 26 – Peer Review Document

Cancer Vanguard

NHS

20th December 2017

Confirmation of the Early Diagnosis Industry Challenge review and selection process

The ALDO project was selected to be supported by the National Cancer Vanguard through the Early Diagnosis Industry Challenge process.

The National Cancer Vanguard consists of three partners; RM Partners, Greater Manchester Cancer and the UCLH Cancer Collaborative, together covering a population of 10.7 million people. It was established to test and roll out innovative ways of delivering high quality cancer care across the whole patient pathway.

In early 2017, the Cancer Vanguard launched an Early Diagnosis Industry Challenge to engage expertise and resource from outside the NHS to work together on a small number of high impact projects, which would deliver tangible improvement in the earlier diagnosis of cancer in the NHS and specifically the following two outcomes:

- Increasing the proportion of cancers detected at the earlier stages 1 and 2.
- Reducing the proportion of cancers detected through emergency presentation to A&E departments.

The Industry Challenge involved a rigorous evaluation and selection process.

Initial review and evaluation of the project proposal was carried out by a panel of staff from the Cancer Vanguard and Academic Health Science Networks (AHSNs), including clinical and non-clinical staff. Projects were evaluated and scored against the following categories:

1 - Expected Intervention Outcomes
2 - Scalability / replicability
3 - Vanguard aims
4 - Financial Implications of Intervention
5 - Credibility of proposed project delivery timescales

Those shortlisted were then invited to present to a panel convened for the purpose. This involved presentation and Q&A session. The panel consisted of the following members:

Panellist	Role	Organisation
Nick Kirby (CHAIR)	National Cancer Vanguard Partner Lead	UCLH Cancer Collaborative
Jenny Scott	National Cancer Vanguard Partner Lead	Greater Manchester Cancer Vanguard
Nicola Hunt	National Cancer Vanguard Partner Lead	RM Partners
Mike Thorpe	Person affected by Cancer	Greater Manchester Cancer Vanguard

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Sara Hiom	External expert – CRUK Director of Early Diagnosis & Cancer Intelligence	Cancer Research UK
Professor Kathy Pritchard-Jones	Chief Medical Officer - London Cancer	UCLH Cancer Collaborative
Linda Magee	AHSN, Executive Director, Industry & Wealth	Greater Manchester AHSN
Axel Heitmueller	AHSN, Managing Director	Imperial AHSN
Ali Malik	National Cancer Vanguard Partner: Head of Financial Strategy	RM Partners

This panel reviewed the proposals in detail and included some follow up actions for each of the projects prior to final selection. For this project, additional due diligence was undertaken, which included discussion of the project with clinical leads within each of the three vanguard areas.

Once completed, this project moved into the initiation phase in August 2017, fully supported by the National Cancer Vanguard.

Emily Collins

Senior Progamme Manager
UCLH Cancer Collaborative

The Cancer Vanguard is a partnership between
Greater Manchester Cancer Vanguard Innovation, RM Partners and UCLH Cancer Collaborative

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Appendix 27 – Funding Confirmation

abcodia

8th February 2018

To whom it may concern

Abcodia Ltd engages in the development of novel tests for the earlier detection of cancer. The ROCA® Test is one of these tests.

The ALDO project came about as a result of the national Cancer Vanguard's Early Diagnosis Industry Challenge process. The national Cancer Vanguard drove the process for selection of NHS site(s) for this project, and Abcodia's support for the project was not dependent on this decision.

Subject to necessary ethics approvals, Abcodia will be providing funding to enable the national Cancer Vanguard to deliver this project to implement surveillance for patients at high risk of developing ovarian cancer.

Abcodia is delighted to be working in collaboration with the national Cancer Vanguard on the ALDO project, supporting its aim to explore ways of diagnosing cancer earlier.

Your Sincerely

Julie Barnes, PhD

Founding CEO
Chief Scientific Officer

Abcodia Ltd
w: abcodia.com

Appendix 28 – Excess Treatment Costs

Expected number of TVUS generated by the project						
Number of women recruited to the study from London and Manchester, and possibly other areas	2000					
Standard ROCA tests over the 12 month period (4 monthly for each woman = 3 per year)	6000					
Proportion of ROCA tests expected to be elevated and require repeat	10%					
Number of repeat/ additional ROCA tests over the 12 month period	600					
Total ROCA tests over the 12 month period	6600					
Proportion of all ROCA tests expected to be significantly elevated and require TVUS follow up	6%					
Number of TVUS required over the 12 month period	396					
Proportion of Ultrasounds indicated for patients who have CA125>35 (and therefore US indicated by existing NICE guidance)	25%					
Number of TVUS needed that are not covered by existing NICE guidance	**297**	15%	of total project participants			
Expected split of 297 excess treatment scans between 4 sites over 12 month period						
St George's (40 patients participating in study)	6					
Barts Health (40 patients participating in study)	6					
UCLH (will provide scans for half of all remaining women*)	143					
St Mary's Manchester (will provide scans for half of all remaining women*)	143					
Cost of TVUS						
Base rate for Transvaginal US (RD40Z Ultrasound Scan with duration of less than 20 minutes, without Contrast)	£40			MFF		
Cost per TVUS at St George's (RJ7: MFF 1.2125)	£48.50			RJ7	ST GEORG	1.2125
Cost per TVUS at Barts Health (R1H: MFF 1.2128)	£48.51			R1H	BARTS HE	1.2128
Cost per TVUS at UCLH (RRV: MFF 1.2976)	£51.90			RRV	UNIVERSIT	1.2976
Cost per TVUS at St Mary's Manchester (RW3: MFF 1.0568)	£42.27			RW3	CENTRAL	1.0568
Expected total costs of excess treatment scans						
Cost of additional TVUS at St George's	£288.08					
Cost of additional TVUS at Barts Health	£288.16					
Cost of additional TVUS at UCLH	£7,399.47					
Cost of additional TVUS at Manchester	£6,026.30					
Cost of all additional TVUS required over the 12 month period	**£13,425.78**					
Expectation of split per impacted CCG (11 in Greater Manchester, 14 in RMP, 13 in NCEL (UCLHCC) - total 38. NB this number may be higher making the cost per CCG lower)	£353.31					
* It is estimated that equal numbers of patients will be recruited from the London region as from the Manchester region and that therefore the prec						

Appendix 29 – Risk Assessment Form

ALDO Risk
Assessment Form v1.(