Evidence of stage-shift in women diagnosed with ovarian cancer during Phase 2 of the UK Familial Ovarian Cancer Screening Study (UKFOCSS)

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Supplementary Appendix to ‘4-monthly Algorithm-based Screening in Phase 2 of the UK Familial Ovarian Cancer Screening Study (UKFOCSS) ’

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Appendix 1. UKFOCSS Phase 2 Inclusion and Exclusion Criteria

Eligibility is determined as follows:

The volunteer must be aged at least 35 years and should either have been affected by one of the following cancers or be a first degree relative (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 - colorectal, endometrial, 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 bilateral 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) bilateral breast cancer in mother (≤40 years onset) or
    c) one MBC and one bilateral 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)*

AJ 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 (<50years) 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*

Exclusion Criteria

1) Past history of bilateral oophorectomy (women with one or both fallopian tubes still present are eligible)
2) Age <35 years
3) Women participating in other ovarian cancer research trials
4) Women who have tested negative for a pathological mutation found in an affected family member. Similarly, those who obtain a negative result after recruitment need to be withdrawn.
5) Breast cancer-only families (inclusion criteria 9-12) and Ashkenazi families (criteria 13-19) are not eligible if full gene mutation screening 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 risk reducing salpingo-oophorectomy (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.

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'.

Appendix 2. UKFOCSS Phase 2 menopause algorithm

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.)

The study database classifies women as premenopausal or postmenopausal according to their responses to these questions (see Table A2 below).

Question		A	B	C	D	E	Classification
INTACT UTERUS	No HRT	Y	N	N	A	A	**Postmenopausal**
		N	N	N	A	A	**Premenopausal**
	HRT	A	N	Y	Y	A	**Postmenopausal**
		A	N	Y	N	Y	**Postmenopausal**
		A	N	Y	N	N	**Premenopausal**
HYSTERECTOMY	HOT FLUSHES	A	Y	A	Y	A	**Postmenopausal**
	NO HOT FLUSHES	A	Y	A	N	Y	**Postmenopausal**
		A	Y	A	N	N	**Premenopausal**

Table A2. Menopause algorithm calculator

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

Appendix 3. Protocol following ROCA/scan results

The first ROC value triaged women to; (i) 4-monthly routine screening ('normal'; <85th percentile ROC), (ii) TVS within two months and repeat CA125 measurement after two months ('intermediate'; 85th percentile ROC up to 1 in 5 ROC) or (iii) referral for clinical assessment by collaborating centre gynaecologist ('elevated'; >1 in 5 ROC). Subsequent TVS and ROC results triggered; (i) return to routine screening, (ii) repeat CA125, (iii) repeat CA125 and TVS, (iv) referral, or (v) triage by CC study clinician (ANR, RM, RH) if ROC was persistently intermediate or TVS unsatisfactory. If ROC remained 'normal', TVS was requested annually. The triage protocol is summarised in the figure below.

In addition to this protocol, CA125 was repeated at CC clinicians' discretion within 2 months if the ROC was 'normal' but CA125 had increased by >50% since the prior test. Woman referred but not undergoing surgery were, at CC clinicians' discretion, transferred to 'high-alert screening', comprising repeat TVS and CA125 at 2, 6 and 10 months.

In 2010 the trial steering committee modified the protocol (implemented 13/05/2010) because some centres could not provide timely scans: the 'intermediate' category was split into 'low intermediate' (85th-92·5th percentile ROC) and 'high intermediate' (>92·5th percentile ROC up to 20% ROC), respectively triggering repeat CA125 within 2 months, and repeat CA125 and TVS within 2 months.

<table>
<tr><th>1st CA125</th><th></th><th></th><th>2nd CA125</th><th></th><th></th><th>3rd CA125</th><th></th><th></th><th>4th CA125</th><th></th></tr>
<tr><th>Result</th><th>Action</th><th>Interval</th><th>Result</th><th>Action</th><th>Interval</th><th>Result</th><th>Action</th><th>Interval</th><th>Result</th><th>Action</th></tr>
<tr><td>ROC N</td><td>RS</td><td colspan="9"></td></tr>
<tr><td rowspan="11">ROC I</td><td rowspan="11">Repeat Scan & CA125</td><td rowspan="11">2 months</td><td>ROC N Scan N</td><td>RS</td><td colspan="5"></td></tr>
<tr><td rowspan="5">ROC N Scan U</td><td rowspan="5">Repeat Scan & CA125</td><td rowspan="5">2 months</td><td>ROC N Scan N/U</td><td>RS</td><td colspan="3"></td></tr>
<tr><td>ROC I Scan N</td><td>Repeat CA125</td><td>2 months</td><td>ROC N</td><td>RS</td></tr>
<tr><td rowspan="3">ROC I Scan U</td><td rowspan="3">Repeat Scan & CA125</td><td rowspan="3">2 months</td><td>ROC I</td><td>CD</td></tr>
<tr><td>ROC E</td><td>Refer</td></tr>
<tr><td>Scan A (ignore ROC)</td><td>Refer</td><td colspan="3"></td></tr>
<tr><td rowspan="3">ROC I & Scan N</td><td rowspan="3">Repeat CA125</td><td rowspan="3">2 months</td><td>ROC N</td><td>RS</td><td colspan="3"></td></tr>
<tr><td>ROC I</td><td>CD</td><td colspan="3"></td></tr>
<tr><td>ROC E</td><td>Refer</td><td colspan="3"></td></tr>
<tr><td rowspan="3">ROC I & Scan U</td><td rowspan="3">Repeat Scan & CA125</td><td rowspan="3">2 months</td><td>ROC N Scan N</td><td>RS</td><td colspan="3"></td></tr>
<tr><td>ROC I Scan U / N or ROC N and Scan U</td><td>CD</td><td colspan="3"></td></tr>
<tr><td>Scan A (ignore ROC)</td><td>Refer</td><td colspan="3"></td></tr>
<tr><td>ROC E or Scan A</td><td>Refer</td><td colspan="5"></td></tr>
<tr><td>ROC E</td><td>Refer</td><td colspan="9"></td></tr>
</table>

Figure A3. Risk of Ovarian Cancer Algorithm (ROCA) triage protocol
The figure should be read from left to right

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

Action:
RS = Routine Screening (i.e. 4-monthly CA125 and annual scan)
CD = Clinical Decision
Refer = Referral for clinical assessment by local study centre gynaecologist

“Clinical Decision” = management at discretion of study clinicians at co-ordinating centre. Clinical decisions will be to (i) refer the woman to a gynaecologist for further investigation, (ii) return to routine screening or (iii) undergo repeat CA125 and or ultrasound sooner than routine screening.

*from 13/05/10 Intermediate results were sub-classified into High Intermediate and Low Intermediate. Actions following these results were as follow:
High Intermediate – scan within 2 months and repeat CA125 after 2 months
Low Intermediate – repeat CA125 after 2 months

Appendix 4. UKFOCSS Ultrasound scan results proforma

FAMILIAL OVARIAN CANCER SCREENING RESULTS

FIRST NAME _____ **SURNAME** _____

DATE OF BIRTH _____/_____/_____ **STUDY ID** _____

PELVIC ULTRASOUND RESULTS

Hospital _____ **DATE OF SCAN** ____/____/____

Department ☐ **ULTRASOUND** ☐ **GYNAECOLOGY** ☐ **OTHER** _____

Grade of scanner ☐ **ULTRASONOGRAPHER** ☐ **RADIOLOGIST** ☐ **GYNAECOLOGIST** ☐ **OTHER**

Scan performed by _____*(Please print)*

Date of last period ___/____/____

Mode of scan ☐ TRANSABDOMINAL ☐ TRANSVAGINAL ☐ BOTH

Using hormones ☐ YES ☐ NO

Reason hormone use ☐ CONTRACEPTION ☐ HRT ☐ TREATMENT ☐ OTHER

Details of hormone use _____

Oophorectomy ☐ LEFT OOPHORECTOMY ☐ RIGHT OOPHORECTOMY

☐ **Hysterectomy**

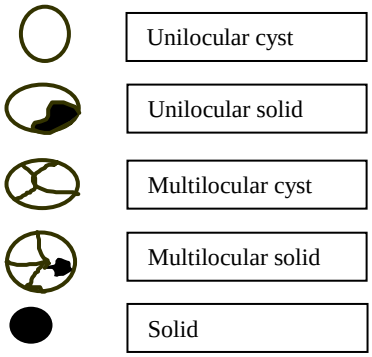
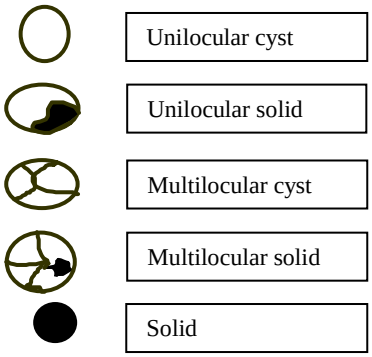
DETAILS OF OVARIAN SCAN

	LEFT OVARY	RIGHT OVARY
Visualisation	☐ SEEN ☐ NOT SEEN / GOOD VIEW ☐ NOT SEEN / POOR VIEW ☐ NOT SEEN / PREVIOUS OOPHERECTOMY	☐ SEEN ☐ NOT SEEN / GOOD VIEW ☐ NOT SEEN / POOR VIEW ☐ NOT SEEN/ PREVIOUS OOPHERECTOMY
Reason not seen	☐ BOWEL ☐ FIBROIDS ☐ PELVIC VARICOSITIES ☐ OTHER	☐ BOWEL ☐ FIBROIDS ☐ PELVIC VARICOSITIES ☐ OTHER
Ovarian dimensions	mm mm mm	mm mm mm
Morphology	☐ NORMAL ☐ SUGGESTIVE OF PCO ☐ SINGLE OR MULTIPLE SIMPLE CYSTS ☐ ALL OTHER MORPOLOGY	☐ NORMAL ☐ SUGGESTIVE OF PCO ☐ SINGLE OR MULTIPLE SIMPLE CYSTS ☐ ALL OTHER MORPOLOGY
Description ovarian morphology		

Max double endometrial thickness _____ mms **Ascites** ☐ YES ☐ NO

Details of any other pelvic abnormality noted

DETAILS OF ANY OVARIAN LESION DETECTED

	LEFT OVARY	**RIGHT OVARY**
Cyst dimensions	mm mm mm	mm mm mm
Cyst wall thickness	mm	mm
Cyst wall structure	☐ Smooth ☐ Irregular	☐ Smooth ☐ Irregular
Fluid in cyst	☐Anechoic ☐ Random Echogenicity ☐Uniform Echogenicity	☐Anechoic ☐ Random Echogenicity ☐Uniform Echogenicity
Cyst structures	☐Septae ☐ Papillations	☐Septae ☐ Papillations
Maximum septa thickness	mm	mm
Size of largest papillation	mm	mm
Solid areas	☐ Yes ☐ No	☐ Yes ☐ No
Overall impression of lesion (Classification using International Ovarian Tumour Analysis criteria)	 Unilocular cyst Unilocular solid Multilocular cyst Multilocular solid Solid	 Unilocular cyst Unilocular solid Multilocular cyst Multilocular solid Solid
Any other details of abnormal area		

DOPPLER STUDY OF ABNORMAL AREA

Doppler performed	☐ YES ☐ NO	☐ YES ☐ NO
Presence of colour signal	☐ YES ☐ NO	☐ YES ☐ NO
Location of colour signal	☐ SEPTAE ☐ WALL ☐ SOLID AREA ☐ PAPILLATIONS ☐ OTHER	☐ SEPTAE ☐ WALL ☐ SOLID AREA ☐ PAPILLATIONS ☐ OTHER
Lowest PI measured		
Peak systolic velocity		

FOLLOW UP PLAN

Report Completed By _____*(Please print)*
Date _____/_____/_____

Appendix 5. UKFOCSS Phase 2 ultrasound protocol

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. 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 her ROC results, 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.

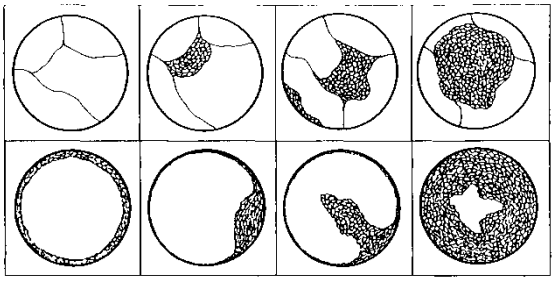
Abnormal

- 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 overleaf.

Examples of Complex Ovarian Morphology

Septae

Walls



The overall scan result is classified as *Normal (N)*, *Unsatisfactory (U)* or *Abnormal (A)*, depending upon the following Table:

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 >10mms, 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.

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”, 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 Appendix 3.

Appendix 6. Protocol for risk-reducing surgery in UKFOCSS Phase 2

Background

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.

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.

For any queries about pathological processing, please contact: Dr. Elizabeth Benjamin, Consultant Pathologist, Dept of Pathology, University College London Hospital, Rockefeller Building, 21 University Street, London WC1E 6JJ. Tel: 020 7679 6045. Email: elizabeth.benjamin@uclh.nhs.uk

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.

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 of 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.

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.

Documention

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)

Appendix 7. Surgical complexity scoring on UKFOCSS Phase 2

Procedure	Points
TAHBSO	1
Omentectomy	1
Pelvic lymphadenectomy	1
Paraaortic lymphadenectomy	1
Pelvic peritoneum stripping	1
Abdominal peritoneum stripping	1
Large bowel resection	2
Diaphragm stripping/resection	2
Splenectomy	2
Liver resection/s	2
Small bowel resection/s	2
Rectosigmoidectomy with anastomosis	3

Table A7. Surgical complexity scoring from Aletti GD, Dowdy SC, Podratz KC, et al. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. *Am J Obstet Gynecol* 2007; **197**: 676.e1-7.

Key: TAHBSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy

To calculate total score per patient, simply add scores from individual procedures undertaken during surgery and allocate to complexity group as follows:

Total score 1-3 = low complexity

Total score 4-7 = intermediate complexity

Total score >7 = high complexity

Appendix 8. Study participant demographics

	n	%
Pre-menopausal at recruitment	2299	52.9
Breast cancer prior to recruitment	576	13.2
Ever used HRT (HQ1)	572	13.2
Never used HRT (HQ1)	2463	56.6
Data missing	1313	30.2
Ever used COCP (HQ1)	1917	44.1
Never used COCP (HQ1)		
Data missing (HQ1)		
Ever been pregnant <6mths (HQ1)	1233	28.4
Ever been pregnant >6 mths (HQ1)	2506	57.6
Never been pregnant (HQ1)		
Data missing (HQ1)	609	14.0
Age at recruitment	45·5 yr (range 34·2 to 84·8) n=3438	
Height (cm) median (range) (HQ1)		
Weight (kg) median (range) (HQ1)	67.9 (39.4 - 168) n=3248	
Ethnic origin (from HQ2 April 2013 n=2694)		
White	2224	51.1
Black	28	0.6
Asian	48	1.1
Other	18	0.4
Data missing	2030	46.7

HQ 1 n= 3325 Jan 2011
HQ 2 n= 2694 April 2013

Appendix 9. Apparent compliance with requested screening tests on UKFOCSS Phase 2

Blood test type	**Tests requested** *n* (% of all requests)	**Tests received** *n* (% of requested)
Routine	29,450 (84·0)	27,138 (92·1)
Repeat after non-normal ROCA and/or scan	4,843 (13·8)	4,716 (97·4)
Clinical decision	766 (2·2)	733 (95·7)
Total	35,059	32,587* (92·9)
Scan type	**Scans requested** *n* (% of all requests)	**Results received** *n* (% of requested)
Annual scans	9,619 (76·3)	9,100 (94·6)
Repeat after non-normal ROCA and/or scan	2,825 (22·4)	2,792 (98·8)
Repeat after unsatisfactory scan	168 (1·3)	146 (86·9)
Total	12,612	12,038 (95·4)

Table A8. Apparent compliance with requested screening tests on UKFOCSS Phase 2

***** of these 2,233 (6·9% were discarded as they were receive by the lab outside the 56 hour post-venepuncture time-limit)

Appendix 9. UKFOCSS Collaborators, Laboratory Team, Data Monitoring Committee, Trial Steering Committee, Outcomes Committee members

Centre	Collaborators
Belfast	Patrick Morrison, Hans Nagar
Birmingham	James Nevin
Bristol	Robert Anderson, John Murdoch
Cambridge	Robin Crawford
Cardiff	Jonathon Gray, Mark Rogers
Cheltenham & Gloucester	Robert Gornall
Chester	Sharon Rowe
Cumberland	Sheila Pearson
Derby	Ian Scott, Howard Jenkins
Durham	Partha Sengupta
Dundee	David Goudie
East Kent	Andy Nordin
Edinburgh	Mary Porteous
Gateshead	Richard Edmondson
Glasgow	Rosemary Davidson
Guys	Gabriella Pichert, Chris Jacobs
Hammersmith	Sadaf Ghaem-Maghami
Hull	Mike Lind, David Poole
Kettering	Robert Haughney
Leeds	Carol Chu, Roger Rand, Richard Hutson, Ian Beck, Cheng Choy
Leicester	Richard Trembath, Quentin Davies
Lincoln	Martin Lamb
Liverpool	Carol Bejamin
London Northwest	Huw Dorkins
London UCLH	Usha Menon, Michelle Johnson
Manchester	Gareth Evans

Mid Essex	Colin Partington, Christopher Goodfellow
Milton Keynes	Christopher B-Lynch
Newcastle	Fiona Douglas
North England	Paul Brennan, Mary George, John McDonald
North Staffordshire	Vijay Menon
North Wales	Alex Murray, Philip Banfield, Simon Leeson, Philip Toon
Northampton	Sue Price, Alistair Duncan
Nottingham	Susan Ritchie, Karin Williamson
Oxford	Cyril Chapman, Anneke Lucassen, Lucy Side, Lisa Walker
Peninsula	Carole Brewer, Tony Falconer, Tito Lopes
Sheffield	Jackie Cook
Somerset West	Robert Fox
Southampton	Diana Eccles
St. George's London	Shirley Hodgson
Surrey	Gareth Beynon
Swansea	Alex Murray, Omar Freites
The Royal Marsden, London	Rosalind Eeles
Wycombe/Stoke	Damien Eustace
West Kent	Andreas Papadopoulos
Co-ordinating Centre lab	Jeremy Ford, Richard Gunu
Data Monitoring Committee	Shehla Mohammed, Mahesh Parmar (chair), Karina Reynolds
Trail Steering Committee	Louise Bayne (lay member), Kate Brain, Derek Cruikshank, Stephen Duffy, Diana Eccles, Lindsay Fraser, Ian Jacobs, Usha Menon, Julietta Patnick (chair), Adam Rosenthal, Steve Skates
Outcomes Committee	Elizabeth Benjamin, Adam Rosenthal, Naveena Singh

Table A9. UKFOCSS Collaborators, Laboratory Team, Data Monitoring Committee, Trial Steering Committee, Outcomes Committee members