The UK Familial Ovarian Cancer Screening Study (UK FOCSS) Phase II

Study Protocol

Version 8: October 2010

This document is a revised version of the previous protocol for UK FOCSS (Revised January 2007)

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1 STUDY SUMMARY

Ovarian cancer kills over 4000 women in the UK annually. Up to 10% of cases can be attributed to an inherited genetic predisposition. Such women are readily identifiable from their family histories. Currently, the only prevention strategy available is prophylactic surgery, which can result in significant morbidity. Consequently, many women opt for screening, even though its efficacy is unproven.

1.1 Aims of the Study

- To develop an optimised screening procedure for ovarian cancer in high-risk women.
- To determine the physical morbidity, resource implications, feasibility and acceptability of screening this high-risk population.
- To establish a serum bank for future assessment of novel tumour markers.

1.2 Screening Strategy

Women will be screened every four months with the serum tumour marker CA125. CA125 levels will be processed by a Risk of Ovarian Cancer Algorithm (ROCA), which stratifies women according to their pattern of CA125 over time. All women will have an annual pelvic ultrasound scan, including those whose ROCA test results are normal. If ROCA results are intermediate or elevated, the date of the scan will be pulled forward (the subsequent scan will occur one year afterwards, unless ROCA testing indicates otherwise). Women with abnormal scans or elevated ROCA results will be referred to a gynaecologist for consideration of surgical investigation.

1.3 Planned Analyses

1. Operating characteristics of the screening program and their respective 95% confidence intervals.

2. Retrospective derivation of a familial risk of ovarian cancer (FROC), which incorporates family history, age, genetic test result (if known), longitudinal CA125 and other biomarker values, and potentially ultrasound results. This will be used to develop an optimal screening strategy for high-risk women.

3. Estimation of FROC-based screening operating characteristics with a retrospective analysis of the data obtained from this screening study.

4. Assessment of physical morbidity as assessed by number of screen-prompted surgical procedures and complications arising from them.

5. Assessment of acceptability as assessed by withdrawal rates from the study and compliance with screening.


7. Psychosocial impact of screening.
Figure 1: Summary of Study Design

5000 Volunteers

Prior Risk Assessment
Detailed documentation of family history obtained by Regional Genetics Centre

Medical Oncology + Gynaecology + GP

Recruitment
Via Regional Genetics Centres

Registration
Confirm Eligibility
Counselling
Consent
Complete Patient Details Form
Provide Confirmations of Cancer & Pedigree

Send patient details form, study consent form, bio consent form, pedigree and confirmation of cancers to Study Coordinating Centre at UCL

Screening
Annual screening for median 6 years with 4-monthly blood samples for CA125 (processed centrally at UCL). All women have an annual pelvic ultrasound scan. Timing of scan depends on CA125 results (analysed using Risk of Ovarian Cancer Algorithm). If ROCA test result intermediate or elevated, date of scan pulled forward. Online Database of screening results informs centre of action to be taken. Study Clinical Lead available for consultation about abnormal results.

Analysis on Completion of Study
Performance of Screening Protocol
Acceptability of Screening
Novel Biomarker Analysis
Posterior Risk Assessment Incorporating ROCA/
Family History/Demographics
2 BACKGROUND AND RATIONALE

2.1 The Current Situation
UK women who are at high risk of developing ovarian cancer (OC) and who are unsuitable for or unwilling to undergo prophylactic bilateral salpingo-oophorectomy are currently being offered annual screening for OC.

The available screening strategies involve tumour markers [1, 2], ultrasonography [3-5] or a combination of both tests [6-9]. However, none of the potential screening tests for ovarian cancer have yet been shown to reduce mortality, although both ultrasound and tumour markers can detect a significant proportion of ovarian cancers preclinically [5-8].

A large randomised controlled study of screening for ovarian cancer has recently commenced in the general population. The United Kingdom Collaborative Trial for Ovarian Cancer Screening (UKCTOCS) initiated by the group with joint funding from the MRC, CR UK and NHS R&D involves 200,000 postmenopausal women from the general population and aims to comprehensively evaluate the role of ovarian cancer screening in the general postmenopausal population [10].

2.2 Issues with Screening the High Risk Population
Screening strategies based on data from large prospective studies in the general population cannot be directly applied to high risk populations. The high risk population differs from the population screened in the former trials in that 60 - 75% of high risk women undergoing screening are pre-menopausal [11]. Screening for OC is based on either ultrasound detected abnormalities in ovarian morphology or detection of elevated levels of the serum tumour marker CA125. Both tests can be problematic in screening premenopausal women who have a variety of both physiological (e.g. menstrual cycle variations) and benign conditions (e.g. endometriosis, ovarian cysts) that can give rise to false positive abnormalities on ultrasound and CA125. Hence criteria for interpretation of both screening tests and the screening strategy undertaken need to be different from that developed for postmenopausal women in the general population.

A recent meta-analysis [11] has raised concerns that annual screening with current tests (transvaginal ultrasound and CA125) may not provide adequate sensitivity for early stage disease in the high risk population, suggesting that screening may not impact significantly on mortality from OC. It has therefore been suggested that screening more frequently than annually may improve the sensitivity for early stage disease.

There is current demand from both clinicians and women in the families at high risk to provide some form of screening, despite the lack of clear evidence of benefit and the risks of false positive results [11].

Although ideally screening would be withheld until a randomised controlled study of screening had been performed amongst high-risk women, such a study is not feasible or practicable for several reasons:
First, many ‘at risk’ women would opt for prophylactic bilateral salpingo-oophorectomy rather than screening.

Second, although there is no evidence as yet of a reduction in mortality as a result of screening there are tests available with high sensitivity for preclinical disease and many would argue that it is unethical to randomise women at high risk to screened and unscreened (control) groups. This was the majority opinion at the UKCCCR meeting on 25/11/94 and again at a UK FOCSS consensus meeting on 27/05/04.

Finally, many women in high risk families may be unwilling to be randomised or may seek screening elsewhere if randomised to the control group.

As a randomised controlled trial cannot be performed in this population the screening options are either: (a) To continue to provide screening as a clinical service; (b) To provide screening within the framework of a research study designed to compare and evaluate the performance of the available screening strategies.

2.3 Screening Test Performance

The performance criteria required on screening a high risk population are different to those required for the general population. The relatively high incidence of OC in high risk women should substantially reduce the level of specificity required to achieve an acceptable positive predictive value. The specificity required to achieve a positive predictive value of 10% in the general population is 99.6%. In the high risk population a specificity of 95% may be acceptable.

We have developed a Risk of OC Algorithm (ROCA) (outlined below) in postmenopausal women. This has been found to increase sensitivity compared with a simple CA125 cut-off value [12]. It has also demonstrated high specificity in the general postmenopausal population [13]. This approach is being used successfully in the UKCTOCS.

2.4 The Risk of Ovarian Cancer Algorithm (ROCA)

Serial values of CA125 derived from population case-control screening studies have been used to derive a Risk of Ovarian Cancer Algorithm (ROCA) in postmenopausal women. This has been achieved by modelling longitudinal CA125 levels in cases and controls to determine the probability of being a case (as distinct from a control) from the sequence of CA125 values and the prior probability based on the age of the subject. This algorithm utilises the fact that women with ovarian cancer have rising levels of CA125, whereas women without ovarian cancer have static or falling levels, even if the levels remain above 30 iu/ml. This approach has been found to increase sensitivity compared with a simple CA125 cut-off value [12] and has been successfully piloted prospectively, demonstrating, a specificity of 99.8% and Positive Predictive Value (PPV) of 19% in the general post-menopausal population [13]. The ROCA is currently being
used to screen 50,000 women in the UKCTOCS. We have now used similar modelling techniques to refine a ROCA for pre-menopausal women.

In the light of concerns about the efficacy of annual screening and the predicted improvement in sensitivity and specificity afforded by the ROCA in premenopausal as well as postmenopausal women, we propose 4-monthly CA125 testing. Within the growing body of knowledge on ovarian screening there is very little information on the benefits of increasing the frequency of serum marker measurement, and this study in a well-motivated, high risk population with prospective analysis of 4-monthly CA125 levels will maximise the chances of early-stage disease detection and allow us to refine the ROCA.

2.5 Serum Bank for Biomarker Discovery

CA125 is the most extensively studied OC serum marker, but it is not perfect and there is a clear need to establish prospective serum banks from well-characterised cohorts of patients to identify new markers. Preclinical samples from OC patients are extremely rare, but provide the ideal sample set for establishing the usefulness of novel biomarkers for screening. UK FOCSS will provide serial preclinical samples on a predicted 85 cases of OC.

3 UK FOCSS OVERVIEW

UK FOCSS is a prospective single-arm study. It will allow us to establish the screening performance of 4-monthly serum CA125 estimation and ultrasound (prompted by high or rising CA125 levels, as well as annually) in a high-risk population. The screening will take place within a structured framework with a high probability of increasing the sensitivity for the detection of early stage disease. It will also provide an extremely valuable serum bank for future biomarker studies. In addition, the study will provide the data required to define a mathematical index for combining the results of epidemiological, genetic, biochemical and imaging factors associated with OC risk. This will enable patients and clinicians to make informed decisions about how to manage OC risk. For example, by establishing the negative predictive value of screening, a woman may be able to delay a decision regarding prophylactic bilateral salpingo-oophorectomy in the knowledge that she is very unlikely to develop OC within a specific timeframe.

4 STUDY OBJECTIVES

1. To develop an optimised screening procedure for OC in women at high risk because of a family history or inherited predisposition.
2. To determine the physical morbidity, resource implications, feasibility and acceptability of screening this high-risk population.
3. To establish a serum bank for future assessment of novel tumour markers.

The primary objective of this study is to develop an optimised screening procedure for OC in terms of most appropriate screening tests, criteria for
interpretation of results and screening interval in women at high risk because of a strong family history or inherited genetic predisposition.

The main analysis will be the estimates of the operating characteristics of the screening program and their respective 95% confidence intervals, namely positive predictive value, sensitivity, and specificity.

A secondary analysis project will occur at the end of the study following measurements of other biomarkers relevant to OC. The aim of the secondary analysis will be to: (a) derive a familial risk of OC (FROC) which incorporates family history, age, longitudinal CA125 and other biomarker values, and potentially ultrasound results, (b) develop an optimal screening strategy for high risk women based on the FROC, and (c) estimate its operating characteristics with a retrospective analysis of the data obtained from this screening trial.

In addition, secondary analyses will also assess the following:

1. Physical morbidity resulting from the UK FOCSS screening strategy
2. Acceptability of the UK FOCSS screening strategy
3. Resource implications of the UK FOCSS screening strategy

5 STUDY ENDPOINTS

Diagnosis/stage/grade of primary invasive epithelial ovarian/fallopian tube cancer during and one year after the end of active screening.

6 SUBJECTS

6.1 Inclusion Criteria
Inclusion in the study will be on the basis of a family history of cancer confirmed by histopathology report or death certification or a documented mutation of an OC causing gene. The UK FOCSS inclusion criteria have been devised to include all women who have a ≥10% life time risk of ovarian cancer. This corresponds to a BRCA carrier probability of ≥25% in the volunteer or ≥50% in a FDR (first degree relative) of the volunteer. Eligibility will be determined as follows:

The volunteer should either have been affected by one of the following cancers or be a FDR of an affected family member:

*NB Tubal & primary peritoneal cancers may be considered equivalent to ovarian cancers*

Families with ovarian or ovarian & breast cancer

1) ≥2 individuals with ovarian cancer who are FDR
2) One ovarian cancer and 1 breast cancer <50 years who are FDR
3) One ovarian cancer and 2 breast cancers < 60 years who are FDR
4) Breast cancer in volunteer/ proband (≤45 years) and mother with both breast and ovarian cancer (in the same person)
5) Breast cancer in volunteer/proband (≤40 years) and sister with both breast and ovarian cancer (in the same person)

6) Criteria 1, 2, and 3 can be modified where paternal transmission is occurring i.e. families where affected relatives are related by second degree through an unaffected intervening male relative and there is an affected sister are eligible.

Families with a known gene mutation

7) The family contains an affected individual with a mutation of one of the known OC predisposing genes e.g. BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS1 and PMS2.

Families with colorectal cancer (HNPCC or Lynch syndrome)

8) The family contains ≥3 individuals with a HNPCC related cancer#, who are FDR and ≥1 case is diagnosed before 50 years and the cancers affect ≥1 generation

*HNPCC related cancers include- colorectal, endometrial, ovarian, small bowel, ureteric and renal pelvic cancers

Families with only breast cancer

9) ≥4 breast cancers
10) 3 breast cancers related by FDR
   a) one ≤30 years or
   b) all ≤40 years or
   c) one MBC (Male Breast Cancer) and one b/l breast cancer
11) Breast cancer in volunteer/proband (≤50 years) and
    a) breast cancer in mother (age of onset being ≤30 years in one and ≤50 years in the other) or
    b) b/l breast cancer in mother (≤40 years onset) or
    c) one MBC and one b/l breast cancer
12) Two MBC (one <40 years) in the family and proband is a FDR of one of them

Families with Ashkenazi Jewish ethnicity (additional criteria)*

Ashkenazi Jewish ethnicity and any one of the following:

13) Breast cancer (<40 years) or bilateral breast cancer (first cancer <50 years) in volunteer/proband, irrespective of FH (family history) of cancer
14) Breast cancer in volunteer/proband (<50 years) and one FDR with breast cancer (<50 years) or ovarian cancer (any age) or MBC (any age)
15) Breast cancer in volunteer/proband (<60 years) and one FDR with breast cancer (<40 years) or ovarian cancer (any age) or MBC (any age)
16) One FDR with ovarian cancer (<50 years)
17) FDR with breast and ovarian cancer in the same woman (any age)
18) Two FDR with breast cancer (<40 years)
19) Two MBC (<60 years) in the family and proband is a FDR of one of them

*Families in these categories negative on full BRCA1 and BRCA2 screening are ineligible
6.2 Exclusion Criteria

1. Past history of bilateral salpingo-oophorectomy. (N.B. Women who have undergone bilateral oophorectomy but who still have one or more Fallopian Tube in situ are eligible as they may be at increased risk of Fallopian Tube Cancer.)
2. Less than 35 years of age.
3. Women participating in other OC screening trials.
4. Women who have tested negative for a pathological mutation found in an affected family member. Similarly, those who obtain a negative result subsequent to joining the study need to be withdrawn, as they do not have a high enough risk of ovarian cancer to justify inclusion in UK FOCSS.
5. Breast cancer-only families (inclusion criteria 9-12) are not eligible if mutation testing has been done and no mutation found (such families are not thought to be at increased risk of developing ovarian cancer).
6. Women should not be recruited if RRSO is imminent, but those with an intention to have RRSO at some (unspecified) date in the future are eligible. Good clinical practice dictates that even if a woman is not recruited to UK FOCSS, she should have a transvaginal ultrasound and CA125 performed shortly before RRSO to reduce the risk that an occult cancer only comes to light at the time of surgery.

6.3 Definition of ‘Ovarian Cancer’
For the purposes of determining a woman’s eligibility based on the occurrence of ovarian cancer in her family history, the term ‘ovarian cancer’ specifically refers to ‘epithelial ovarian cancer’ and does not include ‘borderline ovarian tumour’.

7 STUDY DESIGN

The design is a prospective single arm study with decision making based on CA125 measurement every 4 months and annual ovarian ultrasound. Each year, approximately 22.5% of volunteers will have the date of their annual scan pulled forward, as a result of high or rising CA125 values. CA125 levels will be processed by the Risk of Ovarian Cancer Algorithm (ROCA), which stratifies women according to their pattern of CA125 over time. Women with normal ROCA results will continue routine screening with 4-monthly CA125 tests and an annual scan, those with intermediate or elevated ROCA results will have the scan date pulled forward and those with abnormal scans or elevated ROCA results will be referred to a gynaecologist in a rapid access clinic for consideration of surgical investigation. 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 spread rapidly and four monthly intervals will give a much higher likelihood of detecting the cancer at an early stage. Furthermore, the higher frequency of serum samples will provide a detailed estimate of the natural history of OC in this high risk cohort. Screening will continue for a median of 6 years and is expected to yield data on approximately 85 OCs. Details of screening pathways can be found in section 7.3 below.
7.1 Sources of Recruitment
Sources of recruitment for the study will be as follows:

1. Women registered with the UK Familial OC Registry.
2. Women attending clinical genetics centres, which are participating in the study.
3. Women identified as at high risk of OC due to their family history in other clinics (e.g. gynaecology clinics, medical oncology clinics, general practitioner clinics).

7.2 Registration
Registration will be performed at a regional collaborating centre by a gynaecologist, oncologist or geneticist with knowledge of the genetic, medical and surgical issues involved, or by a genetic counsellor. In some centres registration will occur in a joint clinic involving a geneticist and an oncologist or gynaecologist. Registration will involve the following:

7.2.1 Confirmation of Eligibility
- The eligibility criteria for the study and the need to confirm the family history will be explained to the volunteer.
- Family details required to document the history of cancer will be obtained (e.g. confirmations of cancers, including death certificates/histology reports).
- Information about the family history will be reviewed. When the necessary information has been provided by a cancer registry or is available from the volunteer registration may occur immediately. In other cases a further visit will be required after enquiries about the family history have been completed.

7.2.2 Counselling
The counselling process will involve an assessment and explanation of risk as well as advice about strategies for prevention and screening. The possible limitations of screening and the risk of false positive results will be explained. Guidance will also be provided about screening for other cancers, which may be appropriate in view of the family history e.g. colonoscopy, mammography.

7.2.3 Consent
Women who wish to participate will complete 2 written consent forms (one to take part in the study and one to consent to storage of DNA materials). It is recognised that some eligible women will decline any intervention whilst others will wish to pursue the option of prophylactic bilateral salpingo-oophorectomy. These women should still be registered for the study if they wish to participate.

7.2.4 Patient Details Form
The Patient Details Form will be completed (e.g. name, address, NHS number, GP, summary of family history of cancer).
7.3 Screening Tests
Decision-making is based on four-monthly serum CA125 measurements and ovarian ultrasound scans (triggered by high or rising CA125 levels and annually in women with normal results). The trial interventions using ultrasound are based on standard screening practice in clinics in the UK that screen ‘high-risk’ women. The trial interventions using CA125 are based on the Risk of Ovarian Cancer Algorithm (ROCA). The ROCA is currently being evaluated in the UKCTOCS trial of general post-menopausal population OC screening. As approximately 60% of the women on UK FOCSS will be premenopausal, we have modified the ROCA to take into account the higher normal fluctuations and baseline levels of CA125 in the premenopausal population. This has been piloted successfully in the US Cancer Genetics Network study of screening the high-risk population. Further details of the ROCA protocol are given in section 7.3.3.

7.3.1 Menopausal Status
This will be determined using an algorithm applied to the volunteers’ responses to the six questions below included in a tear-off slip returned by the volunteer with her blood sample identification. The algorithm also incorporates the volunteer’s age. Once a woman is classified as postmenopausal, she will no longer need to answer these questions (and therefore the information will not be requested on subsequent blood sample identification slips). Once a premenopausal woman has answered “Yes” to question B, she will no longer be asked this question.

Menopause algorithm questions:

A. Is it more than 12 months since you have had a period?
B. Have you had a hysterectomy (an operation to remove your womb)?
C. Are you taking hormone replacement therapy?
D. Have you ever had hot flushes and/or night sweats for more than 1 month?
E. Age = Equal to or greater than 56 years old? (The database automatically calculates the response to this question.)
F. Reason you have not had a period for 1 year? (Mirena intra-uterine device, breast feeding and having chemotherapy for breast cancer)

The study database classifies women as premenopausal or postmenopausal according to their responses to these questions (see Table 1 below).
Table. 1 Menopausal Algorithm

<table>
<thead>
<tr>
<th>Question</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTACT UTERUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>N</td>
<td>Pre</td>
</tr>
<tr>
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<td>N</td>
<td>N</td>
<td>A</td>
<td>Y</td>
<td>Post</td>
</tr>
<tr>
<td>HRT</td>
<td>A</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>A</td>
<td>Post</td>
</tr>
<tr>
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<td>A</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Post</td>
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<td></td>
<td>A</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Pre</td>
</tr>
<tr>
<td><strong>HYSTERECTOMY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOT FLUSHES</td>
<td>A</td>
<td>Y</td>
<td>A</td>
<td>Y</td>
<td>A</td>
<td>Post</td>
</tr>
<tr>
<td>NO HOT FLUSHES</td>
<td>A</td>
<td>Y</td>
<td>A</td>
<td>N</td>
<td>Y*</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Y</td>
<td>A</td>
<td>N</td>
<td>N*</td>
<td>Pre</td>
</tr>
</tbody>
</table>

Y = Yes, N = No, A = not applicable (i.e. answer does not contribute to classification)

* Age cut-off for this combination is 51 years, NOT 56 years

In addition to the above five questions, volunteers will also be asked the reason they have not had a period for more than 12 months. Where a volunteer answers the question by stating that she is using Mirena, breastfeeding or has had chemotherapy, she will be classified as Postmenopausal until her periods have returned.

**7.3.2 Ultrasound**

Transvaginal ultrasonography will be performed at collaborating centres. All scans will be performed by ultrasonographers, gynaecologists or radiologists with particular expertise in transvaginal ultrasonography.

Pelvic ultrasound will occur annually. The timing of scans will be determined by the ROCA results (see section 7.3.5). These scans will be organised by the local UK FOCSS collaborators. If after 12 months of screening a woman has not had a scan prompted by an intermediate or elevated ROC (see Table 3, page 19), she will have an annual scan performed.

As ovarian appearance varies with different aspects of the ovarian cycle in premenopausal women, where possible, scans will be scheduled for the early follicular phase (day 3-6 of the cycle). Two aspects will be assessed:

Ovarian Size: Ovarian diameter will be measured in 3 dimensions and used to calculate ovarian volume using the formula for an ellipsoid \( d_1 \times d_2 \times d_3 \times 0.523 \).

Ovarian Morphology: Ovarian echogenicity will be assessed for the presence of cysts, cyst septae, solid areas and solid papillations.
Morphology will be classified as normal or abnormal as follows:

**Normal**
- Uniform ovarian echogenicity or
- One or both ovaries not visualised despite a good view of the pelvic side wall (i.e. iliac vessels visualised) or
- Polycystic ovaries with classical scan features of small peripheral cysts and increased stromal echogenicity, or
- Simple cysts (i.e. cysts with no septae or papillations and thin wall with regular internal outline) < 5 cm in diameter or 60 cc in volume.

**Abnormal**
- Single simple cysts > 5 cm in diameter, or 60 cc in volume, or
- Multiple simple cysts or
- All complex morphology (non-uniform ovarian echogenicity)

Examples are shown in Figure 2.

Nb. in Premenopausal women, complex ovarian cysts considered by the person performing the scan to be follicles, collapsing follicles, corpus luteum and other physiological structures can be classified as “Normal” as long as the scan report clearly states that this is the nature of the cyst.

**Figure 2. Examples of Complex Ovarian Morphology**

![Diagram of Septae and Walls](image)

The overall scan result is classified as *Normal* (N), *Unsatisfactory* (U) or *Abnormal* (A), depending upon the following Table 2.
### Table 2. Transvaginal Scan Classification Algorithm

<table>
<thead>
<tr>
<th>Ovary 1</th>
<th>Ovary 2</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not visualised, poor view</td>
<td>Not visualised, poor view</td>
<td>U</td>
</tr>
<tr>
<td>Not visualised, poor view</td>
<td>Normal morphology</td>
<td>U</td>
</tr>
<tr>
<td>Not visualised, poor view</td>
<td>Simple cyst of ≤60cc or mean diameter ≤5cms</td>
<td>U</td>
</tr>
<tr>
<td>Not visualised, poor view</td>
<td>Not visualised, good view of iliac vessels</td>
<td>U</td>
</tr>
<tr>
<td>Abnormal morphology</td>
<td>Normal morphology</td>
<td>A</td>
</tr>
<tr>
<td>Abnormal morphology</td>
<td>Not visualised, good view of iliac vessels</td>
<td>A</td>
</tr>
<tr>
<td>Abnormal morphology</td>
<td>Not visualised, poor view</td>
<td>A</td>
</tr>
<tr>
<td>Abnormal morphology</td>
<td>Simple cyst of any size</td>
<td>A</td>
</tr>
<tr>
<td>Simple cyst &gt;60cc or mean diameter &gt;5cms</td>
<td>Normal morphology</td>
<td>A</td>
</tr>
<tr>
<td>Simple cyst &gt;60cc or mean diameter &gt;5cms</td>
<td>Not visualised, poor view</td>
<td>A</td>
</tr>
<tr>
<td>Simple cyst &gt;60cc or mean diameter &gt;5cms</td>
<td>Simple cyst &gt;60cc or mean diameter &gt;5cms</td>
<td>A</td>
</tr>
<tr>
<td>Simple cyst &gt;60cc or mean diameter &gt;5cms</td>
<td>Not visualised, good view of iliac vessels</td>
<td>A</td>
</tr>
<tr>
<td>Ascites or fluid in POD &gt;10mms, irrespective of ovarian findings</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Normal morphology</td>
<td>Normal morphology</td>
<td>N</td>
</tr>
<tr>
<td>Normal morphology</td>
<td>Simple cyst of ≤60cc or mean diameter ≤5cms</td>
<td>N</td>
</tr>
<tr>
<td>Normal morphology</td>
<td>Not visualised, good view of iliac vessels</td>
<td>N</td>
</tr>
<tr>
<td>Not visualised, good view of iliac vessels</td>
<td>Not visualised, good view of iliac vessels</td>
<td>N</td>
</tr>
</tbody>
</table>

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

Blood flow: Colour Doppler measurements (presence of a signal, site) are recorded in cases where a simple cyst or complex ovarian morphology is detected.

Fallopian Tube Morphology: This will be recorded as Normal or Abnormal for each tube. Abnormal morphology will result in the volunteer being placed on “Clinical Decision” (see Table 3, page 19), unless the overall classification of the scan (using the ovarian morphology criteria in Table 2 above) is Abnormal, in which case the volunteer will be referred to her named rapid access gynaecologist for assessment.

The management of women according to scan results is described in Figure 3 and Table 3 on pages 18 & 19.

### 7.3.3 CA125

CA125 measurement will occur every 4 months. Serum will be assayed for CA125 by radioimmunoassay in the serum laboratory at University College London (UCL), which is currently processing the samples from the UKCTOCS trial. Serial CA125 results will be analysed using a version of the ROCA currently used on UKCTOCS but with modifications to take into account premenopausal status where appropriate. This algorithm calculates the probability of a woman having OC at a certain point in time, depending on her age, menopausal status and change in the level of CA125 over time in serial blood samples up to that point. This probability is given as the risk of OC (ROC).
ROC results will be classified as follows:

**Normal** <1:1000*
**Low Intermediate** 1:1000 - 1:400 *
**High Intermediate** 1:399 - 1:5*
**Elevated** >1:5

*The exact ROCA level above which a result is classified as intermediate varies slightly depending on how many CA125 tests a volunteer has had. This is to ensure that the 7.5% of the population at highest risk (high intermediate and elevated group) according to the ROCA are recalled for an early ultrasound scan and repeat CA125, and the 7.5 – 15% centile (low intermediate) are recalled for a repeat CA125 test. If on repeat testing the ROCA has increased above the approx. 1:400 threshold, then the volunteer will be recalled for a scan.

Because of the need for 4-monthly screening and the use of the ROCA, the serum CA125 results will be automatically uploaded from the laboratory to the UK FOCSS database, which will calculate the ROC and indicate any action required as described in Table 3, page 18. This method of coordinating screening is identical to that already being used successfully to screen 50,000 women on the UKCTOCS trial.

### 7.3.4 Specimen Handling and Tracking
Volunteers will be asked to provide three tubes of blood, two for serum and one for plasma at their 4-monthly screen. The Coordinating Centre will send blood packs for specimen collection to volunteers in advance of the screen date. The packs include a Vacuette Quickshield (Safety Tube Holder)/Vacuette needle, two 8 ml red-top serum tubes and a 9 ml purple-top EDTA plasma tube (with sample ID barcodes), packing materials and Freepost return envelope. Tubes will be posted by the volunteer on the day of venepuncture to the laboratory at UCL for separation and storage. A blood sample identification slip summarising the date and time of venepuncture (along with information to determine current menopausal status) will be returned with each blood sample. The cut-off for the time interval between the blood sample being taken and being processed in the laboratory will be 56 hours. This ensures CA125 test reliability. On the day the samples arrive in the laboratory, a CA125 will be performed on the serum. The remaining serum and plasma will be spun, aliquoted, databased and stored in liquid nitrogen (−70°C). The volunteers identifying details are not recorded on the straws (these are identified with a unique sample ID linked to the volunteer through a separate database). The stored serum will be used for assessing other cancer markers, both current and future. No genetic analysis will be done.

### 7.3.5 Management
Management decisions will be based on both CA125 and ultrasound results as summarised in Figure 3 below and in more detail in Table 3 on page 19.
Figure 3. UK FOCSS Screening Protocol Overview

UK FOCSS Screening Protocol Overview

Obtain blood samples for CA-125 assay and for storage at baseline and every 4 months
Send blood samples to the UCL serum tumour marker lab
UCL will perform CA125 assay and aliquot sample for serum bank
Study database will calculate OC Risk using ROCA on serial CA125 results
Report OC risk within 5 working days of blood draw. Online database will notify collaborating center of any extra scans or blood tests required as a result of ROCA

Normal
Low Intermediate
High Intermediate
Elevated

Blood
Scan

Normal
Abnormal

At least one ovary remaining

Standard clinical intervention for potential ovarian cancer, including work-up for recurrence of any previous cancer (subject is considered to be under standard clinical practice, and is not on research protocol during this intervention)

No Malignancy

Bilateral oophorectomy

Withdraw from Study

In addition to the above, centres will perform annual scans even if ROCA results are normal. These will be acted on in the same way as the ROCA-triggered scans. A more detailed protocol explaining how all possible combinations of blood and scan results will be acted upon is provided in Table 3.

*The exact ROCA level above which a result is classified as intermediate varies slightly depending on how many CA125 tests a volunteer has had. This is to ensure that the 7.5% of the population at highest risk according to the ROCA are recalled for an early ultrasound scan.*
Table 3. Protocol Following Blood Assays

<table>
<thead>
<tr>
<th>Routine CA125</th>
<th>1</th>
<th>REPEAT RESULT</th>
<th>2</th>
<th>REPEAT RESULT</th>
<th>3</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Action</td>
<td>Int</td>
<td>Result</td>
<td>Action</td>
<td>Int</td>
<td>Result</td>
</tr>
<tr>
<td>ROC N</td>
<td>RS</td>
<td></td>
<td></td>
<td>ROC N</td>
<td>RS</td>
<td></td>
</tr>
<tr>
<td>ROC Low I</td>
<td>rpt CA125</td>
<td>2 mth</td>
<td>ROC N</td>
<td>RS</td>
<td>ROC N</td>
<td>CD</td>
</tr>
<tr>
<td>ROC High I</td>
<td>rpt scan and CA125</td>
<td>2 mth</td>
<td>ROC N + (Scan N or U)</td>
<td>RS</td>
<td>Scan U + ROC I (H or L) OR Scan N + ROC I (H or L)</td>
<td>CD</td>
</tr>
<tr>
<td>ROC E</td>
<td>REFER</td>
<td></td>
<td></td>
<td>ROC E</td>
<td>REFER</td>
<td>Scan A irrespective of ROC or ROC E irrespective of scan</td>
</tr>
<tr>
<td>ROC High I</td>
<td>Scan and CA125</td>
<td>2 mth</td>
<td>ROC N + (Scan N or U)</td>
<td>RS</td>
<td>ROC N</td>
<td>CD</td>
</tr>
<tr>
<td>ROC E</td>
<td>REFER</td>
<td></td>
<td></td>
<td>ROC E</td>
<td>REFER</td>
<td>Scan A irrespective of ROC or ROC E irrespective of scan</td>
</tr>
<tr>
<td>ROC E or Scan A</td>
<td>REFER</td>
<td></td>
<td></td>
<td>ROC E</td>
<td>REFER</td>
<td>Scan A irrespective of ROC or ROC E irrespective of scan</td>
</tr>
</tbody>
</table>

Because vol has now had 3 intermediates in a row.
ROC = Risk of Ovarian Cancer (as determined by ROCA)

**Results Classification:** ROC: N = Normal; I = Intermediate; E = Elevated. Scans: N = Normal; U = Unsatisfactory; A = Abnormal

**Action:** Int = Interval; RS = Routine Screening; CD = Clinical Decision; Refer = Consider referral to rapid access gynaecologist

“Clinical Decision” (Table 3, page 19) means that the management is at the discretion of the clinicians on the UK FOCSS team. It may result in 1) referral to a rapid access gynaecologist for further investigation, 2) return to routine screening or 3) repeat testing.

After referral, the gynaecologist may decide not to operate. The blood assay and scan will be repeated after two months, and the results reviewed by a UK FOCSS clinician, who will determine next action.

Annual scan results (see Table 2 on page 16 for definitions) will be acted upon as follows:

**Normal:** continue routine screening unless ROCA determines other action.

**Unsatisfactory:** repeat scan within 2 months, unless the last ROCA result was Normal, in which case repeat CA125 in 2 months and manage according to next ROCA result.

**Abnormal:** consider referral to gynaecologist.

### 7.3.6 Communication of Results
All results for volunteers at a collaborating centre will be available for the collaborator to view on the password-protected online database. The collaborator will only be able to view results for the women being managed by their own centre.

Volunteers will be notified of their results and the next action (repeat blood test or scan) via letter. Volunteers will be able to discuss results with a named contact at their local collaborating centre or with the UK FOCSS team at the Coordinating Centre. Volunteers requiring referral to a rapid access clinic gynaecologist because of abnormal results will be contacted directly by the research nurse (Primary Contact) at the local collaborating centre, who will arrange a suitable appointment for them.

All abnormal results triggering referral to a gynaecologist will be copied to the volunteers’ GP, named gynaecologist and local collaborator. Normal results will not be copied to these individuals as this would generate three letters per year, none of which would require any action by that individual.

Results of any surgery triggered by screening will be communicated to the volunteer by the clinical team performing her surgery.
7.4 Referral for Further Investigation
Referrals for clinical assessment and further investigation will be to a named consultant gynaecologist at the rapid access clinic linked to the volunteer’s collaborating centre. The UK FOCSS Coordinating Centre at UCL will liaise with the volunteer’s named research nurse (Primary Contact) at the collaborating centre, who will contact the volunteer and arrange a suitable appointment with the gynaecologist. The Coordinating Centre will provide a summary of the volunteer’s screening results for the gynaecologist managing the volunteer. The volunteer’s GP will also be notified of the referral. The final decision as to whether or not to proceed to surgery and the method of surgical investigation to employ will be entirely at the discretion of the gynaecologist receiving the referral. Advice from the study Coordinating Centre will be available, however it is emphasised that surgery will remain a local clinical decision. Women not undergoing surgery following an assessment by a consultant gynaecologist will be placed on “high alert screening” for the next year. This entails 4-monthly pelvic ultrasound scans and CA125 tests analysed by the ROCA.

7.5 Protocol for risk reducing surgery
All women on UK FOCSS are aged over 35 years and are estimated to be at >10% lifetime risk of developing ovarian/ fallopian tube or primary peritoneal cancer. They should therefore have been counselled about the possibility of risk-reducing surgery when they were initially recruited to the study. Women on UK FOCSS are entitled to request further advice about prophylactic surgery at any point and centres should provide easy access to a gynaecologist who regularly performs laparoscopic risk reducing salpingo-oophorectomy (RRSO). Any premenopausal woman opting for surgery should receive detailed counselling about the risks and benefits of RRSO in terms of the effect on subsequent risk of ovarian/fallopian tube or primary peritoneal cancer. In addition, the effect of RRSO on subsequent reduction in breast cancer risk and the consequences of receiving/declining HRT following RRSO should also be explained. Irrespective of menopausal status, all women should be counselled about the risks of the procedure. These will depend on individual circumstances, such as body mass index, previous surgery and medical comorbidity. UK FOCSS has produced an information leaflet for women considering RRSO. This can be found as an Appendix to this protocol. Clinicians counselling women about RRSO are encouraged to provide this leaflet to women considering the procedure.

Surgical Approach
Because BRCA-carriers are at increased risk of tubal cancer as well as ovarian cancer, it is mandatory to remove the Fallopian tubes. These should be removed as close to their insertion on the uterus as is technically feasible. It is therefore recommended that formal excisional techniques (e.g. bipolar diathermy and laparoscopic scissors or harmonic scalpel) are used. Microscopic occult cancers occur predominantly at the distal end of the tube and have not as yet been reported as occurring in the intramural portion of the tube, so removal of intramural portion of the tube is not required.
Peritoneal washing are essential because in the event of an occult ovarian or fallopian tube cancer being identified on histology positive washings upstage an apparent stage 1a cancer to a Stage 1c cancer, possibly altering management in terms of adjuvant chemotherapy. Positive washings have also been reported in the absence of occult ovarian or tubal cancers raising the possibility of an occult primary peritoneal cancer.

A thorough inspection of the entire pelvic and abdominal cavity is mandatory to exclude the presence of peritoneal cancer. This should include the upper abdomen, paying particular attention to the liver, diaphragmatic surfaces and the omentum. Any suspicious area should be biopsied. Surgical specimens should be removed in an endobag to avoid seeding occult malignancy into the port sites.

Pathology Protocol
Meta-analysis of published RRSO series suggests that when a strict histopathological specimen sectioning protocol is used, the rate of occult ovarian and tubal cancers increases from 2.5 to 5%. Therefore, not only is such a protocol mandatory, but also, women undergoing RRSO should be counselled about the possible need for completion staging in the event of an occult cancer being detected.

A suggested protocol follows:

**Ovaries**
1. After standard recording of size and macroscopic appearance, each ovary should be serially sectioned transversely at 2-3 mm intervals from pole to pole and processed in toto.

**Fallopian tubes**
1. The overall length, diameter and macroscopic appearance of each fallopian tube should be stated.
2. Transverse serial sections at 2-3 mm intervals to be taken from the isthmic to the fimbrial end and placed in cassettes sequentially, with 2-4 slices per cassette, to include the entire tube and any mesosalpinx.
3. Cassettes should be labelled to indicate isthmic, ampullary and infundibular segments.
4. An alternative approach suggested to maximise exposure of the fimbrial mucosa is to amputate the infundibular segment which is then serially sectioned longitudinally, the remainder of the tube being transversely sectioned.

**Peritoneal/Omental biopsies**
1. If submitted, these should be processed in their entirety.

**Peritoneal Washings**
1. Cytological examination of fluid obtained after instillation of normal saline into the peritoneal cavity.
1. **Optimum age of RRSO**

The age of onset of ovarian cancer is younger in BRCA1 mutation carriers than in BRCA2 carriers. Our current recommendation is that once child-bearing is complete, RRSO is reasonable from 40 years in BRCA1 carriers and from 45 years in BRCA2 carriers, with HRT until age 50 years (for women who have not had breast cancer). However, the decision is further individualised based on age of diagnosis of the youngest women in the family to have ovarian cancer (RRSO is undertaken at least 5 years ahead of this age), the patient’s decisions with regard to management of her breast cancer risk, her willingness to take HRT until 50 years and other individual views about surgery and oophorectomy.

2. **Need for Hysterectomy**

Hysterectomy is recommended in women on UK FOCSS if they are known to carry a HNPCC mutation (such women are at 40%-60% lifetime risk of developing endometrial cancer). Occult endometrial cancer has also been demonstrated at hysterectomy in women with HNPCC or Lynch Syndrome (LS). Peritoneal washings should be obtained for cytology (as described above) in these women too. All women with HNPCC or LS should have endometrial sampling before prophylactic hysterectomy.

Hysterectomy at the time of RRSO may also be justifiable in some women who are symptomatic from benign gynaecological pathology.

Some of the women on UK FOCSS who have had breast cancer may be on Tamoxifen. There is a small increased incidence of endometrial cancer in women over 50yr taking Tamoxifen (0.3% per annum vs. 0.06% in women on placebo). These cancers are usually Stage 1. It is not usual to suggest hysterectomy based solely on tamoxifen usage, but it does need to be discussed with the patient. It is sensible to perform dilation and curettage on all women on tamoxifen undergoing PBSO.

3. **Post-surgical management**

1. Women who have not had breast cancer should be prescribed HRT until the age of 50. It is best to start this directly after surgery.
2. The situation for women who have had breast cancer should be discussed in advance of surgery with the woman’s breast oncology team. The plan should be documented prior to surgery to avoid subsequent confusion.

4. **Documentation**

Following RRSO, the Primary Contact should send hard copies of the following to the UK FOCSS coordinating centre:

1. **Operation note**
2. **Histology report**
3. **Cytology report** (peritoneal washings)
4. **GP discharge summary** (or other documentation of post-operative course)
7.6 Withdrawal of Volunteers
Volunteers can withdraw from the study at any time, e.g. if they have a prophylactic bilateral salpingo-oophorectomy or through personal choice. In this situation, the collaborating centre should send a withdrawal form to the UK FOCSS Coordinating Centre, indicating the reason for withdrawal. Volunteers who wish to temporarily suspend their screening, e.g. because they are travelling abroad, can be placed “on hold”. Volunteers who are pregnant should be placed “on hold” because neither CA125 nor ultrasound scanning can be used reliably to screen for ovarian cancer during pregnancy, because pregnancy itself causes elevation in CA125 and the pregnant uterus makes imaging the ovaries using ultrasound extremely difficult. Screening of volunteers “on hold” can recommence as soon as the Coordinating Centre is notified of the volunteer’s return from abroad or six weeks after the end of their pregnancy.

If, during the course of the study, a volunteer receives a gene test result indicating that she does not carry the deleterious mutation found in a live affected relative, then her risk of ovarian cancer would be considered to be at general population level and therefore she should be withdrawn from UK FOCSS. Similarly, if subsequent to recruitment further information about a volunteer’s family history of cancer becomes available and this indicates that she was inappropriately classified as being at high risk, then she should be withdrawn from the study.

7.7 Follow Up
Women will receive a health questionnaire twice during the course of the study. The first questionnaire will be sent out in 2007 and again at the end of 2011. The purpose of the questionnaire will be to act as a failsafe, so that any women who have developed OC or undergone bilateral salpingo-oophorectomy (e.g. as part of a hysterectomy for menorrhagia) on whom the Coordinating Centre had not received the necessary study withdrawal form will be identified and withdrawn from the study. In addition, the questionnaire will provide an opportunity to establish whether a participant’s family history of relevant cancers or mutation status has changed. All women are also being flagged by the NHS Information Centre for Health and Social Care cancer registry (or equivalent organisation for Northern Ireland) as another failsafe to ensure the Coordinating Centre is aware of all women who develop OC. We have previously shown that these two methods of follow-up are complementary and ensure maximum pick-up of OC cases [14].

7.8 Documentation of Ovarian Cancer
Where any method of follow up raises the possibility of OC, further information will be requested from the GP and/or hospital where treatment was provided. Histological slides will be obtained and the diagnosis reviewed at the Coordinating Centre by an independent pathologist blinded to the clinical and previous pathology data.
7.9 Physical Morbidity
In addition to calculating the overall Positive Predictive Value (PPV) of the screening strategy, details of all surgical procedures undertaken to investigate screening results will be obtained from the relevant collaborating centre. This will include the nature of the procedure, the surgical findings, the histopathological findings, details of the postoperative course and of any complications.

7.10 Acceptability
This will be assessed by withdrawal rates from the study (with each subsequent year of screening) due to personal choice and due to undergoing prophylactic bilateral salpingo-oophorectomy (which may be in part prompted by a woman’s dissatisfaction with screening). Withdrawal due to reasons such as death, or being found not to harbour a predisposing mutation present in the family will not be included in the analysis of screening acceptability. In addition, compliance with screening will be assessed by calculating the proportion of women who undergo annual ultrasound and one, two and three venepunctures per year in each year of screening.

8 STUDY ORGANISATION

8.1 Collaborating Centres
These are mostly clinical genetics departments, regional genetics centres, or outreach clinics run by genetics centres at district general hospitals, which identify high risk patients. There are also some gynaecological oncology departments with a special interest in this area. They have responsibility for recruiting women and for the clinical care of study participants, organising scans and managing screening results, according to the recommendations of the study Coordinating Centre.

8.2 Mandatory Requirements
In order to manage women’s screening safely and ensure those with raised CA125s have a scan arranged in a timely manner, centres need to nominate a named Primary Contact (e.g. nurse, clinician) to arrange scans for this subgroup within 8 weeks and to enter the scan appointment date on the online study database. In addition, each woman needs to have a named Gynaecologist to ensure rapid intervention for those with elevated ROCA results or abnormal scans, to whom a 2-week rapid referral can be made.

8.3 Screening Hospitals
If screening is not available at the collaborating centre, volunteers are referred on to local screening hospitals. These are responsible for providing urgent and annual ultrasound scans. They will also provide urgent consultations with a rapid access gynaecologist who can assess women with abnormal screening results, liaise with the Clinical Lead at the UK FOCSS Coordinating Centre and where appropriate, provide surgical intervention or referral to a gynaecological oncologist.
8.4 Coordinating Centre
This is based in the Gynaecology Cancer Research Centre at the Institute for Women's Health, UCL. The Coordinating Centre is responsible for:

- Confirming eligibility of potential participants and registration with the study.
- Liaison with collaborating centres over further investigation of family histories.
- Regular review of data and follow up of queries related to eligibility and consent through the collaborating centres.
- Answering queries about the study and referring as appropriate to the regional centres.
- Analysis of serum samples for CA125.
- Storage of serum samples for future biomarker analysis.
- Liaison with collaborating centres for follow up of screening.
- Enquiring about outstanding blood samples and scan results.
- Liaising with collaborating centres about management of abnormal scan and CA 125 results.
- Data review for the annual Data Monitoring Committee (DMC) meetings and Trial Steering Committee (TSC).
9 REFERENCES