PROTOCOL

Long term impact of screening on ovarian cancer mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

ISCRTN No: 22488978

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SUMMARY

Identifiers	
REC Reference No	00/8/34
Sponsor Reference No	UCL Data Protection Registration: Z6364106
Other research reference number(s) (if applicable)	ISCRTN No: 22488978
Health condition(s) or problem(s) studied	Ovarian cancer
Study Type i.e. Cohort etc	Randomised controlled trial
Sample size	202,546 postmenopausal women
STUDY TIMELINES	
Study Duration/length	3 years
Expected Start Date	1st January 2017
End of Study definition and anticipated date	31st December 2019
Key Study milestones	Collating medical notes for women identified as requiring Outcome Committee review in each calendar year Completion of Outcomes Review Mailing of the Quality of Life (QoL) questionnaire to newly diagnosed ovarian cancer survivors Compilation of dataset for final analysis Completion of final analysis Publication of specified analyses
KEY STUDY CONTACTS	
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1 ABSTRACT

Ovarian cancer continues to kill more women than any other gynaecological cancer.[1] A key reason is diagnosis at advanced stage.[2] The 30% diagnosed in Stage I have 5-year survival rates of 90%.[3] This has led to sustained efforts to improve early detection. A key part of the latter has been UKCTOCS, the largest randomised controlled trial of ovarian cancer screening. UKCTOCS is one of the world's largest multicentre randomised controlled trials and has involved 202,638 women from the general population, 673,765 annual screens and 2.2 million women-years of follow-up. At censorship on 31st December 2014, in women with invasive epithelial ovarian/tubal/peritoneal cancers, a significant stage shift was noted in the multimodal screening (MMS) arm compared to no screening control (C) arm but not in the ultrasound screening (USS) arm. Compared to the C arm, the reduction in OC deaths was not conventionally significant with 'average' estimated relative mortality reductions of 15% (p=0.10) MMS and 11% (p=0.21) USS on the primary Cox analysis. But it was significant (p=0.021) in the MMS versus C pre-specified analysis excluding prevalent cases and in a single post-hoc weighted log rank analysis (p=0.023). As noted in other screening trials, the mortality reduction was delayed and only apparent after about 7 years. The issue is that with the current length of follow-up, 45% (157/347) of OC deaths in the C arm occur before 7 years where there is no evidence of a difference. Long term follow-up till 2018 would result in approximately 73% (420/547) of estimated OC deaths in the C arm occurring after 7 years. This would allow us to assess whether the observed stage shift in the MMS arm translates into a difference in mortality. In support of this possibility, we note that at censorship, the C group OC mortality rate continuing to rise linearly, whereas the rates in MMS and USS groups appear to be plateauing.

We propose to continue follow-up of the participants to 31st Dec 2018 to determine whether ovarian cancer screening (1) improves disease-specific mortality and (2) is cost effective. In addition we will (3) undertake further more detailed analysis of the data to improve our understanding of ovarian cancer diagnosis, treatment and management and the cost-effectiveness of screening.

The primary outcome for the mortality and cost-effectiveness analysis will continue to be ovarian cancer death. Ovarian cancer will be defined by WHO 2014 criteria and include malignant neoplasms of the ovary, fallopian tube and undesignated malignancies of the ovaries/tube/peritoneum. Cases previously designated as primary peritoneal cancer by WHO 2003 criteria are likely to be reclassified as ovarian or tubal cancers.

We will continue to identify those who develop/die from ovarian/tubal/peritoneal cancer through established data linkage with national registries, Hospital Episode Statistics and National Cancer Intelligence Network data. All relevant records will be retrieved from GPs/hospitals/hospices and reviewed by the Independent Outcomes Review Committee who will confirm primary cancer site and cause of death.

The primary analysis will continue to be a modified intention-to-screen comparison using the Cox proportional hazards model of MMS versus C and USS versus C separately. Additional analysis will include fitting Royston-Parmar models11 for a delayed effect and estimating the long term screening effect by excluding prevalent cases. A cost-effectiveness analysis will involve both within trial analysis and modelling of screening in the NHS screening over a longer timeframe using the primary mortality endpoint.

We will also undertake data analysis to explore in this unbiased population cohort OC management in the UK, trends with time, novel epidemiological risk factors and symptoms/ routes to diagnosis (in the C arm).

In addition to publication in scientific journals, our final results will be disseminated through UKCTOCS website, sponsor / funder websites, media and via ovarian cancer charities.

2 BACKGROUND

OC is the foremost cause of gynaecological cancers death in the UK. Every day 20 women are diagnosed with the disease[4] and 11 die.[5] UK 5- and 10-year age standardised survival rates are lower than for other cancers such as breast and were 46.2% and 34.5% respectively for England in 2010-11.[6] These rates are lower than that of other countries with comparable wealth and universal access to health care.[7] Advanced Stage at diagnosis is a key contributor to poor prognosis. Significant efforts have been made to raise symptom awareness and support earlier diagnosis in primary care. However, in England during 2013, 58% of women were diagnosed in Stage III/ IV.[2] Late Stage has significant implications for patient morbidity, treatment costs (£5,328/per patient at Stage 1 compared to £15,081 at Stage 4 in England)[8] and survival (5-year survival rates of 90% in Stage I and 19% and 4% respectively for Stage III and Stage IV).[3] Hence the need to develop cost-effective strategies for earlier detection of OC.

Expressed need: Earlier diagnosis of OC is a key part of the government's efforts to improve cancer outcomes.[9] It is one of the key cancers in all major Department of Health early diagnosis cancer initiatives such as International Cancer Benchmarking Partnership,[10] The National Awareness and Early Diagnosis Initiative,[11] Be Clear on Cancer.[12]

Sustained interest and intent: In the UK, 1 in 52 women will develop OC with over half the cases diagnosed in women aged >65.[4] While overall OC mortality rates have decreased since 1970, they have increased by 20% in women aged 70-79 and 75% in those >80.[13] With an aging population, developing a cost effective OC screening strategy remains highly relevant and important to the future needs of the NHS. Equally important in 2014, 58% of women were detected in Stage III/IV[2] and there is little evidence that these rates are likely to decrease significantly through symptom awareness alone.[14]

UKCTOCS as one of the largest RCT ever undertaken has already made a significant impact on scientific literature (41 papers-11 core trial,15 secondary studies, 4 reviews and 8 from other groups about UKCTOCS). It has provided the first real indication that screening can reduce OC deaths. Further follow up is essential to assess whether this long term impact. It will also provide a unique opportunity to explore the long term health and economic impacts of OCS. There is no other trial of this size and none planned as per a literature search conducted using the strategy outlined in Jacobs Menon et al.[15]

In this randomised controlled trial, two screening strategies - multimodal (MMS - CA125 based with ultrasound as a second line test) and ultrasound (USS) were compared separately to control (C - no screening).[16] 202,638 women were randomised to achieve 80% power at a two-sided 5% significance level for a 30% mortality reduction. At initial censorship (31st December 2014), there was a significant Stage shift in invasive epithelial ovarian/tubal/peritoneal cancers in the MMS but not USS arm compared to C.[15] The mortality reduction was less than 30% (Cox model based 'average' mortality reductions of 15% (p=0.10) MMS and 11 (p=0.21) USS) but with evidence of an increasing mortality reduction over time, as noted in other screening trials.[17-19] The reductions in the MMS arm were significant in a pre-specified analysis excluding prevalent cases and a post-hoc weighted log rank analysis.[15]

The study addresses the question 'In the general population, can earlier detection of OC through screening reduce disease specific mortality and is it cost effective? The continued follow-up of UKCTOCS participants till 31st December 2018, with the aim of obtaining a definitive answer to these questions. If affirmative, this would support introduction of an ovarian cancer screening programme in the NHS and impact on OC outcomes worldwide.

The trial was run through 13 NHS Trusts with OC patients diagnosed and treated in the NHS.[16] The screening strategies involve routine tests that are widely used in the NHS. There are already well defined pathways/protocols for diagnosis and treatment of OC[20] which would facilitate any OC screening programme. Positive results are likely to lead to implementation of an OC screening programme.

The study builds on the significant contribution of >200,000 women and the huge investment by the NIHR/Department of Health, MRC, CRUK, Eve Appeal, the research teams and their host organisations**.**

3 LITERATURE REVIEW

In 1998 prior to the initial grant application, a systematic review commissioned by the NHS HTA which included 25 ovarian cancer screening studies reported that although ultrasound and multimodal screening can detect ovarian cancer in asymptomatic women, the effect of screening on ovarian cancer was unproven. The authors concluded that screening should not be introduced into clinical practice until further information was available from randomised trials designed to assess the effect of ovarian cancer screening on mortality, adverse effects and cost-effectiveness.[21] There is currently a Cochrane Review Protocol on the impact of screening for epithelial ovarian cancer in postmenopausal women.[22]

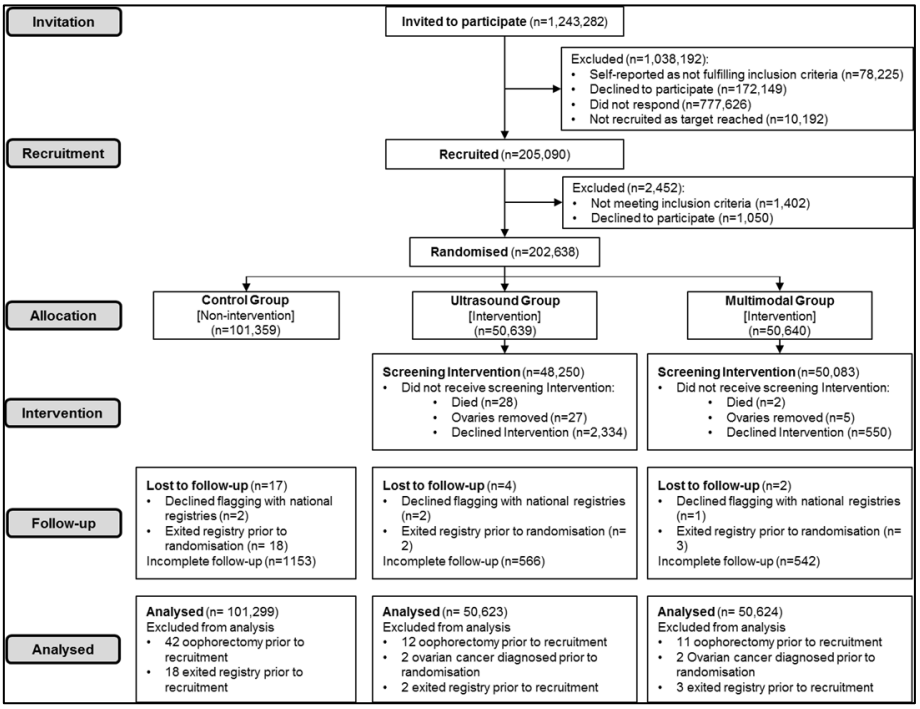
Using the methodology described in the Cochrane protocol by Mosch and colleagues,[22] we searched MEDLINE between Jan 1, 2001, and Nov 31, 2015, using the following search terms: “ovarian neoplasms”, “Fallopian tube neoplasms”, “ovar*”, “fallopian tub* OR adnex*”, “tumo*”, “malignan*”, “carcinoma* OR adenocarcinoma* OR neoplasm* OR mass*”, “mass screening”, “early detection of cancer”, “randomized controlled trial”, “controlled clinical trial”, “randomized”, “placebo”, “clinical trials”, “randomly”, and “trial”. This search yielded 234 publications, which, when limited to RCT of human female adults published in the English language resulted in 64 articles, 11 of which were duplicates. The remaining 53 articles consisted of 28 pertaining to the PLCO Cancer Screening Trial, 11 from our own group, and one from the Shizuoka Cohort Study of Ovarian Cancer Screening.

We identified five RCT in OC screening.
(1) A RCT from our group of 22 000 postmenopausal women with the study arm undergoing 3 annual screens using serum CA125 (normal <30U/ml) with pelvic ultrasound as a second line test. Women with index cancers in the screened group had a significantly higher median survival (72.9months) compared to the control group (41.8months; p=0.0112). However, the number of deaths from an index cancer did not differ significantly between the control (18/10,977) and screened (9/10,958, relative risk 2.0 [95% CI 0.78-5.13]) groups.[23]
(2) A pilot RCT from our group of 13,688 postmenopausal women which established the feasibility of undertaking an RCT with multimodal screening using CA125 interpreted with the ROC algorithm.[24] No survival or mortality data is available from this trial.
(3) The Shizuoka Cohort Study of Ovarian Cancer Screening which randomised 41,688 women, with those in the study arm undergoing an average of 5.4 annual screens using CA125 (normal <35U/ml) and pelvic ultrasound. It reported encouraging performance characteristics in 2008.[25] There was a Stage shift between the screen and control arm. This trial has not reported on deaths.
(4) The ovarian component of the PLCO Cancer Screening Trial - A RCT of 68,557 eligible postmenopausal women with the study arm undergoing 6 annual CA125 (normal <35U/ml) screens, the first 4 of which include a pelvic ultrasound as well. At median follow-up of 12.4 years, there was no difference (RR 1.18; 95% CI, 0.91-1.54) in OC deaths between the screen (118) and usual care (100) groups.[26] There was a 15% serious complication rate reported in screen positive women who underwent surgery where normal ovaries or benign adnexa were found. On extended follow up (median follow up of 14.7 years), there was no difference in OC deaths (RR 1.06; 95% CI, 0.87-1.30) between the screen (187) and usual care (176) groups.[27]
(5) UKCTOCS - It is the largest RCT of ovarian cancer screening with 202,638 women (Figure 1), 673,765 annual screens and 2.19 million women/years of follow-up.[15] At a median follow-up of 11.1 years, there was a highly significant Stage shift with multimodal screening (MMS), on an intention to screen analysis of invasive epithelial ovarian/tubal and peritoneal cancer (responsible for most of the deaths due to ovarian cancer). The proportion diagnosed in Stage I and II in the MMS group was 36.1% (108 of 299, p=0.00013) compared to 23.9% (137 of 574) and that of low-volume disease (Stage I, II, and IIIa) 40% (120 of 299; p<0.0001) compared to 26% (149 of 574) in the C group. There was no difference in the USS versus C group (62 [24%] of 259; p=0.57) comparison.

4 STUDY RATIONALE

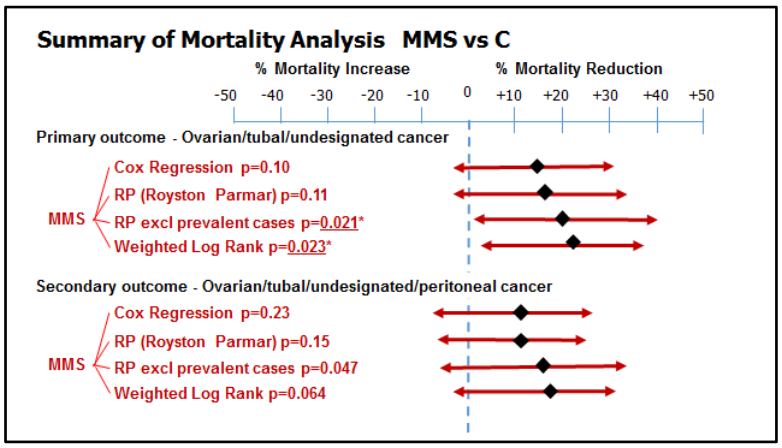
Between 2001 and 2005, women aged 50 to 74 were randomly invited from age/sex registers of 27 participating Primary Care Trusts adjoining the 13 UKCTOCS regional centres 202,638 women were randomised and 202,546 were found to be eligible (Figure 1).[16, 28]

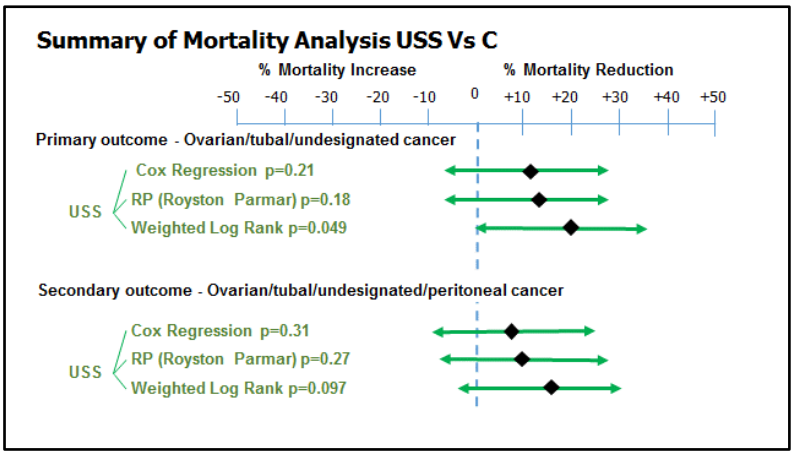
Figure 1: UKCTOCS Consort



Following censorship on 31st December 2014, the initial mortality analyses are performed the results of which are summarised in Figure 2 below. It suggests that MMS screening (MMS) may lead to a mortality reduction but the results are not definitive at present. Hence, the impact of this Stage shift noted above on mortality remains uncertain and can only be resolved through further follow-up.

Figure 2: Summary of Ovarian cancer mortality analysis in UKCTOCS





Additional follow-up till 31st December 2018 would allow us to determine the true extent of the reduction in OC deaths as a result of screening. We anticipate that there will be approximately another 230 control arms deaths (in addition to the 347 deaths included in the primary analysis). As noted in other screening trials,[17-19] the mortality reduction seen in UKCTOCS was delayed and only seemed to appear after about 7 years. Crucially, all the 230 deaths will occur beyond 7 years from randomisation, the time-point at which the mortality curves appear to start separating. With the current length of follow-up, 45% (157/347) of OC deaths in the C arm occurred during 0-7 years when there was no evidence of a mortality difference. With this extended follow-up, 73% (420/547) of OC deaths in the C arm will occur after 7 years, allowing us to assess whether the observed Stage shift in the MMS arm translates into a difference in mortality. In support of this possibility, we note that at censorship, the C group OC mortality rate continuing to rise linearly, whereas the rates in MMS and USS groups appear to be plateauing. Also extrapolated cost-effectiveness estimates to 25 years show much improved value for money in the MMS group.

A search of clinical trial databases (ClinicalTrials.gov; EU Clinical Trials Register; International Clinical Trials Portal), was undertaken. There is no ongoing or planned OC screening RCT listed**.** Thus UKCTOCS remains the only OC screening RCT which can answer the question as to whether Stage shift resulting from screening can impact on OC mortality. A trial of similar size and quality is unlikely to be repeated population with mortality as an end point.

5 ETHICAL APPROVAL / CONSENT

The UKCTOCS trial was approved by the North West Multicentre Research Ethics Committee on the 21st June 2000 (MREC Reference 00/8/34). The extension of the study with a follow up of the entire cohort until 31st December 2024 was approved on the 4th Sept 2014.

All women provided written informed consent at recruitment to UKCTOCS (between 17th April 2001 and 29th September 2005). In 2015, we obtained Section 251 approval for accessing medical notes and continuing linkage (as due to the length of time since recruitment, issues were raised as to the validity of the written informed consent obtained at recruitment).

6 AIMS AND OBJECTIVES

6.1 Primary Aims

AIM 1: To assess the long term impact of ovarian cancer screening on disease-specific mortality in women at population risk of OC

Objective 1: To identify and confirm OC diagnosis/cause of death during extended follow up of UKCTOCS participants.

Objective 2: To re-review all peritoneal cancers so that primary site assignment follows WHO 2014 definition.[29] All cases will also need to be re-reviewed to update Stage as per FIGO 2014.[30]

Objective 3: To compare OC deaths in each of the screened groups (MMS and USS) separately to the C group

Objective 4: To model the effect of screening beyond the study period to estimate the impact of a screening programme over a lifetime (>= 50 years of age).

AIM 2: To determine the cost-effectiveness of OC screening

Objective 1: To perform within-trial analysis to calculate the cost-effectiveness ratios relating to protocol-driven resource use.

Objective 2: To undertake modelling analysis reflecting the implementation of a National Screening Programme using standard practice (as this may differ from study protocol resource utilisation), and extrapolation of cost-effectiveness estimates over a longer time frame to include lifetime benefits of screening.

6.2 Secondary Aims

AIM 3: To improve our understanding of OC through analysis of data from a population cohort

Objective 1: To describe symptoms, routes to diagnosis, treatment, disease progression, recurrence in women who developed OC

Objective 2: To explore novel epidemiological risk factors for OC

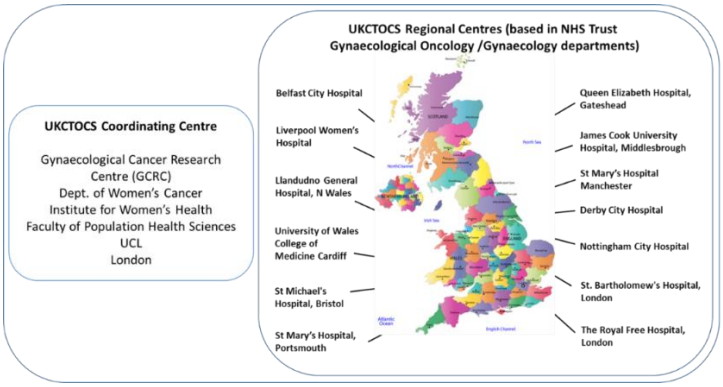
7 STUDY DESIGN

This is an observational study to follow the 202,546 eligible UKCTOCS participants. The relevant details of the original randomised controlled trial appear below.

7.1 Setting

The trial participants were recruited and underwent screening at 13 regional centres based in England (10), Wales (2) and Northern Ireland (1) (Figure 3). All were based within Gynaecological Oncology / Gynaecology departments at NHS Trusts. The Coordinating Centre is at the Gynaecological Cancer Research Centre (GCRC), Department of Women's Cancer, Institute for Women's Health, UCL. The extended follow-up phase will be entirely managed from the coordinating centre with input from co-investigators based in the UK, USA and Australia.

Figure 3: UKCTOCS Trial Centres



7.2 Eligibility criteria

7.2.1 Inclusion Criteria

The current study includes women who were consented and randomised into UKCTOCS. They fulfilled the criteria[16] listed below at recruitment.

(1) Age 50-74 years

(2) Postmenopausal: This was defined as either (a) >12 months amenorrhoea following a natural menopause or hysterectomy, or (b) >12 months of hormone replacement therapy commenced for menopausal symptoms.

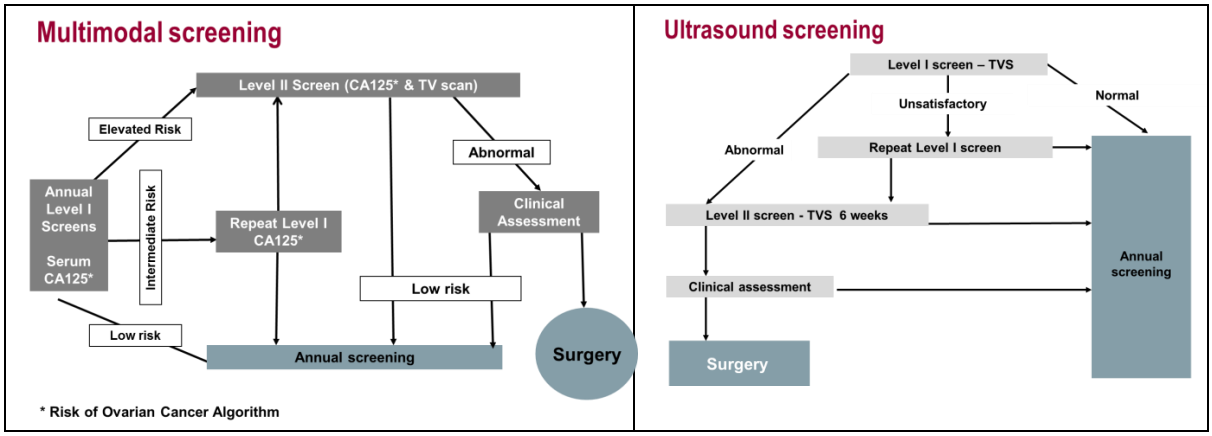
7.2.2 Exclusion Criteria

(1) Previous ovarian malignancy
(2) History of bilateral oophorectomy
(3) Active non-ovarian malignancy
(4) Increased risk of familial ovarian cancer as defined by the eligibility criteria for the United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS).
(5) Participation in other ovarian cancer screening trials

7.3 Health technologies assessed

Participants randomised to the study group underwent annual screening using one of two strategies (Figure 4), neither of which are currently available on the NHS. Annual screening was undertaken from April 2001 to December 2011.[16]

Figure 4: UKCTOCS screening strategies



MMS group: The annual (Level I) screen involved venepuncture. Serum CA125 levels were assayed in the blood sample using a commercial enzyme immunoassay (Roche EIA Elecsys 2010 system) at the central trial laboratory. The CA125 pattern over time was interpreted using the Risk of Ovarian Cancer (ROC) calculation,[31] which identifies significant rises in CA125 concentration above baseline. The first risk estimate was based upon a single measurement of CA125 and the participant's age. Subsequent ROC estimates were based upon the age of the woman, absolute CA125 level and the CA125 trend. Based on the risk estimate, women were triaged to annual screening (normal risk), repeat CA125 in 3 months (intermediate risk) or repeat CA125 and transvaginal ultrasound scan (Level II screens) (Figure 4).[16]

USS group: An annual TVS (Level I screen) was used to assess two aspects of the ovary - volume and morphology. Scans were classified based on findings in both ovaries into normal, abnormal or unsatisfactory.[16] On results of the Level I scan, women were triaged as shown in the Figure 4. Those with abnormal scans had a repeat TVS (Level II screen) in 6-8 weeks.

In either group if an abnormality persisted, they were referred for clinical assessment with a view to surgery.

8 OUTCOMES

8.1 Primary outcome

Death due to ovarian cancer. Ovarian cancer will be as defined by WHO 2014 criteria and include malignant neoplasms of the ovary (ICD-10 C56) malignant neoplasms of the fallopian tube (ICD-10 C57.0) and undesignated malignancies of the ovaries, fallopian tube, or peritoneum. Cases that were previously defined by WHO 2003 criteria[32] as primary peritoneal cancer in the previous UKCTOCS mortality analysis[15] will be reviewed. It is likely majority will be reclassified as ovarian or tubal cancers based on the new criteria.[29, 33] The latter states that presence of any cancer on the tubes or ovarian will lead to a diagnosis of ovarian or tubal cancer respectively.

Death is assigned as due to ovarian cancer on the basis of disease progression evidenced by appearance of new lesions on imaging, increase in size of previously documented disease on imaging, clinical worsening or rising biomarker levels.

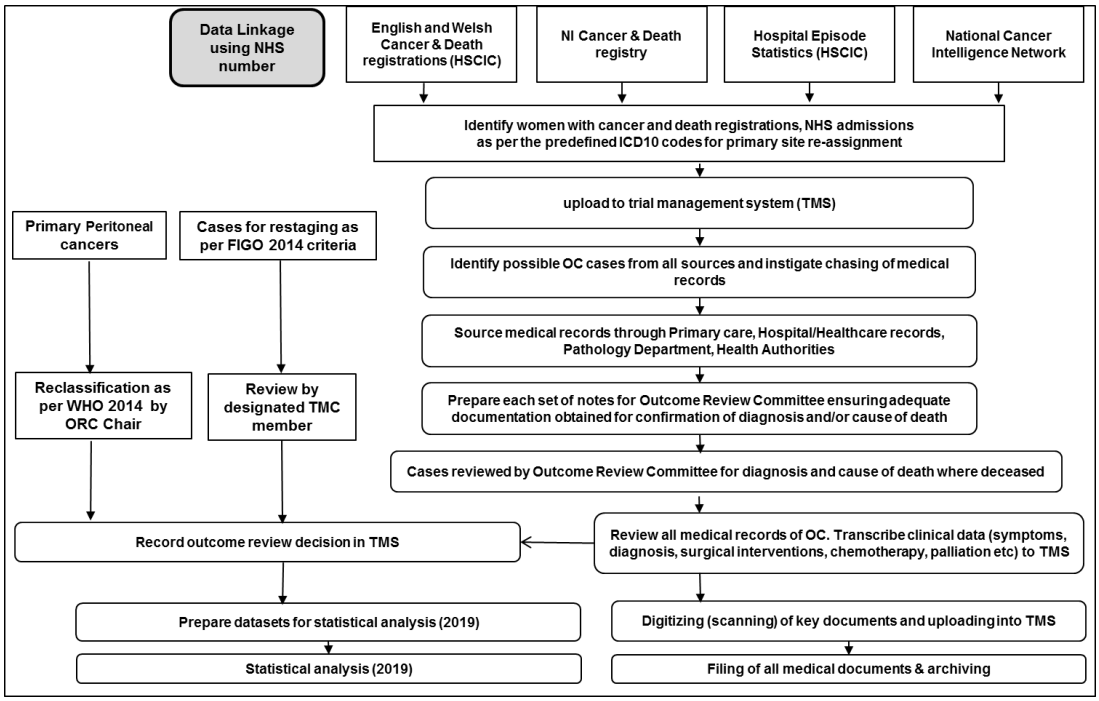
8.2 Secondary outcome

Cost-effectiveness of ovarian cancer screening. This will be assessed using individual patient data from English (Hospital Episodes Statistics), Welsh (Patient Episode Database for Wales) and Northern Ireland hospital administrative databases. The data will be augmented with resource data collected on individual diagnostic tests and treatment through medical record review. All unit costs will be based on NHS Reference Costs with additional costs as reported by the relevant Personal Social Services Research Unit Cost exercise.

9 DATA COLLECTION

Follow up is through linkage to national databases (Figure 5)

Figure 5: Schematic for identification and confirmation of primary outcome (ovarian cancer death)



9.1 Aim 1: Long term impact of OC screening on disease-specific mortality

9.1.1 Identifying women with possible OC

Data from the sources previously described, will be interrogated to identify women diagnosed with any of 19 International Classification of Diseases (ICD)-10 codes as detailed in UKCTOCS protocol.[16] Copies of medical notes (referral letter, information on symptoms, surgery notes, multidisciplinary team meeting reports, histology/cytology/imaging reports, discharge / medical oncology summaries, hospital letters) will be retrieved by contacting GPs/hospitals/hospices. The only exception will be women with ICD-10 C80 (malignant neoplasm of uncertain origin) who also have another specific non-ovarian or non-peritoneal cancer registration where detailed notes will not be retrieved.

9.1.2 Confirming OC diagnosis and death

The protocol is detailed in Appendix 1. In summary, all collated notes will be reviewed by an independent outcomes review committee (two pathologists and two gynaecological oncologists) who are blinded to the randomisation group. A pre-specified algorithm which has been audited previously will be used to assign final diagnosis. Stage, grade, morphology, type of ovarian cancer are also abstracted by the outcomes review team from the available documentation using forms documented in UKCTOCS trial protocol.[16] A record of types of documents such as discharge summary, histology etc made available to reviewers are recorded.

9.1.3 Identifying women who are ineligible through undergoing oophorectomy

This will be done using HES data. Where there is uncertainty, histological records will be retrieved for confirmation.

9.2 Aim 2: Cost-effectiveness of OC screening

To establish resource use and cost for the cost-effectiveness analysis, HSCIC HES data will be used for all our trial population in England (157,925). All approvals are in place and we have recently received up-to-date data till mid-2016. We are in the process of formal application to the Welsh PEDW and the Northern Ireland DoH & HSC for similar data on the 31,055 women recruited through the 2 Welsh centres and 13,566 women recruited in Belfast. It is our understanding that we have all the necessary processes in place to get approval. NHS number data linkage, allows for us to receive individual patient data. This will allow identification of all hospital visits during the entire study and follow-up period. It will be augmented with resource data collected as previously on individual diagnostic tests/surgery/ chemotherapy/radiotherapy via retrieval of case notes. All unit costs will be based on NHS Reference Costs and additional costs as reported by the relevant PSSRU Unit Cost exercise.

Quality of life data to supplement our main outcome variable (OC mortality) will be based on estimating the EQ5D-5L tariffs and will be obtained by (1) mapping as described previously[34] of FACT-O collected in the parallel MRC funded Psychosocial Study to the EQ5D-5L. Data on the FACT-O instrument is available on 134 UKCTOCS women (89MMS; 45USS) who were diagnosed with ovarian/tubal/peritoneal cancer during the period (2001-2010) when the psychosocial study was active. (2) Mailing EQ5D-5L and FACT-O questionnaires to all women in UKCTOCS who are identified through Cancer Registry/HES and confirmed on retrieved histology/case notes to be diagnosed with ovarian/peritoneal cancer between mid-2016 and mid-2018. Vital status will be checked using the most recent HSCIC death data before the mailing. We have used the EQ5D-5L instrument to explore quality of life in endometrial cancer survivors in UKCTOCS between September 2013 and December 2015 in a similar fashion.

9.3 Aim 3: Improve our understanding of OC

Additionally the above medical records will be interrogated and data transcribed for the following categories using forms documented in UKCTOCS Trial Protocol:[16]

- Symptoms – type, onset, duration, severity, frequency, treatment;
- Route to diagnosis – symptom reporting, GP examination, referral to specialist;
- Imaging (pre- and post-op) – type and mode of imaging, date, operator, location, imaging summary, abnormalities;
- Surgical treatment – date, location, surgeon, procedure, oophorectomy, hysterectomy, omentectomy, lymph node dissection, complication type, readmissions and further surgery, blood tests and further imaging;
- Chemotherapy Treatment – type, line, agent, dose, cycles, start and end dates, clinician responsible, causes of change to or discontinuation of chemo therapy, maintenance therapy;
- Recurrence – diagnosis date, site, imaging performed;
- Palliation – referral date, hospice admission, surgery or other palliative treatment.

10 STATISTICAL METHODS

10.1 Aim 1: Long term impact of OC screening on disease-specific mortality

For reasons of continuity and statistical integrity the statistical analysis plan will broadly follow that used previously.[15] The primary analysis will be a modified intention-to-screen comparison using the Cox proportional hazards model of MMS versus C and USS versus C separately. Analysis time will be the

interval from date of randomisation to date of death from ovarian cancer. Censorship will be 31st December 2018, or at date of death from other cause or loss to follow-up, if earlier. As with all screening trials where an effect was detected, we have observed a delayed screening effect which cannot occur with proportional hazards, hence we will also fit a Royston-Parmar non-proportional hazards model[11] as done previously. We will also estimate the long term screening effect by excluding prevalent cases and cases arising after the end of screening. An alternative method for addressing the delayed effect of screening is the weighted log-rank (WLR) test with weights increasing with time on study. As an additional analysis, we will apply the WLR using the weights pre-specified by the PLCO trialists[26] with weights equal to the combined ovarian cancer mortality in the screened arm (MMS or USS as appropriate) and the control arm.

10.2 Aim 2: Cost-effectiveness of OC screening

For the cost effectiveness analysis we will calculate the cost-effectiveness ratios relating to protocol-driven resource use and model the costs of screening in the NHS over the full study time period. We will also extrapolate costs over a longer timeframe to match the modelling of lifetime benefits. We will estimate the Incremental Cost-effectiveness ratio (ICER) for the screening programmes relative to the control group who have had no screening. This is a particularly important analysis given that current extrapolation of the within trial economic analysis to beyond the trial period has indicated that the ICER associated with a screening programme falls dramatically, in contrast to the within the trial period ICER which remains relatively high reflecting the long lead time for mortality benefits from screening to be established. The economic analysis that incorporates the follow-up data will establish whether this indicative result is upheld or not. The treatment effect will be augmented by use of EQ5D-5L data. The QALY information gained would be accepted as indicative rather than authoritative and a representative sample of EQ5D-5L values will be sought, rather than a sample established through statistical calculation.

10.3 Aim 3: Improve our understanding of OC

Statistical analysis relevant to the following key analyses

Table 1: Planned analyses

Objectives	Year 1 (September 2016 to December 2017)	Year 2 (January 2018 to December 2018)
Improving our understanding of ovarian cancer, presentation, treatment and progression	Accuracy of OC diagnosis - a comparison of national cancer registry data and outcomes review in UKCTOCS	Analysis of OC symptom data collected through a prospective cohort study within UKCTOCS and correlation with OC diagnosis on follow-up
	Detailed analysis of symptoms, routes to diagnosis and patterns of care of OC patients - a population based cohort study in	Association between socioeconomic status and tumour stage at diagnosis of ovarian cancer
	Symptoms reported by women with screen detected invasive epithelial ovarian cancer	Detailed comparative analysis of women who die within 30 days of OC diagnosis and those who survive longer
Risk factors for OC	Hysterectomy and OC risk	Endometrial Thickness as a risk factor for hormone-sensitive cancers

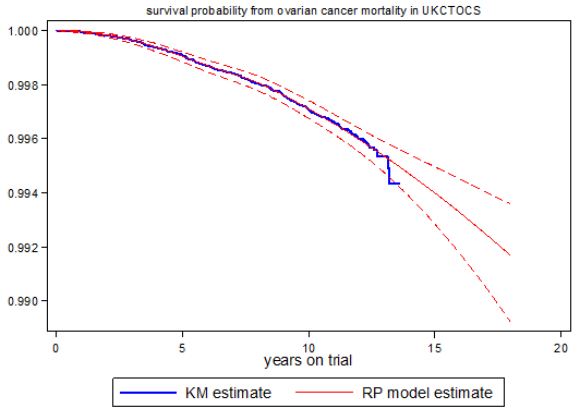
11 POWER CALCULATION AND ASSUMPTIONS

During the follow up of the 186,427 remaining women (not lost to follow-up or dead on 1st January 2015) for a further 4 years until 31st December 2018, we estimate there will be approximately a further 232 OC deaths in the C arms (Figure 6), in addition to the 347 deaths as of 31st December 2014. Crucially, all 232 OC deaths will occur beyond 7 years from randomisation, the time-point at which the mortality curves appear to start separating. This would result in 73% (422/579) of OC deaths in the C arm at 31st December 2018 being more than 7 years from randomisation. A conditional power calculation on the assumption of (1) an average mortality reduction (MR) of 25% over the subsequent period of follow-up of 2015-2018 and (2) the average MR for 2001-2014 of 15%,[15] estimates power will be 90% with testing at the 5% level of significance, and 81% if the Dunnett correction for multiple tests compared to a control

is applied. The 25% MR is, we believe, a conservative estimate given the average MR of 23% across years 7-14 and over 35% across years 10-14.

The estimate of 232 C arm deaths was obtained by fitting a flexible parametric survival (Royston-Parmar) model to the existing C arm data, with OC death as the event of interest (n=347). To predict all-cause mortality at a given future date (rather than a point in analysis-time) we used the RP model to predict a survival probability for each woman in UKCTOCS at $time_{i\_2018}$, where $time_{i\_2018}$ is the amount of time each woman *i* would be followed-up for by December 2018. The expected number of predicted events is the sum of the complement of each survival probability (1-*p*) predicted at this date.

Figure 6: Probability of survival from ovarian cancer in UKCTOCS. Blue line is the Kaplan-Meier (KM) estimate of the C arm ovarian cancer survival curve up to 13.58 years (31st December 2014) and the red line (with dashed 95% confidence bands) is the Royston-Parmar (RP) model estimate, which includes predictions of survival 4 years into the future.



Furthermore, the Figure 7 below from our previous publication[15] depicts divergent hazard rates for the control (blue) and MMS (red) arm over the latter period.

Figure 7: Rates of ovarian cancer deaths

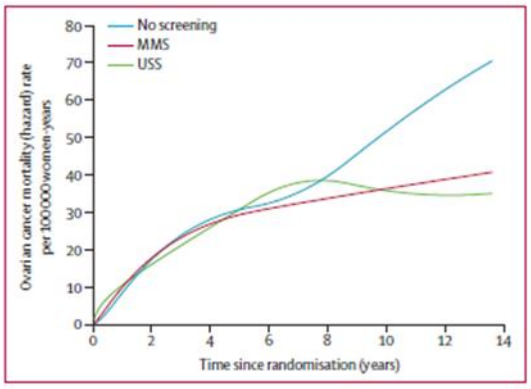


Figure 3: Rates of ovarian cancer
The figure including confidence limits is in the appendix (p 14).
MMS=multimodal screening. USS=ultrasound screening.

12 PUBLICATION AND DISSEMINATION POLICY

The main knowledge products outputs will be publications (scientific journals/HTA monograph) on mortality impact of OC screening in the general population, cost-effectiveness analysis and risks/benefits of a screening programme. The key aim is to provide the information such that the NHS can make a decision as to whether OC screening should be introduced.

The additional publications on an unbiased population cohort of women with ovarian cancer will be very informative for the NHS especially with regards to routes to diagnosis, symptoms and treatment. While there is population level data with the NCIN, the depth of detail is not available.

Additional stake holders for dissemination are

1. Scientific community via traditional routes
(a) *Publications* in high impact journals with a wide readership internationally. All UKCTOCS publications thus far are open access and UCL are committed to continuing to provide open access via UCL Discovery. We anticipate between 6-8 papers being published prior to the final results of extended follow-up. Findings from these will also be disseminated as appropriate.
.
(b) *Scientific conferences/local meetings*: We will target three main conferences (NCRI, ASCO, and BSGC,) for submission of abstracts for during the course of the extended follow-up. Where relevant press releases will be organised together with UCL press office.

(c) *Clinical trial databases:* These will be updated as and when required. Summary of final results will be added following publication of results.

2. Sponsor/Ethics/Funders: As well as annual reports to the sponsor/ethics and funders, we will provide a full report for the HTA journal at the end of the funding period.

3. Trial participants: They remain a priority for UKCTOCS for dissemination of trial news. Results will be available on the UKCTOCS/Institute for Women's Health (IfWH)/UCL Institute/UKCTOCS website. The trial team will work with women's support groups and cancer (eg CR-UK) and OC charities (eg Target Ovarian Cancer, The Eve Appeal, Ovacome) to produce summaries for their respective newsletters and websites. The press office at UCL will co-ordinate this effort and assist with regional press releases.

4. General public: Press releases will be prepared in collaboration with journal/UCL/funder and a press briefing held in advance of the publication date of final results with appropriate embargoes in place.

13 APPENDIX 1: Outcome Review Protocol

13.1 Introduction

The purpose of the outcome committee's review is to assign diagnosis or cause of death due to ovarian/tubal cancer.

13.2 Identification of potential ovarian/tubal cancer

The UKCTOCS team receive notification of new and potential cases of ovarian/tubal cancers (OC) through a variety of sources.

Cancer registrations and death registrations are two of the most important sources of information. For England and Wales, the Office for National Statistics collate this data and make it available through NHS Digital (formerly HSCIC). For Northern Ireland (NI) cancer registrations are available through N. Ireland Cancer Registry while death data is available via HSC BSO. Quarterly (E&W) or annual (NI) updates are obtained electronically. After each update, a query is run to identify potential new cases of ovarian/tubal cancer. The query flags up a list of ICD-10 codes that could be related to a diagnosis of OC (Table 2).

The cohort has also been linked to the Hospital Episode Statistics (HES) in England through NHS Digital. HES is a comprehensive dataset of volunteers' hospital admissions and corresponding disease codes from 2000. Accident and Emergency, Admitted Patient Care, Adult Critical Care and Outpatients data on UKCTOCS women has been obtained from 2000 to (provisional) 2015. Due to the unreliability of the diagnosis codes assigned to the clinical diagnosis fields in HES data only the terms "C56*", "C57*" and "C48*" are used to search for cases of ovarian, tubal or peritoneal cancer. Hospital episode data for Welsh and NI treatment centres will be sought through Patient Episode Data Wales (PEDW) and Northern Ireland DoH & HSC respectively.

Data will also be obtained from the National Cancer Intelligence Network (NCIN).
Occasionally, the volunteer (or her relative) may inform the team directly of her ovarian cancer diagnosis.

13.3 Review Process

Once a volunteer is "flagged" as potentially having or having died due to OC, copies of all her medical notes relating to the cancer diagnosis/death are obtained from the treating hospital(s), GP surgeries, hospices and cancer registries.

The only exception is when alongside a diagnosis or cause of death of "C80" (Malignant neoplasm without specification of site), there is an additional ICD10 code of a primary cancer site (death certificate or cancer registration) other than those listed in Table 2. The latter cases are reviewed by a designated additional gynaecological oncologist on ORC using only the death certificate and cancer registration records. However, if the C80 code is accompanied by a "secondary" cancer code then medical notes are retrieved as described above and reviewed as described below.

The collected notes, arranged in chronological order and stripped of any evidence of volunteer group allocation in the trial and/or screen-detection of the cancer, are presented to a member of the outcomes review committee (ORC). Generally, at least three documents are required for 'confirmation' of diagnosis or death due to OC. Where surgery has been performed, one of these documents must be a histology report. Other relevant information includes death certificates, ONS cancer registrations, biopsy/cytology reports, diagnostic imaging results, multidisciplinary team meeting (MDT) summaries, discharge summaries, chemotherapy schedules, hospital letters and HES diagnosis and operation codes. The clinical records, submitted to reviewers, must also contain a clear letter of diagnosis by the clinical team such as an MDT review, letter to GP or hospital letter prior to chemotherapy commencement.

Table 2: ICD-10 Codes of interest

ICD-10 code	Description
C56	Malignant neoplasm of ovary
C57·0	Malignant neoplasm of fallopian tube
C57·4	Uterine adnexa, unspecified
C57·7	Other specified female genital organs
C57·8	Malignant neoplasm of overlapping lesion of female genital organs
C57·9	Malignant neoplasm of female genital organ, unspecified
C48·0	Retroperitoneum
C48·1	Specified parts of peritoneum
C48·2	Malignant neoplasm of peritoneum, unspecified
C48·8	Overlapping lesions of retroperitneum and peritoneum
C76·2	Malignant neoplasm of abdomen
C76·3	Malignant neoplasm of pelvis
C80	Malignant neoplasm without specification of site
D07·3	Carcinoma in situ of other/unspecified female genital organ
D28·2	Benign neoplasm of fallopian tube
D28·9	Benign neoplasm of female genital organ, unspecified
D36·9	Benign neoplasm of unspecified site
D39·1	Neoplasm of uncertain or unknown behaviour of ovary
D39·9	Neoplasm of uncertain or unknown behaviour of female genital organ, unspecified
Abbreviations: ICD, International Classification of Diseases.	

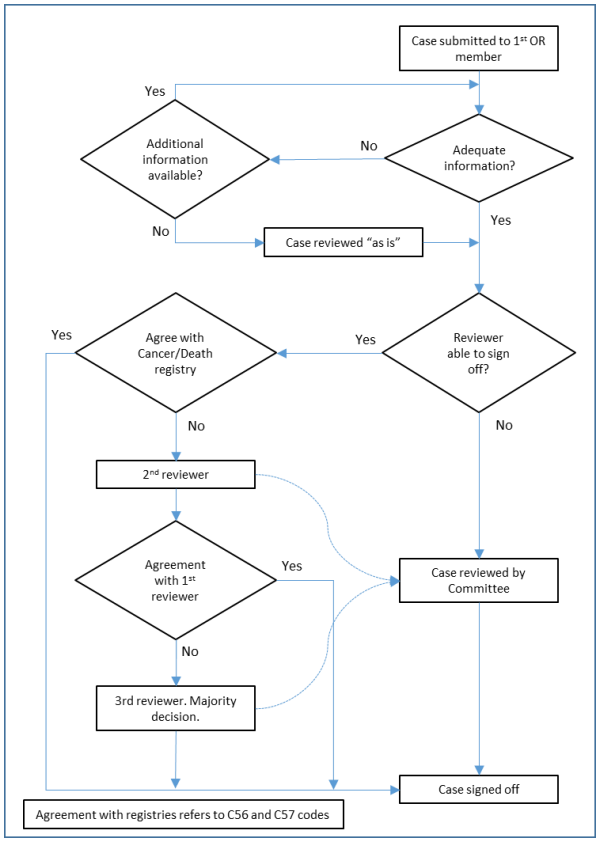
Table 3: Morphology codes corresponding to ICD-10 cancer codes of interest

Morphology Code	Description
M8380/3	Endometriod carcinoma (C56)
M8381/3	Endometriod adenofibroma, malignant (C56)
M8441/3	Serous cystadenocarcinoma NOS (C56)
M8442/3	Serous cystadenoma, borderline malignancy (C56)
M8450/3	Papillary cystadenocarcinoma NOS (C56)
M8451/3	Papillary cystadenoma, borderline malignancy (C56)
M8460/3	Papillary serous cystadenocarcinoma (C56)
M8461/3	Serous surface papillary carcinoma (C56)
M8462/3	Papillary serous cystadenoma, borderline malignancy (C56)
M8470/3	Mucinous cystadenocarcinoma NOS (C56)
M8471/3	Papillary mucinous cystadenocarcinoma (C56)
M8472/3	Mucinous cystadenoma, borderline malignancy (C56)
M8473/3	Papillary mucinous cystadenoma, borderline malignancy (C56)
M8620/3	Granulosa cell tumour, malignant (C56)
M9000/3	Brenner tumour, malignant (C56)
M9090/3	Struma ovarii, malignant (C56)

(1) If the submitted information is deemed adequate and there is agreement between the reviewer's assigned cancer diagnosis/cause of death and either cancer registration (CR) or death certificate (DC) registration, the process is considered "complete". A completed case will have primary cancer site, grade, stage and morphology (Table 3; and cause of death, where applicable) assigned.
(2) If the reviewer disagrees with either of CR/DC, the case will be forwarded to a second ORC member for an independent review. If the two ORC members are concordant in their assignments, the case will be signed off; otherwise, a third ORC member will independently review the case; and cancer diagnosis and cause of death will be signed off based on the majority reviewers' assignment.
(3) If there is uncertainty regarding assignment even after review by three ORC members, the case will be set aside for outcome committee's discussion, where two pathologists and two oncologists will review the case together. Reviewers can also refer cases to outcome committee's discussion, when they cannot independently ascertain cancer diagnosis and/or cause of death.

If the submitted information is insufficient for verification of cancer diagnosis/cause of death, the reviewer may either request further information or histology slides for pathological review to determine stage/grade of diagnosed ovarian/tubal cancer. In such cases, the UKCTOCS research assistant will obtain the requested information or histology slides. Once the slides have been reviewed, the case will be re-submitted to the original reviewer with the additional histology report. Where further information is impossible to obtain the review will be carried out by Outcome Committee using the available evidence.

Figure 8: Outcomes review process



Upon review of the documents, the reviewer completes a trial cancer review form (CRF) and death review form (DRF; where applicable) for each volunteer. A pre-specified algorithm (Figure 9) which has been audited previously will be used to assign final diagnosis.[16] Stage, grade, morphology, type of ovarian cancer are also abstracted by the outcomes review team from the available documentation using forms documented in UKCTOCS trial protocol.[16] A record of types of documents such as discharge summary, histology etc made available to reviewers are recorded.

Figure 9: Algorithm for allocating primary cancer site by outcome review committee

Documentation available:									Primary cancer site
Histology definite of ovarian or fallopian tube origin						☐			C56/C57.0
Ovarian/tubal histology suggestive of PP						☐			C48
Histology suggestive of other primary						☐			Other primary
Clinical details	**CA125**	**Adnexal imaging**		**Imaging**		**Cytology (ascites)**	**Pathology**		
Clinical history and/or findings in keeping with OV/FT/PP malignancy	CA125 elevated	Adnexal mass	Normal-sized ovaries	Peritoneal/omental disease in keeping with OV/FT/PP malignancy	Imaging suggests non- OV/FT/PP malignancy	Adenocarcinoma cells	Pathology (any site) compatible with OV/FT/PP malignancy	Pathology (any site) indicates/confirms non-OV/FT/PP malignancy	Primary cancer site
☐	☐	☐	☐	☐	☐	☐	☐	☐	
√		√					√		C56/C57
√		√				√			
√		√		√					
√	√			√			√		
√	√			√		√			
√	√		√	√			√		C56/C57/C48
√	√		√	√		√			
√	√		√		√		√		
		√			√				C80 but NOT OV/FT/PP
			√		√				
					√				
	√							√	
√						√ (Malignant cells)			C80

Irrespective of whether this column is positive or negative

13.4 Updating of FIGO stage

At the end of 2013 FIGO announced new definitions for ovarian cancer staging which have been adopted from 1/1/2014 (Table 4). All new cases reviewed by Outcome reviewers will be staged using the new definitions. Furthermore ORC will re-stage all previously completed OC cases. This re-staging will be performed by the designated additional gynaecological oncologist on ORC. Where re-staging alters the major stage (eg II to I) the case will be reviewed by one of the four core members of ORC.

Table 4: FIGO Ovarian Cancer Staging. Effective Jan.1, 2014 *(Changes are in italics)*

STAGE I: Tumor confined to ovaries				
OLD			NEW	
IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings/ascites.		IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.
IB	Tumor involves both ovaries otherwise like IA.		IB	Tumor involves both ovaries otherwise like IA.
IC	Tumor involves 1 or both ovaries with any of the following: capsule rupture, tumor on surface, positive washings/ascites.		*IC Tumor limited to 1 or both ovaries*	
			IC1	*Surgical spill*
			IC2	*Capsule rupture before surgery or tumor on ovarian surface.*
			IC3	*Malignant cells in the ascites or peritoneal washings.*

STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer				
OLD			NEW	
IIA	Extension and/or implant on uterus and/or Fallopian tubes		IIA	Extension and/or implant on uterus and/or Fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues		IIB	Extension to other pelvic intraperitoneal tissues
IIC	IIA or IIB with positive washings/ascites.			

Old stage IIC has been eliminated

STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes				
OLD			NEW	
IIIA	Microscopic metastasis beyond the pelvis.		*IIIA (Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis)*	
			IIIA1	*Positive retroperitoneal lymph nodes only*
			IIIA1(i)	*Metastasis ≤ 10 mm*
			IIIA1(ii)	*Metastasis > 10 mm*
			IIIA2	*Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes*
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm in greatest dimension.		IIIB	*Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.*
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm in greatest dimension and/or regional lymph node metastasis.		IIIC	*Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.*

13.5 Reassigning of WHO guidelines on definition of primary peritoneal cancer

In 2014 WHO published guidance on the classification of tumours of the female reproductive organs.[29] In the new guidance many cases previously classified at primary peritoneal cancer (PPC) would now be classified as ovarian. All cases previously classified as PPC will be reviewed and reclassified by the Chair of the ORC.

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