A randomised trial of non-Selective versus selective adjuvant Therapy in high risk Apparent sTage 1 Endometrial Cancer

Trial Sponsor: University College London
Trial Sponsor reference: UCL/13/0630
Trial funder: Cancer Research UK
Funder reference: CRUK/14/043
Clinicaltrials.gov no: NCT02566811

Protocol version no: 2.0
Protocol version date: 13th December 2016
Protocol version 2.0 13th December 2016

Authorisation signatures

<table>
<thead>
<tr>
<th>Name &amp; Role</th>
<th>Signature</th>
<th>Date authorised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chief Investigator:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mr Tim Mould</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultant Gynaecological Oncologist</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5.17</td>
</tr>
<tr>
<td>For the Sponsor:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professor Jonathan Ledermann</td>
<td></td>
<td>3.5.17</td>
</tr>
<tr>
<td>Director, UCL CTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laura Farrelly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Trials Group Manager</td>
<td></td>
<td>4.5.17</td>
</tr>
</tbody>
</table>

Please note: This trial protocol must not be applied to patients treated outside the STATEC trial. UCL CTC can only ensure that approved trial investigators are provided with amendments to the protocol.
COORDINATING CENTRE:
For general queries, supply of trial documentation and central data management please contact:

STATEC Trial Coordinator
Cancer Research UK & UCL Cancer Trials Centre
90 Tottenham Court Road
London
W1T 4TJ
United Kingdom

Tel: +44 (0) 20 7679 9872
Fax: +44 (0) 20 7679 9871
09:00 to 17:00 Monday to Friday, excluding Bank Holidays (UK time)

Email: ctc.STATEC@ucl.ac.uk

Other trial contacts:
Chief Investigator: Mr Tim Mould
Consultant Gynaecological Oncologist
Address: University College London Hospital
250 Euston Road
London
NW1 2PG
United Kingdom

Trial Management Group (TMG):
Prof Henry Kitchener  Professor of Gynaecological Oncology  University of Manchester (UK)
Prof Richard Edmondson  Professor of Gynaecological Oncology  University of Manchester (UK)
Mr Jeremy Twigg  Consultant Gynaecological Oncologist  The James Cook University Hospital (UK)
Dr Emma Hudson  Consultant Clinical Oncologist  Velindre Cancer Centre (UK)
Prof Hans Nijman  Professor of Gynaecological Oncology  University of Groningen (Netherlands)
Prof Carien Creutzberg  Professor of Radiation Oncology  Leiden University Medical Centre (Netherlands)
Associate Prof Alison Brand  Associate Professor and Gynaecological Oncologist  University of Sydney (Australia)
Prof Jonathan Ledermann  Professor of Gynaecological Oncology  UCL CTC (UK)
Dr Naveena Singh  Consultant Histopathologist  St Bartholomew's Hospital (UK)
Dr Raji Ganesan  Consultant Histopathologist  Birmingham Women’s Hospital (UK)
<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof Allan Hackshaw</td>
<td>Professor of Epidemiology and Medical Statistics</td>
<td>UCL CTC (UK)</td>
</tr>
<tr>
<td>Laura Farrelly</td>
<td>Clinical Trials Group Manager</td>
<td>UCL CTC (UK)</td>
</tr>
<tr>
<td>Mandy Feeney</td>
<td>Senior Trial Coordinator</td>
<td>UCL CTC (UK)</td>
</tr>
<tr>
<td>Lee Webber</td>
<td>Trial Coordinator</td>
<td>UCL CTC (UK)</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS

1. PROTOCOL SUMMARY ........................................................................................................... 1
   1.1. SUMMARY OF TRIAL DESIGN ................................................................. 1
   1.2. TRIAL SCHEME .................................................................................. 6

2. INTRODUCTION .................................................................................................................... 7
   2.1. BACKGROUND ................................................................................... 7

3. TRIAL DESIGN .................................................................................................................... 10
   3.1. TRIAL OBJECTIVES ......................................................................... 10
   3.2. TRIAL ENDPOINTS ......................................................................... 11
   3.3. TRIAL ACTIVATION ......................................................................... 12

4. SELECTION OF SITES/SITE INVESTIGATORS .............................................................. 13
   4.1. SITE SELECTION .............................................................................. 13
       4.1.1. Selection of Principal Investigator and other investigators at sites .......... 13
       4.1.2. Training requirements for site staff ........................................... 13
   4.2. SITE INITIATION AND ACTIVATION .................................................. 14
       4.2.1. Site initiation ............................................................................ 14
       4.2.2. Required documentation ......................................................... 14
       4.2.3. Site activation letter ................................................................ 14

5. INFORMED CONSENT ....................................................................................................... 16

6. SELECTION OF PATIENTS .............................................................................................. 18
   6.1. PRE-RANDOMISATION EVALUATION .................................................. 18
   6.2. SCREENING LOG ............................................................................. 21
   6.3. PATIENT ELIGIBILITY ...................................................................... 21
       6.3.1. Inclusion criteria ....................................................................... 21
       6.3.2. Exclusion criteria ...................................................................... 22

7. RANDOMISATION PROCEDURES ..................................................................................... 23
   7.1. RANDOMISATION ............................................................................. 23

8. TRIAL TREATMENT .......................................................................................................... 25
   8.1. TREATMENT SUMMARY ................................................................. 25
   8.2. TRIAL TREATMENT DETAILS .......................................................... 25
       8.2.1. Surgery .................................................................................... 25
       8.2.2. Hysterectomy and BSO .............................................................. 26
       8.2.3. Lymphadenectomy – Arm 1 only .............................................. 26
       8.2.4. Sentinel lymph node (SLN) sub-study – Arm 1 only i.e. lymphadenectomy arm ............................................................................. 27
       8.2.5. Positive lymph nodes – Arm 1 only i.e. lymphadenectomy arm .......... 27
       8.2.6. Pathological and Surgical Quality Assurance (QA) ..................... 28
       8.2.7. Management of patients with intraoperative findings of more advanced stages of endometrial cancer ............................................................... 29
       8.2.8. Adjuvant therapy ....................................................................... 30
       8.2.9. Management of patients with final pathology not showing high risk endometrial cancer .............................................................. 30
   8.3. SUPPORTIVE CARE .......................................................................... 30
   8.4. CLINICAL MANAGEMENT AFTER SURGERY ................................... 30

9. ASSESSMENTS AND DEFINITION OF RECURRENCE ................................................. 32
   9.1. PRE-TREATMENT ASSESSMENTS ..................................................... 32
   9.2. DAY OF SURGERY ............................................................................ 32
9.3. Post-operative visit ................................................................. 32
9.4. Assessments during follow up .................................................. 32
9.5. Defining recurrence ............................................................... 38

10. Translational Research .................................................................. 39

11. Data Management and Data Handling Guidelines ............................. 40
11.1. Entering data onto the eCrf ......................................................... 40
11.2. Corrections to eCrf .................................................................... 40
11.3. Missing Data ............................................................................. 40
11.4. Timelines for eCrf completion .................................................. 40
11.5. Data Queries ............................................................................ 40

12. Safety Reporting ........................................................................... 42
12.1. Definitions of adverse events ..................................................... 42
12.2. Reporting procedures ............................................................... 43
12.2.1. All adverse events (Aes) ......................................................... 43
12.2.2. Serious adverse events (SAEs) ............................................... 44
12.3. Related and unexpected serious adverse reactions (RUSARs) ......... 47
12.4. Safety Monitoring ................................................................. 48

13. Incident Reporting ......................................................................... 49
13.1. Incident Reporting ................................................................... 49

14. Trial Monitoring and Oversight ...................................................... 50
14.1. Central Monitoring ................................................................. 50
14.2. ‘For cause’ on-site monitoring .................................................. 50
14.3. Oversight committees .............................................................. 51
14.3.1. Trial Management Group (TMG) ........................................... 51
14.3.2. Trial Steering Committee (TSC) ............................................ 51
14.3.3. Independent Data Monitoring Committee (IDMC) ............... 51
14.3.4. Role of UCL CTC ............................................................... 52

15. Withdrawal of Patients ................................................................. 53
15.1. Reasons for withdrawing patients .............................................. 53
15.2. Future data collection .............................................................. 53
15.3. Future use of samples ............................................................. 54
15.4. Losses to follow-up ................................................................. 54

16. Trial Closure ................................................................................ 55
16.1. End of trial .............................................................................. 55
16.2. Archiving of trial documentation .............................................. 55
16.3. Early discontinuation of trial .................................................... 55
16.4. Withdrawal from trial participation by a site ................................ 55

17. Statistics ....................................................................................... 56
17.1. Sample size ............................................................................ 56
17.2. Statistical analyses ................................................................. 56
17.2.1. Primary analysis ................................................................. 56
17.2.2. Secondary analyses ............................................................ 57
17.2.3. Health economic analyses .................................................. 58
17.2.4. Quality of life sub-study ...................................................... 59
17.2.5. Sentinel node sub-study ...................................................... 60

18. Ethical Approvals ........................................................................... 61
18.1. Ethical approval ....................................................................... 61
18.2. Site approvals ......................................................................... 61
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.3. Protocol Amendments</td>
<td>62</td>
</tr>
<tr>
<td>18.4. Patient Confidentiality &amp; Data Protection</td>
<td>62</td>
</tr>
<tr>
<td>19. Sponsorship and Indemnity</td>
<td>63</td>
</tr>
<tr>
<td>19.1. Sponsor Details</td>
<td>63</td>
</tr>
<tr>
<td>19.2. Indemnity</td>
<td>63</td>
</tr>
<tr>
<td>20. Funding</td>
<td>64</td>
</tr>
<tr>
<td>21. Publication Policy</td>
<td>65</td>
</tr>
<tr>
<td>22. References</td>
<td>66</td>
</tr>
<tr>
<td>Appendix 1: Abbreviations</td>
<td>68</td>
</tr>
<tr>
<td>Appendix 2: Quality of Life Sub-Study</td>
<td>70</td>
</tr>
<tr>
<td>Appendix 3: Sentinel Lymph Node (SLN) Sub-Study</td>
<td>76</td>
</tr>
<tr>
<td>Appendix 4: Adjuvant Treatment Regimens</td>
<td>84</td>
</tr>
<tr>
<td>Appendix 5: Expected Surgical Adverse Events</td>
<td>85</td>
</tr>
<tr>
<td>Appendix 6: FIGO Staging for Endometrial Cancer, 2009</td>
<td>97</td>
</tr>
<tr>
<td>Appendix 7: FIGO Grading for Endometrial Cancer, 1988</td>
<td>98</td>
</tr>
<tr>
<td>Appendix 8: ECOG Performance Status</td>
<td>99</td>
</tr>
<tr>
<td>Appendix 9: Protocol Version History</td>
<td>100</td>
</tr>
</tbody>
</table>
1. PROTOCOL SUMMARY

1.1. Summary of Trial Design

| Title: | A randomised trial of non-selective versus selective adjuvant therapy in high risk apparent stage 1 endometrial cancer |
| Short Title/acronym: | STATEC |
| Sponsor name & reference: | University College London – UCL/13/0630 |
| Funder name & reference: | Cancer Research UK CRUK/14/043 |
| Clinicaltrials.gov no: | NCT02566811 |
| Design: | Randomised (1:1), controlled, two-arm, phase III, multicentre, international, non-inferiority trial |
| Overall aim: | To determine whether lymphadenectomy, used to restrict adjuvant therapy (other than vaginal brachytherapy) to node positive women, results in a non-inferior survival as compared to adjuvant therapy given to all women with high risk apparent stage I endometrial cancer |
| Primary endpoint: | Overall survival |
| Secondary endpoints: | Disease-free, endometrial cancer-event free and endometrial cancer-specific survival Pelvic and extra-pelvic relapse-free survival Cost effectiveness Surgical adverse events (acute and late) Quality of Life Performance of sentinel lymph node assessment |
| Target accrual: | 2000 (minimum 1720) |
| Inclusion & exclusion criteria: | Inclusion criteria  
- Histologically confirmed high risk apparent FIGO stage I endometrial cancer according to one of the following criteria. Confirmation must be based on either diagnostic endometrial sampling OR hysterectomy and BSO specimen if randomisation occurring after hysterectomy and BSO: |
FIGO grade 3 endometrioid or mucinous carcinoma
- High grade serous, clear cell, undifferentiated or dedifferentiated carcinoma or mixed cell adenocarcinoma or carcinosarcoma

- Surgery to be performed < 5 weeks after randomisation in patients randomised prior to hysterectomy and BSO. Patients randomised after hysterectomy and BSO must have undergone hysterectomy and BSO < 28 days prior to randomisation. Patients randomised after hysterectomy and BSO who are allocated lymphadenectomy must undergo lymphadenectomy < 5 weeks after randomisation
- Written informed consent
- No prior anticancer therapy for endometrial cancer
- ECOG performance status 0-2
- Life expectancy > 3 months
- Age ≥ 16 years
- Adequate organ and bone marrow function
- Ability to undergo post-operative chemotherapy with or without radiotherapy
- Adjuvant treatment to commence < 8 weeks after surgery
- Willingness and ability to complete Quality of Life questionnaires

Exclusion criteria
- Grossly enlarged node(s) of > 10 mm short axis on baseline radiological imaging
- Invasion of the cervical stroma on baseline radiological imaging or obvious cervical disease on clinical examination
- Involvement of uterine serosa or metastatic disease seen outside the uterus on baseline radiological imaging
- Small cell carcinoma with neuroendocrine differentiation
- Concurrent anti-cancer therapy
- Previous malignancy < 5 years prior to randomisation or concurrent malignant disease
- Women who are pregnant or lactating

Planned number of sites: 30-40 sites
<table>
<thead>
<tr>
<th><strong>Expected countries:</strong></th>
<th>UK, Netherlands, Australia, New Zealand, South Korea</th>
</tr>
</thead>
</table>
| **Treatment summary:**  | Patients will be randomised to one of the following two arms, either prior to surgery or following hysterectomy and bilateral salpingo-oophorectomy (BSO):  

Arm 1: Randomised treatment will be hysterectomy and BSO, plus intraoperative bilateral pelvic and para-aortic lymph node dissection. Patients randomised after hysterectomy and BSO will receive bilateral pelvic and para-aortic lymph node dissection as a separate operation. Adjuvant treatment will then be determined by lymph node status. Node positive patients will receive systemic adjuvant treatment to include chemotherapy +/- pelvic external beam radiotherapy, while node negative patients will receive vaginal brachytherapy only (see Appendix 4 and Adjuvant Treatment Guidance Document)  

Arm 2: Randomised treatment will be a hysterectomy and BSO without lymph node dissection. Patients randomised after hysterectomy and BSO will receive no further surgery. Patients will then receive systemic adjuvant treatment to include chemotherapy +/- pelvic external beam radiotherapy (see Appendix 4 and Adjuvant Treatment Guidance Document) |
| **Anticipated duration of recruitment:** | 4 years |
| **Duration of patient follow up:** | 5 years:  
- 3 monthly in Year 1  
- 4 monthly in Year 2  
- 6 monthly in Year 3  
- Annually in Years 4 and 5 |
| **Definition of end of trial:** | When the last patient alive has been followed up for 5 years |
| **Translational Research:** | Patients who consent to participate in the main trial will have the option to donate the following for the purposes of future molecular and biomarker research into endometrial cancer:

- The tissue sample from their surgical resection to be used in future research;
- A baseline blood sample;
- A randomly selected 10% of UK patients will be subject to central pathology QA – see Quality Assurance (QA)

An international consortium with participating experts representing the collaborating international trial groups will agree the programme of translational work, focusing on molecular and biomarker studies. All translational research will be subject to separate grant and ethics applications |
| **Other related research:** | Quality of Life (QOL) sub-study (all sites) according to the listed trial objectives and endpoints (please refer to sections 3.1, 3.2 and Appendix 2)

**Sentinel lymph node (SLN) sub-study (open to sites who wish to participate):**
Prior to randomisation, patients will be able to opt into a sub-study focusing on sentinel lymph node dissection. If randomised to the lymphadenectomy arm, and as part of bilateral pelvic and para-aortic lymph node dissection, additional review will be performed on sentinel lymph nodes in order to consider whether sentinel lymph node dissection is as effective as full lymph node dissection in detecting cancer spread |
| **Quality Assurance (QA):** | There are 3 components to the STATEC QA programme outlined within the protocol as follows. Please refer to the STATEC QA Manual for full details:

- Surgical Specimen Processing and Microscopy, providing guidance to local specialist gynaecological oncology site pathologists in the assessment of resected hysterectomy and BSO +/- lymphadenectomy/sentinel lymph node specimens as part of routine site pathological review |
- Central Pathology QA of a randomly selected 10% of surgical resections from UK patients – also see Translational Research
- Surgical Imaging QA of all Arm 1 patients i.e. the lymphadenectomy arm. Local surgical teams will be required to obtain photographic images of the surgical site after lymph node dissection. A Surgical Imaging QA sub-group of the TMG will review these images and provide site feedback
1.2. Trial Scheme

Histologically confirmed high risk apparent FIGO stage I endometrial cancer based on diagnostic endometrial sampling OR hysterectomy and BSO specimen if randomisation occurring after hysterectomy and BSO:
- FIGO grade 3 endometrioid or mucinous
- High grade serous, clear cell, undifferentiated or dedifferentiated carcinoma or mixed cell adenocarcinoma or carcinosarcoma

RANDOMISE

Sentinel node sub-study

ARM 1: Hysterectomy and BSO* + lymphadenectomy

ARM 2: Hysterectomy and BSO* with no lymphadenectomy

Lymph node negative ~ 80%

Vaginal brachytherapy only

Lymph node positive ~ 20%

Systemic adjuvant treatment to include chemotherapy +/- pelvic external beam radiotherapy

Lymph nodes unknown

Follow-up, adverse events and quality of life 5 years

*Lymphadenectomy alone if randomisation occurs after hysterectomy and BSO

+No further surgery if randomisation occurs after hysterectomy and BSO
2. INTRODUCTION

2.1. Background

Endometrial cancer is the most common gynaecological cancer and the fourth most common cancer in women: its incidence has risen 40% since the 1990’s. The annual incidence in the European Union is 88,068 and 287,000 worldwide (1). Survival is 77.6% for high risk patients and approximately 50% if lymph glands are involved (2).

In apparent stage I cancer, where the tumour appears to be confined to the uterus, the initial management is surgical removal of the uterus, tubes and ovaries. Most of those patients will have a favourable prognosis with 5-year survival rates exceeding 85%. However, some of the patients will relapse and eventually die of their disease.

Traditionally, cases were regarded as high-risk for metastases based on the following risk factors: aggressive histological subtype (such as endometrioid histology grade 3, serous, clear cell or carcinosarcoma), deep invasion into the muscle layer of the uterus, (myometrial invasion ≥50%) or lymphovascular space invasion (LVSI). These women have a less favourable prognosis with 5-year survival rate of 77% (3). Approximately 25% of all new cases can be categorised as high-risk. Prevalence of metastases to the lymph nodes in this population is 15-20%. Lymphadenectomy has been suggested as a procedure to guide treatment for these women.

Several retrospective studies have reported a beneficial effect of lymphadenectomy on survival. Additionally, the extent of the procedure has been reported to be of significance as extensive lymph node sampling has also been shown to give superior survival when compared to the removal of fewer lymph nodes (4-11).

Two randomised trials have studied the influence of lymphadenectomy on survival and concluded that there was no survival benefit to lymphadenectomy. The ASTEC trial randomised 1408 patients to standard surgery with or without pelvic lymphadenectomy. After surgery patients who were eligible for adjuvant radiotherapy were further randomised to receive radiotherapy independent of lymph node status (12). The Benedetti-Panici trial included 514 patients who were randomised to pelvic lymphadenectomy or not. Para-aortic lymphadenectomy was performed at the discretion of the surgeon and was done in 26% in the lymphadenectomy arm and in 2% of the non-lymphadenectomy arm. Adjuvant treatment after surgery was not mandated in the protocol, but was performed at the discretion of the physician (13). A meta-analysis of those trials showed no difference in risk of death or disease recurrence between the treatment arms (14). Women treated with lymphadenectomy had a significantly higher risk of surgery-related morbidity. Most of the differences in morbidity were due to lymphocysts and lymphedema. Both trials also reported lymphadenectomy to be associated with an increased operating time, post-operative ileus, deep venous thrombosis, wound...
dehiscence and increased length of hospital stay. The authors of these two studies concluded that systematic pelvic lymphadenectomy could not be recommended as a routine procedure in this group of women outside a clinical trial.

But both trials suffer from several limitations.

- Neither of the two studies included high-risk patients only. Lymphadenectomy, like pelvic radiotherapy, may not be beneficial for most women with endometrial cancer given their overall good prognosis. Any additional surgery would benefit only a minority of the women to the detriment of the majority who would be cured by hysterectomy and bilateral salpingo-oophorectomy (BSO) alone. It is therefore crucial that any trial assessing the role of lymphadenectomy carefully selects patients with a sufficiently high risk for lymph node metastasis and recurrent disease.

- The extent of lymphadenectomy varied significantly between the two trials. The Italian trial considered pelvic lymphadenectomy to be appropriate only if 20 or more lymph nodes were removed. A considerable proportion of patients also underwent para-aortic lymphadenectomy. The ASTEC trial included pelvic lymphadenectomy only (12) and the median number of nodes removed in the lymphadenectomy arm was only 10, with 35% of the patients having 9 or less nodes removed. Thus the extent of the procedure may not have been sufficient to improve outcome.

- The studies also differed with respect to adjuvant therapy. In the ASTEC trial, post-surgical high-risk women who were eligible for adjuvant radiotherapy were further randomised to radiotherapy independently of lymph node status. This resulted in identical proportions receiving adjuvant radiotherapy between the lymphadenectomy and no lymphadenectomy arm. In the Italian study, a higher proportion of women in the lymphadenectomy arm received chemotherapy.

- Quality of Life (QOL) for women following treatment is an extremely important outcome, as treatment related morbidity very often impairs the quality of life for patients who survive their cancer. This is especially important in this group of patients who otherwise have relatively good survival rates. QOL was not sufficiently addressed in the above trials as highlighted by the Cochrane review (14). They only reported the increased incidence of post-operative complications, mainly due to lymphoedema in the lymphadenectomy group. The clinical validity of patient-reported lymphoedema measures has been demonstrated, with a prevalence of self-reported lymphoedema around 50% among endometrial cancer patients after lymphadenectomy (15-17). Similarly, presence of lymphoedema is linked to poor patient-reported outcomes (PROs) and increased medical costs (16).

Due to the limitations of these trials, there remains uncertainty regarding the benefit of lymphadenectomy. A meta-analysis including retrospective trials and the randomised studies above concluded that systematic lymphadenectomy improved survival in patients with higher risk cancer (18). The latest Cochrane review re-emphasised the lack of evidence to support lymphadenectomy, even
in women with higher risk of recurrence (19). Unsurprisingly, the practice of lymphadenectomy varies across Europe, Australia, the USA and other countries. The main explanation for the continued practice is not that lymphadenectomy by itself may improve prognosis by removal of involved nodes, but that lymph node status is used to tailor adjuvant treatment by determining which women need adjuvant treatment and those in whom it could be avoided.

Furthermore, despite the probably detrimental effects of lymphadenectomy on QOL, comprehensive surgical staging of endometrial cancer patients as a result of lymphadenectomy may offer benefits in PROs compared to giving all high-risk women chemotherapy with or without radiation. All treatment modalities have specific short and long-term side effects known to affect QOL (20). Radiation is more commonly associated with vaginal, urological and gastrointestinal toxicity, while chemotherapy may cause haematological and gastrointestinal side effects, fatigue and neuropathy. The impact of short and long term toxicity of both vaginal brachytherapy and external beam radiation treatment on PROs has been extensively studied in the PORTEC trials (21-23). Short-term assessments of PROs after sequential chemoradiation have also been reported (24), but only in a non-randomised study, while the results from current randomised clinical trials (i.e. GOG0258) are still pending.

This study is not designed to test which adjuvant therapy is the most efficacious but rather to test if lymphadenectomy can effectively tailor which patients require adjuvant therapy. Adjuvant therapy is being studied at present in the PORTEC-3, GOG#249 and GOG#258 trials. These studies explore the roles of concurrent chemoradiation and/or adjuvant chemotherapy compared to chemotherapy or radiation alone, on the basis that trials comparing combined radiation and chemotherapy have shown improved progression-free survival compared to radiation alone (25). These trials will resolve many of the uncertainties regarding adjuvant therapies, and guide STATEC trial sites as to the appropriate adjuvant therapy to use. Thus the adjuvant treatment used may change as the trial progresses.

In summary, there is an impasse in the debate between continuing with staging lymphadenectomy, versus the use of uterine pathology prognostic factors to select adjuvant therapy, with an increasing trend toward the indiscriminate use of adjuvant chemotherapy. Although only improved control of distant disease will enhance survival, adjuvant chemotherapy should be considered only for women at high risk of disease relapse after surgery. This will inevitably be associated with more toxicity and therefore optimal selection for adjuvant therapy is essential. It would benefit the patient if adjuvant treatment were given only to those at truly high risk for distant disease and relapse.
3. **TRIAL DESIGN**

This is a randomised (1:1), controlled, two-arm, phase III, multicentre, international, non-inferiority trial.

STATEC is a surgical trial designed to evaluate the use of nodal status after lymph node dissection to tailor adjuvant treatment in patients with high risk apparent stage I endometrial cancer.

Patients will be randomised to one of the following two arms, either prior to surgery or following hysterectomy and bilateral salpingo-oophorectomy (BSO). Hysterectomy is defined as an extrafascial hysterectomy whereby the cervix is removed completely but no radical dissection of the parametria is required (26).

Arm 1: Randomised treatment will be hysterectomy and BSO, plus intraoperative bilateral pelvic and para-aortic lymph node dissection. Patients randomised after hysterectomy and BSO will receive bilateral pelvic and para-aortic lymph node dissection as a separate operation. Adjuvant treatment will then be determined by lymph node status. Node positive patients will receive systemic adjuvant treatment to include chemotherapy +/- pelvic external beam radiotherapy, while node negative patients will receive vaginal brachytherapy only (see Appendix 4 and Adjuvant Treatment Guidance Document).

Arm 2: Randomised treatment will be a hysterectomy and BSO without lymph node dissection. Patients randomised after hysterectomy and BSO will receive no further surgery. Patients will then receive systemic adjuvant treatment to include chemotherapy +/- pelvic external beam radiotherapy (see Appendix 4 and Adjuvant Treatment Guidance Document).

3.1. **Trial Objectives**

**Primary Objective**

To determine whether lymphadenectomy, used to restrict adjuvant therapy (other than vaginal brachytherapy) to node positive women, results in a non-inferior survival as compared to adjuvant therapy given to all women with high risk apparent stage I endometrial cancer.

Results from this trial have the potential to change practice whatever the results: either lymphadenectomy will become recommended practice if a non-inferior outcome is obtained; otherwise the procedure can be safely abandoned.

**Secondary Objectives**

- Disease-free, endometrial cancer-event free and endometrial cancer-specific survival
- Distribution of pelvic and extra-pelvic relapse
- Cost effectiveness
- Surgical adverse events
There are also two sub-studies (outlined in Appendices 2 and 3):

1. Quality of life – all patients
   i. Describe the trajectory of key patient reported outcomes (PROs) from baseline up to 5 years post-surgery
   ii. Compare the specific PRO domains between the trial arms at several specific time points
   iii. Determine the proportion of women in each trial arm reporting long-term symptoms after treatment as measured by the symptom-specific subscales of the measures (gastrointestinal symptoms, urological symptoms, attitude to disease and treatment, vaginal symptoms, lymphoedema)
   iv. Determine the correlation between physician rating (CTCAE v4.03) and patient-report (corresponding PRO subscale) for various symptoms reported by both physicians and patients
   v. Assess the correlation between self-assessed lymphoedema (Self-report lower-extremity lymphoedema screening questionnaire) and the lymphoedema subscale of the QLQ-EN24

   We hypothesise that quality of life will be better in patients in the lymphadenectomy arm because a considerable proportion will be spared systemic adjuvant treatment, from which they may not benefit.

2. Sentinel lymph node (SLN) – optional for Arm 1 patients

   The aim of this sub-study is to assess SLN status in comparison with the overall lymph node status after full lymph node dissection (LND), and so determine whether SLN is as accurate as systematic node dissection.

   i. We aim to determine the diagnostic performance of the SLN procedure compared to the gold standard of LND
   ii. To evaluate whether SLN status is a prognostic marker of survival
   iii. To model patient relapse and survival based on low volume micrometastatic (LVM) and individual tumour cell (ITC) status

3.2. Trial Endpoints

Primary Endpoint
Overall survival measured from the date of randomisation until the date of death from any cause

Secondary Endpoints
- Disease-free survival measured from the date of randomisation until date of first recurrence, a new secondary tumour or death from any cause, whichever occurs first
- Endometrial cancer-event free survival measured from the date of randomisation until recurrence or death from endometrial cancer, or treatment related deaths, whichever occurs first
• Endometrial cancer-specific survival measured from the date of randomisation until death from endometrial cancer, or treatment-related deaths
• Pelvic and extra-pelvic relapse-free survival as assessed by radiological imaging at time of relapse with documentation of site/s of relapse
• Cost effectiveness using the EQ-5D-5L for economic evaluation
• Surgical adverse events (acute and late) as assessed by the Common Terminology Criteria for Adverse Events v4.03

Key endpoints in the two sub-studies
• Patient reported Quality of Life as measured using validated questionnaires (i) EORTC QLQ-C30 and the endometrial cancer module QLQ-EN24 (ii) additional items from other EORTC cancer modules: QLQ-OV28 (items 52-54), QLQ-CX24 (items 41, 43, 44), QLQ- PR25 (items 39-40) and (iii) Self-report lower-extremity lymphoedema screening questionnaire.
• Accuracy, sensitivity and specificity (i.e. diagnostic performance) of SLN, and the ratio of sensitivity to false positive rate (called likelihood ratio).

3.3. Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial. International sites should refer to their group specific appendix:

• Health Research Authority (HRA) approval, including Research Ethics Committee approval
• ‘Adoption’ into NIHR portfolio
• Adequate funding for central coordination
• Confirmation of sponsorship
• Adequate insurance provision
• ARSAC approval prior to submission of individual applications by participating sites
4. SELECTION OF SITES/SITE INVESTIGATORS

4.1. Site Selection

In this protocol trial ‘site’ refers to a hospital where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatment, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the Research Governance Framework, and all amendments
- Data collection requirements, including adherence to eCRF data entry timelines as per section 11.4
- Biological sample collection, processing and storage requirements
- Monitoring requirements, as outlined in protocol section 14 (Error! Reference source not found.) and trial monitoring plan
- ARSAC licensing accreditation
- Non-UK sites: all local regulations governing clinical trials

4.1.1. Selection of Principal Investigator and other investigators at sites

Sites must have an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site and/or ethics committee, to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. All investigators must be gynaecological oncology multi-disciplinary team members.

4.1.2. Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). An up-to-date, signed copy of the CV for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.
4.2. Site initiation and Activation

4.2.1. Site initiation
Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will either be performed for each site by teleconference, or for at least one site as part of a pre-planned trial launch meeting.

4.2.2. Required documentation
The following documentation must be submitted by the site to UCL CTC prior to a site being activated by the UCL CTC trial team:

- Trial specific UK Site Registration Form (identifying relevant local staff)
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- Completed site contacts form (with contact information for all members of local staff)
- A signed and dated copy of the PI’s current CV (with documented up-to-date GCP training, or copy of GCP training certificate)

In addition, the following agreements must be in place:

- For UK sites: a signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually an NHS Trust/Health Board)
- For non-UK sites: a signed International Clinical Trials Site Agreement (ICTSA).
- For countries with a country coordinating centre (CCC):
  - a signed International Country Coordinating Centre Agreement
  - a signed clinical trial agreement between the CCC and the relevant institution

4.2.3. Site activation letter
Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Following site activation, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol;
- all relevant site staff are trained in the protocol requirements;
- appropriate recruitment and medical care of patients in the trial;
- timely completion of eCRF (including assessment of all adverse events);
- prompt notification and assessment of all serious adverse events;
• that the site has facilities to provide **24 hour medical advice** for trial patients.
5. **INFORMED CONSENT**

Sites are responsible for assessing a patient’s capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet(s), are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form(s).

Sites must assess a patient’s ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheet(s) for the trial should be discussed with the patient. A **minimum of twenty four (24) hours should be allowed for the patient to consider and discuss participation in the trial.** Written informed consent on the current approved version of the consent form(s) for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Site staff are responsible for:

- checking that the current approved version(s) of the patient information sheet(s) and consent form(s) are used;
- checking that information on the consent form(s) are complete and legible;
- checking that the patient has initialled all relevant sections and signed and dated the form;
- checking that an appropriate member of staff has countersigned and dated the consent form(s) to confirm that they provided information to the patient;
- checking that an appropriate member of staff has made dated entries in the patient’s medical notes relating to the informed consent process (i.e. information given, consent signed etc.);
- following randomisation, adding the patient’s trial number to all copies of the consent form(s), which should be filed in the patient’s medical notes and investigator site file, and, for UK patients only, sending a copy to UCL CTC. Please note that, for this trial, UK patients have consented to their names being supplied to UCL CTC. This is to confirm the patient’s consent to participate in the sentinel lymph node (SLN) sub-study and/or translational research (including central pathological QA);
- following randomisation, giving the patient a copy of their signed consent form(s), patient information sheet(s) and patient contact card.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 15 (Withdrawal of Patients).
Non-UK Sites will need to consent patients to the trial according to local practice and regulatory and/or ethical requirements.
6. SELECTION OF PATIENTS

6.1. Pre-randomisation Evaluation

Patients must give written informed consent before any trial specific screening investigations may be carried out. The following assessments or procedures are required to evaluate the suitability of patients for the trial. A summary of the screening procedures are shown in Table 1 overleaf. For ease of reference, two groups are defined within each trial arm as follows:

Group 1A: Randomised to Arm 1 prior to hysterectomy and BSO
Group 1B: Randomised to Arm 1 after hysterectomy and BSO
Group 2A: Randomised to Arm 2 prior to hysterectomy and BSO
Group 2B: Randomised to Arm 2 after hysterectomy and BSO

Prior to any screening procedure:

- Signed written informed consent
- In patients who have not had surgery, review of diagnostic histological specimen by endometrial sampling. Review must be undertaken by a specialist gynaecological oncology pathologist according to the recruiting site’s routine practice. Non-UK sites may have additional requirements according to their country’s group specific appendix.

< 28 days prior to randomisation

- Review inclusion and exclusion criteria
- In patients who have undergone hysterectomy and BSO, this surgery must have been performed < 28 days prior to randomisation.
- In patients who have undergone hysterectomy and BSO, review of hysterectomy and BSO specimen. Review must be undertaken by a specialist gynaecological oncology pathologist according to the recruiting site’s routine practice. Non-UK sites may have additional requirements according to their country’s group specific appendix.
- Medical, surgical and obstetrical history
- Physical examination including vaginal examination
- ECOG performance status (see Appendix 8)
- Height and weight
- Adverse events according to CTCAE v4.03
- MRI abdomen pelvis or CT abdomen pelvis. If randomisation occurs after hysterectomy and BSO, imaging must be < 28 days prior to this surgery
- Chest CT or chest X-ray. If randomisation occurs after hysterectomy and BSO, imaging must be < 28 days prior to this surgery
- Transvaginal ultrasound (optional). If randomisation occurs after hysterectomy and BSO, imaging must be < 28 days prior to this surgery
• Pregnancy test (serum or urine) for women of childbearing potential randomised prior to surgery (Groups 1A and 2A), to be repeated on day of hysterectomy and BSO
• Full blood count – absolute neutrophil count, haemoglobin, platelets
• Biochemistry – serum urea, serum creatinine, creatinine clearance (GFR, estimated using a validated creatinine clearance calculation e.g. Cockcroft-Gault or Wright formula), bilirubin, AST or ALT
• Quality of Life questionnaires (EORTC QLQ-C30, EORTC QLQ-EN24), QLQ-OV28 (items 52-54), QLQ-CX24 (items 41, 43, 44), QLQ-PR25 (items 39-40), Self-report lower-extremity lymphoedema screening questionnaire
• Health Economics questionnaire (EQ-5D-5L)
• Optional 7 ml blood sample for translational research (see section 10, Translational Research)
### Table 1 Pre-randomisation Assessments

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Prior to any study procedure</th>
<th>≤ 28 days prior to randomisation</th>
<th>Day of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written informed consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FOR REVIEW BY SPECIALIST GYNAECOLOGICAL ONCOLOGY PATHOLOGIST AS PER ROUTINE PRACTICE AT RECRUITING SITE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients who have not had surgery, review of diagnostic histological specimen by endometrial sampling</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FOR REVIEW BY SPECIALIST GYNAECOLOGICAL ONCOLOGY PATHOLOGIST AS PER ROUTINE PRACTICE AT RECRUITING SITE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients who have undergone hysterectomy and BSO, review of hysterectomy and BSO specimen This surgery must have been performed ≤ 28 days prior to randomisation</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Assessment of medical, surgical and obstetrical history</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination, to include vaginal examination</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG performance status (see Appendix 8)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height and weight</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events (CTCAE v4.03)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT abdomen pelvis OR MRI abdomen pelvis. If randomisation occurring after hysterectomy and BSO, imaging must be ≤ 28 days prior to this surgery</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest CT OR Chest X-ray. If randomisation occurring after hysterectomy and BSO, imaging must be ≤ 28 days prior to this surgery</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transvaginal ultrasound (optional) If randomisation occurring after hysterectomy and BSO, imaging must be ≤ 28 days prior to this surgery</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test (serum or urine) for women of childbearing potential randomised prior to surgery (Groups 1A and 2A) to repeated on day of hysterectomy and BSO</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Haematology: ANC, Hb, Plts</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemistry: serum urea, serum creatinine, creatinine clearance (GFR), bilirubin, AST or ALT</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life questionnaires:</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-EN24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-OV28 (items 52-54)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-CX24 (items 41, 43, 44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-PR25 (items 39-40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-report lower-extremity lymphoedema screening questionnaire</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Economics questionnaire (EQ-5D-5L)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optional 7 ml blood sample for translational research</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.2. Screening Log

A screening log must be maintained by the site and kept in the Investigator Site File. This must record each patient screened for the trial, and the reasons if not randomised. The log must be sent to UCL CTC when requested, with patient identifiers removed prior to sending where applicable.

6.3. Patient Eligibility

There will be no exception to the eligibility requirements at the time of randomisation. Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Queries in relation to the eligibility criteria must be addressed prior to patient randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria apply. The CI and TMG must review criteria carefully to ensure they are appropriate.

6.3.1. Inclusion criteria

- Histologically confirmed high risk apparent FIGO stage I (see Appendix 6) endometrial cancer according to one of the following criteria. Confirmation must be based on either diagnostic endometrial sampling OR hysterectomy and BSO specimen if randomisation occurring after hysterectomy and BSO:
  - FIGO grade 3 (see Appendix 7) endometrioid or mucinous carcinoma
  - High grade serous, clear cell, undifferentiated or dedifferentiated carcinoma or mixed cell adenocarcinoma or carcinosarcoma
- Surgery to be performed ≤ 5 weeks after randomisation in patients randomised prior to hysterectomy and BSO. Patients randomised after hysterectomy and BSO must have undergone hysterectomy and BSO ≤ 28 days prior to randomisation. Patients randomised after hysterectomy and BSO who are allocated lymphadenectomy must undergo lymphadenectomy ≤ 5 weeks after randomisation
- Written informed consent
- No prior anticancer therapy for endometrial cancer
- ECOG performance status 0-2 (see Appendix 8)
- Life expectancy > 3 months
- Age ≥ 16 years
- Adequate organ and bone marrow function as follows:
  - Absolute neutrophil count ≥ 1.5 x 10⁹/l
  - Platelet count ≥ 100 x 10⁹/l
  - Haemoglobin ≥ 95 g/L
  - Bilirubin ≤ 2 x upper limit of normal
  - AST or ALT ≤ 2 x upper limit of normal
  - Serum creatinine ≤ 1.5 x upper limit of normal
  - Serum urea ≤ 1.5 x upper limit of normal
- Calculated creatinine clearance (GFR) ≥ 30 ml/min estimated using a validated creatinine clearance calculation e.g. Cockcroft-Gault or Wright formula
- Ability to undergo post-operative chemotherapy with or without radiotherapy
- Adjuvant treatment to commence ≤ 8 weeks after surgery
- Willingness and ability to complete Quality of Life questionnaires

6.3.2. Exclusion criteria
- Grossly enlarged node(s) of ≥ 10mm short axis on baseline radiological imaging
- Invasion of the cervical stroma on baseline radiological imaging or obvious cervical disease on clinical examination
- Involvement of uterine serosa or metastatic disease seen outside the uterus on baseline radiological imaging
- Small cell carcinoma with neuroendocrine differentiation
- Concurrent anti-cancer therapy
- Previous malignancy < 5 years prior to randomisation or concurrent malignant disease with the exception of:
  - carcinoma in situ of cervix
  - non-melanoma skin cancer
  - basal cell carcinoma
  - melanoma in situ
- Women who are pregnant or lactating
7. RANDOMISATION PROCEDURES

STATEC is a randomised (1:1), controlled, two-arm, phase III, multicentre, international, non-inferiority trial. Patients will be randomised in a 1:1 ratio according to the following stratification factors:

- participating site (and hence their choice of adjuvant therapy)
- histology:
  - FIGO grade 3 endometrioid carcinoma, FIGO grade 3 mucinous carcinoma;
  - high grade serous carcinoma, carcinosarcoma;
  - undifferentiated carcinoma, dedifferentiated carcinoma, mixed cell adenocarcinoma;
  - clear cell carcinoma.
- lymphovascular space invasion (presence; absence; suspicious; not known)
- timing of hysterectomy and BSO (pre-randomisation; post-randomisation)

7.1. Randomisation

Patient randomisation will be performed by authorised site staff via an online randomisation program hosted by UCL CTC. This program is separate to the eCRF database which will be used for remote entry of data at participating sites (see also section 11, Data Management and Data Handling Guidelines). Patients must be confirmed as eligible and have given consent prior to randomisation. Following pre-randomisation evaluations (section 6.1), confirmation of eligibility and consent of a patient at site, the randomisation should be completed using the online randomisation program. Randomisation must take place prior to commencement of any trial treatment. Site staff delegated as responsible for patient randomisation must register for access to the online randomisation program. Details and instructions will be provided by UCL CTC.

Please note that patient initials and date of birth are required to randomise a patient, unless data protection legislation in the randomising country does not allow this. Non-UK sites should refer to their group specific appendix for additional instructions.

Upon successful randomisation a unique trial number will be assigned to the patient, and confirmation of randomisation will appear on the online randomisation program. The trial number must be recorded in the patient notes. Email confirmation of successful randomisation will automatically be sent to the member of site staff who performed the randomisation.

Sites should contact UCL CTC if there are any difficulties in accessing the online randomisation program.
Once a patient has been randomised onto the trial they must be provided with the following:

- A copy of their signed consent form(s) and patient information sheet(s);
- A patient contact card. Site on-call contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial.

Non-UK sites should refer to their group specific appendix for additional instructions.
8. TRIAL TREATMENT

8.1. Treatment Summary

Please refer to sections 1.1, 1.2 and 3.

8.2. Trial Treatment Details

8.2.1. Surgery

For ease of reference, two groups are defined within each trial arm as follows:

- Group 1A: Randomised to Arm 1 prior to hysterectomy and BSO
- Group 1B: Randomised to Arm 1 after hysterectomy and BSO
- Group 2A: Randomised to Arm 2 prior to hysterectomy and BSO
- Group 2B: Randomised to Arm 2 after hysterectomy and BSO

Randomisation prior to surgery: patients meeting the eligibility criteria will be randomised prior to hysterectomy and BSO to undergo one of the following ≤ 5 weeks after randomisation, with hysterectomy defined as an extrafascial hysterectomy whereby the cervix is removed completely but no radical dissection of the parametria is required (26):

- Group 1A - hysterectomy and bilateral salpingo-oophorectomy (BSO) with bilateral pelvic and para aortic node dissection
- Group 2A – hysterectomy and BSO without lymph node dissection

Randomisation after hysterectomy and BSO: patients meeting the eligibility criteria can be also randomised ≤ 28 days after hysterectomy and BSO to undergo one of the following:

- Group 1B - bilateral pelvic and para- aortic node dissection to be performed ≤ 5 weeks after randomisation;
- Group 2B - no further surgical treatment.

All surgery performed on the trial is to be undertaken and/or supervised by an appropriately trained and delegated gynaecological oncology surgeon.

Patients randomised prior to surgery who then do not undergo hysterectomy and BSO +/- lymphadenectomy (Group 1A and Group 2A), for whatever reason, are to be replaced in the accrual. Key data will still be collected on them: relapse, survival, date last seen alive, and any treatment/s given after the decision not to proceed with surgery (see also section 15, Withdrawal of Patients).
8.2.2. Hysterectomy and BSO

Hysterectomy and BSO may be performed abdominally, laparoscopically, robotically or vaginally.

Hysterectomy is defined as extraperitoneal hysterectomy involving removal of the uterus with cervix without adjacent parametria. The uterine arteries are transected medial to the ureters at the level of the isthmus and the uterosacral ligaments are transected at the level of the cervix. Surgeons should pay special attention to make sure that the whole cervix is removed.

8.2.3. Lymphadenectomy – Arm 1 only

To be performed intraoperatively as part of hysterectomy and BSO.

A complete pelvic node and para aortic node dissection is considered protocol therapy. All the nodes will be submitted to a specialist gynaecological oncology pathologist according to the recruiting site's routine practice for pathological review as per the QA Manual.

Pelvic

This procedure can be performed by open or laparoscopic or robotic technique. Bilateral skeletonisation is to be performed with removal of all lymph node tissue from lower half of common iliac vessels, external iliac vessels, internal iliac vessels and the obturator fossa.

Anatomic boundaries of pelvic lymphadenectomy are:

- Superior border – mid common iliac vessels
- Inferior border – circumflex iliac vein
- Lateral border – psoas muscle
- Medial border – internal iliac artery
- Deep border – fascia of lateral pelvic side wall, and obturator nerve

Para aortic

This procedure can be performed by open or laparoscopic or robotic technique.

The right sided para-aortic lymphadenectomy will involve removal of all lymph node tissue anterior to the inferior vena cava including pre-sacral tissue, and between the vena cava and aorta, from the upper half of the common iliac artery distally to at least the level of the inferior mesenteric artery proximally. Dissection to the level of the left renal vein is ideal but not mandatory.

The left sided para-aortic lymphadenectomy will involve removal of all lymph node tissue between the aorta and left ureter from the upper half of the left common iliac artery to at least the level of the inferior mesenteric artery proximally. Dissection to the level of the left renal vein is ideal but not mandatory.
Anatomic boundaries of para-aortic lymphadenectomy are:

**Left para aortic**
- Superior border – Left renal vein preferred, or inferior mesenteric artery
- Inferior border – mid common iliac vessels
- Lateral border – left gonadal vein
- Medial border – left border of aorta
- Deep border – fascia of psoas

**Right para aortic**
- Superior border – level of left renal vein* or inferior mesenteric artery
- Inferior border – mid common iliac vessels and sacrum
- Lateral border – right gonadal vein, right ureter, psoas
- Medial border – right border of aorta
- Deep border – IVC, fascia between IVC and aorta

* Aorto caval dissection stops where the left renal vein crosses the space between the IVC and the aorta. Removal of tissue on, or the right of the IVC stops at the level where the left renal vein arises.

**Omentectomy**
Omental biopsy or omentectomy can be performed at the surgeon’s discretion.

**8.2.4. Sentinel lymph node (SLN) sub-study – Arm 1 only**
**i.e. lymphadenectomy arm**

All participating sites are invited to take part in the SLN sub-study, and must indicate this as part of setup prior to activation to recruitment. The site investigator must identify whether a patient is suitable for sentinel node as part of screening i.e. prior to approaching them for written informed consent. Entry into the sub-study is covered by the written informed consent process for the main trial.

If a patient has been recruited to the sentinel node sub-study, the sentinel nodes should be removed according to Appendix 3. After sentinel node identification and removal, full bilateral pelvic and para-aortic lymphadenectomy should be completed as per protocol treatment.

**8.2.5. Positive lymph nodes – Arm 1 only i.e. lymphadenectomy arm**
The sentinel nodes will undergo two levels of histological assessment.

The first level with be standard H&E and is the same assessment as the rest of the lymphadenectomy specimen. Any lymph node with metastatic disease on routine H&E stained section, whether sentinel or otherwise, will represent a positive lymph node result. These patients will proceed to systemic adjuvant treatment, to include chemotherapy +/- pelvic external beam radiotherapy. This includes any size of disease seen on routine H&E stained section.
The second level is ultrasection with a) further H&E and b) immunohistochemistry (IHC). This will not be standard for all the lymph glands. This means that patients in the sentinel lymph node (SLN) sub-study will have a different level of analysis of some lymph nodes, than those women not enrolled in the SLN study. In view of this, the ultrasection results will be regarded as research information, and will not be used in patient management. Women with disease on ultrasection node assessment only will not be regarded as a positive lymph node result, and will not proceed to systemic adjuvant treatment (to include chemotherapy +/- pelvic external beam radiotherapy) on the basis of this alone.

In summary, if the SLN is the only positive node after total node analysis following full lymphadenectomy, only the presence of metastases visible on routine H&E examination will be used to direct post-operative adjuvant therapy according to the STATEC protocol.

8.2.6. Pathological and Surgical Quality Assurance (QA)
There are three separate components to the STATEC trial QA as follows:

**Surgical Specimen Processing and Microscopy**

There are two sub-sections:

1. *Post hysterectomy and BSO – all patients*

Surgical specimens will be reviewed by a specialist gynaecological oncology pathologist according to the site’s routine practice. Please see the QA manual for detailed guidance on handling the hysterectomy and BSO +/- lymphadenectomy specimens. Non-UK sites may have additional requirements according to their country’s group specific appendix.

2. *Pathological analysis of lymph nodes – Arm 1 only i.e. lymphadenectomy arm*

Lymph node specimens will be submitted by anatomical region to the specialist gynaecological oncology pathologist for pathological review. Sites will be given guidance regarding the preferred method of pathological analysis (see QA manual).

**Central Pathological QA – UK only**

In the UK only there will be retrospective central pathological QA review of a randomly selected 10% of patients – also see section 10 (Translational Research). This QA will be performed by a central pathology specialist. Sites will be required to provide stained slides and unstained formalin-fixed paraffin-embedded blocks. Further details will be provided at a later date.
**Surgical Imaging QA – Arm 1 only i.e. lymphadenectomy arm**

This will be supervised by a Surgical Imaging QA sub-group within the Trial Management Group. QA methodology will entail scrutinising photographic images of the final appearance of the surgical site after removal of the lymph nodes from all patients randomised to this arm of the trial. The Surgical Imaging QA sub-group will include three gynaecological oncology surgeons, and one surgeon will review the images from each operation. If the surgeon requires a second opinion in order to complete their review, the images will be reviewed by a second member of the Surgical Imaging QA sub-group. Feedback will be communicated to the relevant site in the form of a score +/- comments, and sent to the PI via the Surgical Imaging QA trial online database.

All QA reviews will be done without knowledge of patient outcomes. Surgical Imaging QA scores may be used in an exploratory sub-group analysis to determine whether adequacy of surgery has an effect on overall survival in patients randomised to the lymphadenectomy arm.

For full details, please refer to the QA manual.

**8.2.7. Management of patients with intraoperative findings of more advanced stages of endometrial cancer**

All patients are expected to undergo their randomised treatment. In some cases, whatever the randomised treatment, obvious evidence of lymph node involvement or extra-uterine spread may be detected during surgery. **If this occurs, then protocol-mandated surgery should be continued.**

In Arm 1 patients i.e. lymphadenectomy, lymph nodes > 1 cm in diameter should be removed as part of the full lymph node dissection. Where there is obvious nodal involvement, these should be removed and the nodal dissection should still be completed.

In Arm 2 patients randomised before hysterectomy and BSO, lymph nodes > 1 cm in diameter are not expected to be found as baseline radiological imaging should have excluded patients with abnormal nodes (see section 6.3.2). In the rare occasions that lymph nodes > 1 cm in diameter, or indeed any lymph nodes highly suspicious of metastasis are found, they may be removed. However, a full lymph node dissection should not be performed. Please note that all of these patients will have had normal baseline radiological imaging and will receive adjuvant therapy according to their randomised treatment allocation (see also Adjuvant therapy paragraph below, and Appendix 4).

Peritoneal deposits may be removed in either arm. If peritoneal deposits are confirmed histologically, systemic adjuvant treatment (to include chemotherapy +/- pelvic external beam radiotherapy) should be given even if the lymph glands are clear on pathology. Patients with histologically confirmed peritoneal deposits and clear lymph glands will be replaced in the accrual.
The numbers of cases with disease outside the uterus is assumed to be small as any patients with pre-operative finding of extra uterine disease are not eligible as per the trial exclusion criteria (see section 6.3.2).

8.2.8. Adjuvant therapy

Adjuvant treatment must commence ≤ 8 weeks after completion of surgery. See Appendix 4, and the separate Adjuvant Treatment Guidance Document, for details of permitted adjuvant treatment options. Each participating site will be asked to specify which of the permitted adjuvant treatments they intend to use for their patients as part of trial setup. This information will be submitted to the UCL CTC, and reviewed and approved by the trial team before site activation with reference to the Adjuvant Treatment Guidance Document.

Randomisation will be stratified by site so that the type of adjuvant therapy used is balanced in each arm.

8.2.9. Management of patients with final pathology not showing high risk endometrial cancer

In patients randomised prior to surgery, if the final hysterectomy and BSO specimen does not show high risk disease e.g. FIGO grade 2 endometrioid carcinoma it should be remembered that the original diagnostic biopsy showed high risk disease e.g. FIGO grade 3 endometrioid carcinoma. Subsequent adjuvant treatment should proceed according to protocol.

8.3. Supportive Care

All patients should be managed with prophylactic antibiotics and anticoagulants pre and post-operatively as per local practice.

Patients requiring treatment for lymphoedema treatment should be referred to local lymphoedema services as required.

Additional medication for intercurrent illness or to manage the adverse events of trial treatment may be prescribed at the investigator’s discretion. However patients should not receive any other anti-cancer therapy or other investigational drugs whilst on the trial.

8.4. Clinical Management after Surgery

Clinical management of patients who complete surgery must adhere to the adjuvant treatment options outlined in Appendix 4 and the separate Adjuvant Treatment Guidance Document. Once adjuvant treatment is complete, any further treatment is at the discretion of the Investigator. Clinical management of patients who never undergo surgery is at the discretion of the Investigator.

All patients must remain in follow-up as per Section 9.2 in order to monitor patients for study endpoints, unless they specifically withdraw their consent for this.
Please also refer to section 15 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.
9. **ASSESSMENTS AND DEFINITION OF RECURRENCE**

9.1. **Pre-treatment Assessments**

Please see section 6.1 for a list of pre-treatment assessments. For ease of reference, two groups are defined within each trial arm as follows:

- **Group 1A**: Randomised to Arm 1 prior to hysterectomy and BSO
- **Group 1B**: Randomised to Arm 1 after hysterectomy and BSO
- **Group 2A**: Randomised to Arm 2 prior to hysterectomy and BSO
- **Group 2B**: Randomised to Arm 2 after hysterectomy and BSO

9.2. **Day of surgery**

A pregnancy test (serum or urine) for women of childbearing potential randomised prior to surgery (Groups 1A and 2A), must be performed on the day of hysterectomy and BSO.

9.3. **Post-operative visit**

On completion of surgery, patients will be seen at a post-operative follow up visit between 3-5 weeks after surgery, Group 2B as these patients will proceed to systemic adjuvant treatment without requiring additional surgery.

For Group 1A and 1B patients, this post-operative visit will include confirmation of the lymphadenectomy result and required adjuvant treatment as per protocol.

All patients must commence adjuvant treatment ≤ 8 weeks after completion of surgery.

Please refer overleaf to Table 2 for Groups 1A and 1B, and Table 3 for Groups 2A and 2B for the requirements assessments at this visit.

9.4. **Assessments During Follow Up**

All randomised patients, irrespective of treatment arm, will be followed up for 5 years according to the schedule detailed in Table 2 for Groups 1A and 1B, and Table 3 for Groups 2A and 2B. Patients will be assessed for local pelvic disease, extra-pelvic relapse, and treatment morbidity. Data collected will include documentation of status of disease, adverse events (including presence of +/- treatment for lymphoedema), health economics and quality of life.

The visit schedule is summarised as follows, as defined:

- In Groups 1A and 2A (i.e. randomised prior to hysterectomy and BSO), from date of hysterectomy and BSO
- In Group 1B (i.e. randomised after hysterectomy and BSO), from date of lymphadenectomy
- In Group 2B (i.e. randomised after hysterectomy and BSO), from date of randomisation
All patients will be seen as follows, as defined by the aforementioned criteria. Patients will be seen by appropriate site staff e.g. surgeon, clinical and/or medical oncologists according to local practice:

- 3 monthly in Year 1
- 4 monthly in Year 2
- 6 monthly in Year 3
- Annually in Years 4 and 5

During adjuvant treatment there will be additional clinic visits as per local policy. Data on adjuvant treatment will be collected as follows:

- CTCAE v4.03 grades 3-5 adverse events requiring treatment (with onset dates, and summary of treatments given for the events) will be reported on an adverse event case report form to be completed at the next relevant follow up visit according to the schedule outlined above.

- In node positive Group 1A and 1B, and all Group 2A and Group 2B patients, there will be a requirement to complete the EORTC QLQ-C30 and EQ-5D-5L questionnaires 3 weeks after starting adjuvant treatment.

- At the end of adjuvant treatment, an adjuvant treatment summary case report form will be completed to capture the following information: treatment given, start dates, duration of treatment. Patients will also complete the following questionnaires: EORTC QLQ-C30, EORTC QLQ-EN24, EORTC QLQ-OV28 (items 52-54), EORTC QLQ-CX24 (items 41, 43, 44), EORTC QLQ-PR25 (items 39-40), EQ-5D-5L.

If a patient fails to attend a clinic visit or cannot be followed up, the site should make every reasonable effort to contact the patient’s GP in order to assess their condition.
## Table 2 – Group 1A and 1B patients: Follow Up Assessments

| Investigation | 3-5 weeks after surgery | 3 weeks after starting adjuvant treatment | End of all adjuvant treatment | Year 1, 3 monthly  
| First visit defined according to section 9.3 | Year 2  
| 4 monthly | Year 3  
| 6 monthly | Year 4 & 5  
<p>| Annually | Months | Months | Months | Months |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vaginal examination | x | | | x | x | x | x | x | x | x | x | x | x |
| ECOG performance status (see Appendix 8) | x | | | x | x | x | x | x | x | x | x | x | x |
| MRI abdomen pelvis or CT abdomen pelvis | If clinically indicated | | | If clinically indicated | | | | | | | | | |
| Transvaginal ultrasound | If clinically indicated | | | If clinically indicated | | | | | | | | | |
| Adverse events according to CTCAE v4.03 | x | | | | | | | | | | | | |
| EORTC QLQ-C30 | x | Node +ve only | x | Node –ve only | x | x | x | x | x | x | x | x | x |
| EORTC QLQ-EN24 | x | | | | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th>Investigation</th>
<th>Time point</th>
<th>3-5 weeks after surgery</th>
<th>3 weeks after starting adjuvant treatment</th>
<th>End of all adjuvant treatment</th>
<th>Year 1, 3 monthly First visit defined according to section 9.3</th>
<th>Year 2 4 monthly</th>
<th>Year 3 6 monthly</th>
<th>Year 4 &amp; 5 Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-OV28 (items 52-54)</td>
<td>Month</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EORTC QLQ-CX24 (items 41, 43, 44)</td>
<td>Month</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EORTC QLQ-PR25 (items 39-40)</td>
<td>Month</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Self-report lower-extremity lymphoedema screening questionnaire</td>
<td>Month</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Economics questionnaire (EQ-5D-5L)</td>
<td>Month</td>
<td>x</td>
<td>Node +ve only</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
### Table 3 – Group 2A and 2B patients: Follow Up Assessments

<table>
<thead>
<tr>
<th>Investigation</th>
<th>3-5 weeks after surgery</th>
<th>3 weeks after starting adjuvant treatment</th>
<th>End of all adjuvant treatment</th>
<th>Year 1, 3 monthly First visit defined according to section 9.3</th>
<th>Year 2 4 monthly</th>
<th>Year 3 6 monthly</th>
<th>Year 4 &amp; 5 Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Months</td>
<td>Months</td>
<td>Months</td>
<td>Months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Vaginal examination</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>ECOG performance status (see Appendix 8)</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>MRI abdomen pelvis or CT abdomen pelvis</td>
<td>If clinically indicated</td>
<td></td>
<td></td>
<td>If clinically indicated</td>
<td></td>
<td>If clinically indicated</td>
<td>If clinically indicated</td>
</tr>
<tr>
<td>Transvaginal ultrasound</td>
<td>If clinically indicated</td>
<td></td>
<td></td>
<td>If clinically indicated</td>
<td></td>
<td>If clinically indicated</td>
<td>If clinically indicated</td>
</tr>
<tr>
<td>Adverse events according to CTCAE v4.03</td>
<td>x</td>
<td></td>
<td></td>
<td>All AEs at 3 months</td>
<td>Grade 3-5 AEs requiring treatment at 6, 9 and 12 months</td>
<td>Grade 3-5 requiring treatment</td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EORTC QLQ-EN24</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
### Investigation

<table>
<thead>
<tr>
<th>Time point</th>
<th>All patients: 3-5 weeks after surgery</th>
<th>3 weeks after starting adjuvant treatment</th>
<th>End of all adjuvant treatment</th>
<th>Year 1, 3 monthly First visit defined according to section 9.3</th>
<th>Year 2 4 monthly</th>
<th>Year 3 6 monthly</th>
<th>Year 4 &amp; 5 Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>16</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-OV28 (items 52-54)</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EORTC QLQ-CX24 (items 41, 43, 44)</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EORTC QLQ-PR25 (items 39-40)</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Self-report lower-extremity lymphoedema screening questionnaire</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Economics questionnaire (EQ-5D-5L)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
9.5. Defining recurrence

Recurrence is defined as evidence of endometrial cancer since study entry, based on new clinical, imaging or cellular/tissue-based specimens. The site of first recurrence (e.g. para-aortic or supraclavicular lymph nodes, lung, liver, bone, etc.) will need to be documented.

Evidence of Disease Recurrence

Evidence of disease recurrence may be based on clinical, imaging or cellular/tissue-based specimen evidence. Ideally, recurrence is based on a cellular or tissue-based analysis.

In specific circumstances, imaging tests may provide compelling evidence of disease recurrence and the subsequent management of the patient is based on these results. Rarely, clinical findings unsupported by a specimen-based analysis or definitive imaging are considered to show sufficient evidence of disease recurrence.

The following policies for determining evidence of disease recurrence will apply to trial patients:

i) Cellular/tissue based specimen evidence: Histologic evidence is considered the gold standard for disease recurrence. When a histologic sample has not been obtained, but there are definitive cytological findings of recurrent endometrial cancer, the patient will be considered to have recurrent endometrial cancer based on the results of a specimen analysis.

ii) Imaging based evidence: Imaging-based evidence will be considered sufficient for a diagnosis of recurrent endometrial cancer if these findings are considered unequivocal OR are subsequently supported by specimen-based evidence.

iii) Clinical evidence: Clinical-based evidence will be considered sufficient for a diagnosis of recurrent endometrial cancer if this evidence is unequivocal (e.g. speculum/colposcopic visualization; a palpable mass) AND is subsequently supported by specimen-based evidence OR unequivocal imaging evidence.

When clinical evidence is supported by imaging findings that are considered sufficient to justify recommencing therapy for endometrial cancer, the imaging findings will be judged as providing unequivocal evidence of recurrent endometrial cancer.

Dating of First Recurrence

The date of first detection of a palpable/visible lesion is acceptable only when this/these finding(s) are unequivocal and a diagnosis of tumour involvement is subsequently established.

The diagnosis of recurrent disease by radiographs or scans should be dated from the date of the first unequivocally positive record, even if this is determined in retrospect. Initial recording of dates of first recurrence and death should be made as they occur by those who are responsible for the care of the patient.
10. TRANSLATIONAL RESEARCH

Translational Sub-Study

Collection of Tissue and Blood Samples

As per the patient information and written informed consent for the main trial, recruited patients have the option to provide the following samples for use in future translational research:

- Tissue samples from the hysterectomy and BSO +/- lymphadenectomy;
- A baseline blood sample to be taken ≤ 28 days prior to randomisation;
- A randomly selected 10% of UK patients will be subject to retrospective central pathological QA – see section 8.2.6 (Pathological and Surgical Quality Assurance (QA))

Samples will be forwarded to a central site within each international trial group and then onto a central laboratory. International sites should refer to their group specific appendix.

An international consortium with participating experts representing the collaborating international trial groups will agree the programme of translational work, to include molecular and biomarker studies. Use of the samples will be subject to separate funding and ethics approval as applicable.

Tissue samples from hysterectomy and BSO +/- lymphadenectomy

Sites must provide formalin-fixed paraffin-embedded (FFPE) tissue from the surgical resection, namely one block containing representative tumour from the hysterectomy and BSO specimen and, for Arm 1 patients only, one block containing tumour from lymph nodes.

Details of shipping will be provided at a later date.

Baseline blood sample

Within 28 days of randomisation, sites must collect a single 7 ml blood sample using an EDTA tube. The sample must be stored at -80°C ≤ 12 hours after collection.

Samples should be labelled with the patient trial ID, patient initials and date of sample collection.

UCL CTC will arrange for a courier to collect the frozen samples. The samples will be transported in dry ice and packaging material to ensure the samples remain frozen during transport.

Details of shipping will be provided at a later date.
11. DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites using an electronic case report form (eCRF) created and maintained by UCL CTC. Data entered onto the eCRF system must be verifiable from source data at site.

11.1. Entering Data onto the eCRF

The eCRF must be completed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. Each authorised staff member will have their own unique login details for the eCRF. They must never be shared among staff as the eCRF audit trail will record all entries/changes made by each user. The PI is responsible for the accuracy of all data reported in the eCRF.

The use of abbreviations and acronyms must be avoided.

11.2. Corrections to eCRF

Corrections can be made to data on the eCRF where necessary. The eCRF audit trail will record the original data, each change made, the user making each change, and the date and time of each change.

11.3. Missing Data

To avoid the need for unnecessary data queries, the eCRF must be checked at site (and CCC if applicable) to ensure there are no blank fields. If data is unavailable, please refer to the eCRF user guide for information on how to indicate that data is “Not Done”, “Not Applicable”, “Not Available” or “Not Known” (only use if every effort has been made to obtain the data).

11.4. Timelines for eCRF Completion

The relevant eCRF forms must be completed as soon as possible after a patient’s visit. Eligibility and randomisation forms must be completed in order for a patient to be randomised onto the study. All other eCRF forms must be completed within 28 days of the patient being seen.

Sites who persistently do not enter data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a ‘for cause’ monitoring visit. See section 14.2 (‘For Cause’ On-Site Monitoring) for details.

11.5. Data Queries

Data entered onto the eCRF will be subject to some basic checks at the time of entry, and any discrepancies will be flagged to the user in the form of a warning.
The data can be corrected immediately, or where this is not possible, the warning can be saved and the data amended at a later stage.

Further data review will be carried out at UCL CTC and queries raised within the eCRF where necessary. Additionally, query reports may be generated from the eCRF and sent to the data contact at site (or CCC where applicable). Further guidance on the process of handling data queries can be found in the eCRF user guide.
12. SAFETY REPORTING

12.1. Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting” and ICH GCP E6:

**Adverse Event (AE)**
Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment.

**Adverse Reaction (AR)**
All untoward and unintended responses to a trial treatment administered. A causal relationship between a trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

**Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)**
An adverse event or adverse reaction that:

- Results in death
- Is life threatening (the term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

**Related and Unexpected Serious Adverse Reaction (RUSAR)**
A serious adverse reaction, the nature or severity of which is not consistent with the reference safety information (RSI).
12.2. Reporting Procedures

12.2.1. All Adverse Events (AEs)

For ease of reference, two groups are defined within each trial arm as follows:

Group 1A: Randomised to Arm 1 prior to hysterectomy and BSO
Group 1B: Randomised to Arm 1 after hysterectomy and BSO
Group 2A: Randomised to Arm 2 prior to hysterectomy and BSO
Group 2B: Randomised to Arm 2 after hysterectomy and BSO

All adverse events will be collected as follows:

- In Groups 1A and 2A i.e. randomised prior to hysterectomy and BSO, between informed consent and 3 months after date of hysterectomy and BSO;
- In Group 1B i.e. randomised after hysterectomy and BSO, between informed consent and 3 months after date of lymphadenectomy;
- In Group 2B i.e. randomised after hysterectomy and BSO, between informed consent and 3 months after randomisation;
- Additionally, and for all patients, grade 3-5 adverse events requiring treatment that persist or occur > 3 months after hysterectomy and BSO (Group 1A and 2A), lymphadenectomy (Group 1B patients) or randomisation (Group 2B patients).

Adverse events occurring during adjuvant therapy and throughout the follow up period will be recorded as part of the next relevant trial follow up visit according to the schedule outlined in section 9.4 i.e. CTCAE grade 3-5 adverse events that require treatment. This includes adverse events fitting the aforementioned criteria that persist or occur after the end of adjuvant therapy. None of these events would be reported or dealt with as a SAE, because the trial is not evaluating adjuvant therapy. The investigators are encouraged to report these events under the national spontaneous adverse event report scheme, e.g. the Yellow Card system in the UK.

Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the trial specific SAE Report. Also refer to section 12.2.2 (Serious Adverse Events (SAEs)).

Pre-existing conditions do not qualify as adverse events unless they worsen.

Adverse Event Term

An adverse event term must be provided for each adverse event:

- The electronic case report form (eCRF) will include a list of expected surgical adverse events known to be associated with hysterectomy, BSO and lymphadenectomy corresponding to Appendix 5. This list will use the appropriate adverse event term from Common Terminology Criteria for Adverse Events (CTCAE) v4.03.
• Otherwise, the adverse event term should be taken from CTCAE v4.03 wherever possible. CTCAE v4.03 is available online at http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20DMCC.pdf

**Severity**

Severity of each adverse event must be determined by using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 as a guideline, wherever possible. The criteria are available online at: http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20DMCC.pdf

In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

1 = Mild (awareness of sign or symptom, but easily tolerated)
2 = Moderate (discomfort enough to cause interference with normal daily activities)
3 = Severe (inability to perform normal daily activities)
4 = Life threatening (immediate risk of death from the reaction as it occurred)
5 = Fatal (the event resulted in death)

**Causality**

The PI, or other delegated site investigator, must perform an evaluation of causality for each adverse event.

Causal relationship to each trial treatment must be determined as follows:

- Related (reasonable possibility) to a trial treatment.
- Not related (no reasonable possibility) to a trial treatment.

UCL CTC will consider events evaluated as related to be adverse reactions.

**12.2.2. Serious Adverse Events (SAEs)**

For ease of reference, two groups are defined within each trial arm as follows:

Group 1A: Randomised to Arm 1 prior to hysterectomy and BSO
Group 1B: Randomised to Arm 1 after hysterectomy and BSO
Group 2A: Randomised to Arm 2 prior to hysterectomy and BSO
Group 2B: Randomised to Arm 2 after hysterectomy and BSO
All SAEs that occur between the signing of informed consent and:

- In Group 1A and 2A patients i.e. randomised prior to hysterectomy and BSO, 3 months after date of hysterectomy and BSO or > 3 months after hysterectomy and BSO if the site investigator assesses causality of the event as related to surgery;
- In Group 1B patients i.e. randomised after hysterectomy and BSO, 3 months after date of lymphadenectomy or > 3 months after lymphadenectomy if the site investigator assesses causality of the event as related to surgery;
- In Group 2B patients i.e. randomised after hysterectomy and BSO, 3 months after randomisation or > 3 months after randomisation if the site investigator assesses causality of the event as related to surgery.

SAEs must be submitted to UCL CTC by fax within 24 hours of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed. If the event is not being reported within 24 hours to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries. International sites should refer to their group specific appendix.

**Exemptions from SAE Report submission**

For this trial, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant section(s) of the trial eCRF:

- In Group 1A and 2A patients i.e. randomised prior to hysterectomy and BSO SAEs that occur > 3 months after hysterectomy and BSO that the site investigator assesses causality of the event as not related to surgery;
- In Group 1B patients i.e. randomised after hysterectomy and BSO, SAEs that occur > 3 months after lymphadenectomy that the site investigator assesses causality of the event as not related to surgery;
- In Group 2B patients i.e. randomised after hysterectomy and BSO, SAEs that occur > 3 months after randomisation that the site investigator assesses causality of the event as not related to surgery;
- Disease progression (including disease related deaths). These should be recorded on the relevant case report form.

Please note that hospitalisation for elective treatment or palliative care does not qualify as an SAE.

**Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to UCL CTC**

Fax: +44 (0)20 7679 9871
Adverse Event Reporting Flowchart

Adverse event

Assign severity grade

Investigator to assess causality
Is the event causally related to the trial treatment?

Was the event serious?
Criteria:
• Results in death
• Is life threatening
• Results in persistent or significant disability/incapacity
• Results in a congenital anomaly or birth defect
• Requires in-patient hospitalisation or prolongs existing hospitalisation
• Is otherwise medically significant

Yes

Event exempt from requiring submission on an SAE Report? (as stated in protocol)

No

Complete SAE Report

Fax Report to UCL CTC within 24 hours of becoming aware of the event

Complete CRF (to be submitted at time point stated in protocol)
SAE Follow-Up Reports

All SAEs must be followed-up until resolution and until there are no further queries. The PI, or other delegated site investigator, must provide follow-up SAE Reports if the SAE had not resolved at the time the initial report was submitted.

SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the RSI for the trial, i.e. the list of expected surgical adverse events in Appendix 5.

The CI, or their delegate (e.g. a clinical member of the TMG), may be contacted to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

12.3. Related and Unexpected Serious Adverse Reactions (RUSARs)

If the event is evaluated as a Related and Unexpected Serious Adverse Reaction (RUSAR), UCL CTC will submit a report to the UK REC within the required timeline. UCL CTC will also distribute to CCCs/CLSs for forwarding to their ethics committee(s) at least 1 business day before the local submission deadline.

Wherever possible, evaluations of causal relationship by both the site and the Sponsor’s clinical reviewer will be reported.

Informing Sites of RUSARs

UCL CTC will inform all UK PIs of any RUSARs that occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

For participating countries outside the UK, UCL CTC will submit reports to CCCs for forwarding to the PIs in their country within one business day. Where there is a CLS, UCL CTC will submit RUSAR reports directly to sites in that country.
12.4. Safety Monitoring

UCL CTC will provide safety information to the TMG and the IDMC on a periodic basis for review.

Trial safety data will be monitored to identify:

- new adverse reactions to the trial treatment regimen or individual trial treatments;
- trial related events that are not considered related to the trial treatment regimen.

Should UCL CTC identify or suspect any issues concerning patient safety at any point throughout the trial, the CI or TMG will be consulted for their opinion.
13. INCIDENT REPORTING

13.1. Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol, QA Manual or GCP immediately. UCL CTC may require a report on the incident(s) and a form will be provided if the organisation does not have an appropriate document (e.g. Trust Incident Form for UK sites).

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

Where the incident has occurred in a site outside the UK, the CCC/CLS in that country must also notify the relevant ethics committee in accordance with local requirements. Where UCL CTC identifies an incident at a site outside the UK, the CCC/CLS in the country where the incident occurred will be informed.

UCL CTC will use an organisation’s history of non-compliance to make decisions on future collaborations.
14. TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Monitoring of non-UK sites will be performed in accordance with the regulatory requirements of each country. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

14.1. Central Monitoring

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at the frequency detailed in the trial monitoring plan or on request and these will be checked for consistency and completeness. Also refer to sections 4.2.2 (Required documentation) and 6.2 (Screening Log).

A copy of the consent form for each UK patient entered onto the trial must be submitted to UCL CTC. These will be checked for completeness and accuracy i.e. the correct version of the form has been used, patient initials in every box, patient name and signature on the form, patient personally completed date of signing, and the person taking consent has signed/dated and is listed on the delegation log as performing this duty. Also refer to section 5 (Informed consent).

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File at the frequency detailed in the trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Data received at UCL CTC will be subject to review in accordance with section 11.5 (Data Queries).

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk, the matter will be raised urgently with site staff and escalated as appropriate (refer to section 13 (Incident Reporting ) and 14.2 (‘For Cause’ On-Site Monitoring) for further details).

14.2. ‘For Cause’ On-Site Monitoring

On-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.
Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial. Refer to section 13 (Incident Reporting) for details.

14.3. Oversight Committees

14.3.1. Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialties and STATEC trial staff from UCL CTC. The TMG will be responsible for overseeing the trial. The group will meet regularly approximately twice a year and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Gynaecological Clinical Studies Group (CSG).

The TMG will review substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

All TMG members will be required to read and sign a UCL CTC TMG Charter.

14.3.2. Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and the Sponsor.

All TSC members will be required to read and sign a UCL CTC TSC Charter.

14.3.3. Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on recruitment, safety, data completeness and efficacy, and problems that may arise. They will meet (face to face or by teleconference) approximately once per year, or more frequently if they wish. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

During the first 2 years of the trial, the IDMC will specifically review accrual rates (approximately every 6 months; by email or meeting), in order to consider whether recruitment is feasible, and that the target sample size is likely to be met. This will depend on number of active sites, size of those sites, and patient acceptance rates.

All IDMC members will be required to read and sign a UCL CTC IDMC Charter.
14.3.4. Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to safety reporting which are conducted in accordance with section 12.
15. WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment e.g. surgery, assessments, follow-up and data collection.

15.1. Reasons for Withdrawing Patients

Patients Who Undergo Surgery

A patient may be withdrawn from the trial whenever continued participation is no longer in the patient’s best interests, but the reasons for doing so must be recorded and data entered onto the eCRF as required. Withdrawn patients will still have data collected for the purposes of follow-up and analysis unless they specifically withdraw their consent for this (see section 15.2).

Reasons for withdrawal may include:

- Disease progression
- Unacceptable adverse event/s
- Intercurrent illness
- Patient choice
- Any alterations in the patient’s condition which justifies the patient withdrawing from the trial in the site investigator’s opinion

If a patient expresses their wish to withdraw from the trial, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. The patient is free to withdraw their consent for this without giving a reason (see section 15.2).

Patients Who Do Not Undergo Surgery

Patients randomised prior to surgery who then do not undergo hysterectomy and BSO +/- lymphadenectomy, or patients randomised to Arm 1 after hysterectomy and BSO who then do not undergo lymphadenectomy, for whatever reason, will remain in the trial for the purposes of follow-up and collection of the following: survival data, date last seen alive, and any treatment/s given after the decision not to proceed with surgery (please also see section 8.1, Trial Treatment Details). The reasons for not performing the surgery must be recorded and entered on the eCRF. Sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. The patient is free to withdraw their consent for this without giving a reason (see section 15.2).

15.2. Future Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected. In this event details should be recorded in the patient’s hospital records and the relevant eCRF form be completed. No further data other than safety data may be sent to UCL CTC (or CCC for non-UK sites).
15.3. Future Use of Samples

If a patient explicitly withdraws their consent for the future use of any samples donated for the purposes of translational research and retrospective central pathological QA, their decision must be respected. In this event:

- Details should be recorded in the patient’s hospital records and the relevant eCRF form be completed;
- Any tissue donated by the patient must be returned to the original site;
- If the patient donated a blood sample then it must be destroyed.

See also section 10, (Translational Research) and section 8.2.6 (Pathological and Surgical Quality Assurance (QA)).

15.4. Losses to Follow-Up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow-up via GP. Details of participating trial sites can be obtained from the UCL CTC (or CCC for non-UK sites) who must be informed of the transfer of care and follow up arrangements.

If a patient is lost to follow-up at a site every effort should be made to contact the patient’s GP to obtain information on the patient’s status. Loss to follow up should be recorded in the patient’s hospital records and the relevant eCRF form be completed.
16. TRIAL CLOSURE

16.1. End of Trial

For regulatory purposes the end of the trial will be when the last patient alive has been followed up for 5 years, at which point the ‘declaration of end of trial’ form will be submitted to participating regulatory authorities and ethical committees, as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

16.2. Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 5 years after the end of the trial, and in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3. Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 14.3.2 Trial Steering Committee (TSC) and 14.3.3 Independent Data Monitoring Committee (IDMC)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

16.4. Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC (or CCC for non UK sites) in writing. Follow up as per protocol must continue for all patients recruited into the trial at that site and other responsibilities continue as per agreement with the site and/or CCC.
17. STATISTICS

17.1. Sample size

The table below shows the expected 5-year overall survival (OS) rate and other parameters in patients:

<table>
<thead>
<tr>
<th></th>
<th>5 year OS rate</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expected rate</td>
<td>Lowest allowable</td>
<td>Hazard ratio(^4)</td>
<td>Allowable absolute difference at 5 years</td>
</tr>
<tr>
<td></td>
<td>for patients</td>
<td>rate(^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node negative</td>
<td>0.87</td>
<td>0.805(^2)</td>
<td>1.558</td>
<td>-0.065</td>
</tr>
<tr>
<td>patients (77%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node positive</td>
<td>0.50</td>
<td>0.50</td>
<td>1.00</td>
<td>0</td>
</tr>
<tr>
<td>patients (23%)(^1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>0.785(^3)</td>
<td>0.735(^3)</td>
<td>1.272</td>
<td>-0.05</td>
</tr>
<tr>
<td>Exponential</td>
<td>0.0040</td>
<td>0.0051</td>
<td></td>
<td></td>
</tr>
<tr>
<td>parameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. These all have adjuvant treatment, so there is no effect on these patients
2. Estimated using the expected rate of 0.87 and specifying an allowable difference of -0.065
3. Weighted average of the rates for negatives and positives
4. Hazard ratio is the ratio of the logarithms of the two OS rates

The overall non-inferiority margin of 5 percentage points was agreed by the investigators to be clinically acceptable to patients and surgeons.

Using the exponential parameter of 0.0040, allowable hazard ratio of 1.272, and assuming 48 months accrual then a further 48 months study follow up (i.e. a maximum length of follow up of 96 months), requires 2000 patients to be recruited (500 deaths), with 85% power, and 5% two-sided statistical significance. With 80% power, the sample size is 1720 patients (430 deaths), and this would be the minimum target. Sample sizes estimated using nQUERY. It should be noted that individual patients could be followed for 5 years, but the first primary statistical analysis could be done after the trial has been running for about 96 months i.e. after 430 deaths have been observed.

17.2. Statistical analyses

The main analyses will be by intention-to-treat, ignoring whether patients in one arm have the surgical method from the other arm. These analyses will exclude randomised patients who did not have surgery at all shortly after randomisation (and have been replaced in the accrual), but a secondary analysis of OS and other endpoints will be performed including these patients.

17.2.1. Primary analysis

OS will be defined as the time from randomisation until death from any cause. For patients who have not died, they will be censored at the date they were last known to be alive. OS will be compared between the trial arms using Kaplan-Meier curves, a logrank test, and the hazard ratio estimated using Cox regression modelling, after adjusting for the randomisation stratification factors.
No formal interim analyses of efficacy are planned in the protocol.

17.2.2. Secondary analyses

- Disease-free survival measured from the date of randomisation until date of first documented recurrence or metastatic disease, a new secondary tumour or death from any cause, whichever occurs first. Patients who have not had any of these events would be censored at the date they were last known to be alive.

- Endometrial cancer-event free survival, measured from the date of randomisation until date of first documented recurrence or metastatic disease, or death from endometrial cancer or treatment-related death, whichever occurs first. Patients who have a new secondary tumour or died from causes other than endometrial cancer are censored at those dates.

- Endometrial cancer-specific survival measured from the date of randomisation until date of death from endometrial cancer or treatment-related deaths. Patients who have died from causes other than endometrial cancer (or treatments for it) would be censored at date of death (and also considered in a competing risk analysis). All other patients are censored at the date they were last known to be alive.

- Pelvic relapse-free survival is defined as the date from randomisation to the date of first documented reappearance (recurrence) of disease provided that this recurrence is limited to the pelvis. Pelvic recurrence is defined as a recurrence within the pelvis, below the pelvic brim and inferior to the L4-L5 vertebral level. Pelvic recurrences will include disease recurrence in the vaginal vault, parametrium and pelvic lymph nodes (including the common iliac nodes).

- Extra-pelvic relapse-free survival is defined as the date from randomisation to the date of first documented reappearance (recurrence) of disease provided that this recurrence is outside of the pelvis. This includes above the pelvic brim and/or superior to the L4-L5 vertebral level, and the para-aortic lymph nodes. Patients found to have more advanced stages of endometrial cancer on intraoperative findings consistent with extra-pelvic disease will be considered to have extra-pelvic disease relapse at the date of the surgical procedure. These patients would be censored at the date of surgery.

- Following sentinel node mapping, pelvic node dissection or other intraoperative findings, there may be patients who are not considered to be disease-free after surgery. These patients would be censored at the surgery date for disease-free survival (and pelvic and extra-pelvic relapse-free survival).

These time-to-event endpoints will be analysed using Cox regression, and hazard ratios will be obtained. Subgroup analyses will also be performed using OS and other time-to-event endpoints, for the following pre-specified factors: age, histology, country, and type of adjuvant therapy.

- We will compare the time from randomisation to surgery (or vice versa, where appropriate) to check that this is similar between the trial groups.
• The different anatomical sites of local relapse as assessed by radiological imaging will be examined, as well as the rate of occurrence of each relapse type, and time to occurrence.
• Surgical adverse events (acute and late) will be assessed using the Common Terminology Criteria for Adverse Events v4.03. The maximum severity grade for each patient and each event type will be obtained, and summarised in frequency tables, and (where appropriate) compared between the trial groups using chi-squared or Fishers exact tests. Another table would be derived indicating the number of patients who had 0, 1, 2, 3 or more adverse events recorded; and again compared between the trial groups.
• Grade 3-5 adverse events during adjuvant therapy will also be assessed using the Common Terminology Criteria for Adverse Events v4.03. The maximum severity grade for each patient and each event type will be obtained and analysed as above.

17.2.3. Health economic analyses
The use of systemic adjuvant treatment in the lymphadenectomy arm, to include chemotherapy +/- pelvic external beam radiotherapy, is expected to be approximately a quarter of that in the no lymphadenectomy arm, in which all patients receive systemic adjuvant therapy. There are two features:

1. The cost of lymphadenectomy should be offset by the savings associated with not giving systemic adjuvant therapy to patients with negative lymph nodes, estimated to be ~77% of patients in this arm of the trial.

2. Fewer treatment associated adverse effects due to reduced chemotherapy/radiotherapy use should lead to reductions in health care resource utilisation which would be used to estimate incremental cost-effectiveness ratios (ICER).

The following will be collected and included in the analysis (and this may be done at selected sites only, depending on local resources for data collection):

- costs of surgery, chemotherapy and radiotherapy (when given)
- in clinic costs (number of patient days)
- outpatient costs – hospitalisations/GP visits
- costs of treating adverse events related to the lymphadenectomy, and subsequent grade 3 or higher adverse events following chemotherapy/radiotherapy/chemoradiotherapy

Quality of life based on EQ-5D-5L will be used to adjust the overall survival times to produce an estimate of QALYs.
17.2.4. Quality of life sub-study

1. Describe the trajectory of key patient reported outcomes (PRO) from baseline up to 5 years-post surgery, specifically:
   i. physical, role and social functioning, and global health status/quality of life (QOL), fatigue, nausea and vomiting, pain, appetite loss, constipation, diarrhoea (as measured by EORTC QLQ-C30);
   ii. lymphoedema, urological symptoms, gastrointestinal symptoms, tingling/numbness, hair loss, taste changes (EORTC QLQ-EN24);
   iii. attitude to disease/treatment; vaginal irritation/soreness, abnormal vaginal bleeding, hot flushes/sweats, daily activities limited by urinary problems, daily activities limited by bowel problems (EORTC item bank); throughout treatment and long term follow up;
   iv. self-assessed lymphoedema, as assessed by the self-report lower-extremity lymphedema screening questionnaire.

2. Compare the following PRO domains between the trial arms at the following time points:
   i. At 3-5 weeks post-surgery, compare physical functioning, social functioning, role functioning, attitude to disease/treatment, pain, fatigue, and global health status/QOL;
   ii. At end of adjuvant treatment, 9 months, 12 months, 16 months and 2 years, 3 years, 4 years and 5 years post-surgery, compare physical, role and social functioning, global health status/QOL, fatigue, nausea and vomiting, pain, appetite loss, constipation, diarrhoea, urological symptoms, gastrointestinal symptoms, tingling/numbness, hair loss, taste changes, attitude to disease/treatment, vaginal irritation/soreness, abnormal vaginal bleeding, hot flushes/sweats, daily activities limited by urinary problems, daily activities limited by bowel problems, lymphoedema, (and sexual interest, activity and enjoyment in sexually active patients only).

3. Determine the proportion of women in each trial arm reporting long-term symptoms after treatment as measured by the symptom-specific subscales of the measures (gastrointestinal symptoms, urological symptoms, attitude to disease and treatment, vaginal symptoms, lymphoedema) 9 months, 12 months, 16 months and 2 years, 3 years, 4 years and 5 years post-surgery.

4. Determine the correlation between physician rating (CTCAE v4.03) and patient-report (corresponding PRO subscale) for lymphoedema, abdominal pain, diarrhoea, nausea, neuropathy, fatigue, vaginal discharge/dryness, any other symptoms rated by both physicians and patients.

5. Assess the correlation between self-assessed lymphoedema (Self-report lower-extremity lymphedema screening questionnaire) and the lymphoedema subscale of the QLQ-EN24.
17.2.5. Sentinel node sub-study

The sentinel lymph node (SLN) sub-study aims to examine the prognostic value of SLN positivity in determining whether the patient has metastatic node chains or not. One analysis involves estimating the relative risk of having metastatic node chains for SLN positive versus SLN negative patients, and this can be done using logistic regression, allowing for patient and clinical characteristics (the relative risk quantifies the strength of the association).

The two statistical measures to evaluate the performance of SLN as a prognostic factor are:

- Detection rate (DR, or sensitivity) = proportion of patients with metastatic node chains who are classified as SLN positive
- False-positive rate (FPR; or 1 minus specificity) = proportion of patients without metastatic node chains who are classified as SLN positive

If SLN is a good marker, it will have high DR and low FPR, and therefore a high likelihood ratio (DR÷FPR). These will be estimated with 95% confidence intervals.
18. ETHICAL APPROVALS

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of Good Clinical Practice
- Human Rights Act 1998
- Data Protection Act 1998
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Mental Capacity Act 2005
- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

All non-UK sites shall comply with all their local laws and statutes applicable to the performance of clinical trials.

18.1. Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled ‘Ethical Principles for Medical Research Involving Human Subjects’ and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the London - Queen Square Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

UCL CTC will submit Annual Progress Reports to the REC, commencing one year from the date of ethical approval for the trial.

Favourable opinion will also be obtained in all participating countries outside the UK in compliance with all local laws, statutes and requirements.

18.2. Site Approvals

Evidence of assessment of capability and capacity by the Trust/Health Board R&D for a UK trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

All non-UK sites must provide confirmation of approval of their local institution(s).
18.3. Protocol Amendments

UCL CTC will be responsible for gaining ethical approval as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments.

18.4. Patient Confidentiality & Data Protection

Patient identifiable data, including initials, date of birth and NHS number (local equivalent if applicable for non-UK sites) will be required for the randomisation process and will be provided to UCL CTC, unless data protection legislation in the randomising country does not allow this. Non-UK sites should refer to their group specific appendix for additional instructions. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.
19. SPONSORSHIP AND INDEMNITY

19.1. Sponsor Details

<table>
<thead>
<tr>
<th>Sponsor Name:</th>
<th>University College London</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>Joint Research Office</td>
</tr>
<tr>
<td></td>
<td>Gower Street</td>
</tr>
<tr>
<td></td>
<td>London</td>
</tr>
<tr>
<td></td>
<td>WC1E 6BT</td>
</tr>
<tr>
<td>Contact:</td>
<td>Director of Research Support</td>
</tr>
<tr>
<td>Tel:</td>
<td>020 3447 9995/2178 (unit admin)</td>
</tr>
<tr>
<td>Fax:</td>
<td>020 3447 9937</td>
</tr>
</tbody>
</table>

19.2. Indemnity

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

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.
20. FUNDING

Cancer Research UK is supporting the central coordination of the trial in the UK through UCL CTC.

Research A costs will be reimbursed to sites as per the finance section of the CTSA.

Country coordinating centres and/or non-UK sites will be sourcing, obtaining and managing distribution of any additional local funding for the trial outside the UK.
21. PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group (TMG). The first publication of the trial results will be in the name of the TMG on behalf of the trial participants, with the TMG forming the writing committee. Authors will be cited by name if published in a journal where this does not conflict with the journal’s policy. Contributing site Principal Investigators will be acknowledged. Data from all sites will be analysed together and published as soon as possible. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data are owned by UCL. The Clinicaltrials.gov number allocated to this trial will be quoted in any publications based upon its results.
22. REFERENCES

23. de Boer SM, Nout RA, Jurgenliemk-Schulz IM et al. Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial. International Journal of Radiation Oncology, Biology and Physics. 2015; 93 (4): 797-809.
# APPENDIX 1: ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine transaminase</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>ARSAC</td>
<td>Administration of Radioactive Substances Advisory Committee</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BSO</td>
<td>Bilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td>CCC</td>
<td>Country Coordinating Centre</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>CLS</td>
<td>Country Lead Site</td>
</tr>
<tr>
<td>CSG</td>
<td>Clinical Studies Group</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised Tomography</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CTSA</td>
<td>Clinical Trial Site Agreement</td>
</tr>
<tr>
<td>DFS</td>
<td>Disease Free Survival</td>
</tr>
<tr>
<td>DR</td>
<td>Detection Rate</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylene Diamine Tetra Acetate</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FFPE</td>
<td>Formalin fixed paraffin embedded</td>
</tr>
<tr>
<td>FIGO</td>
<td>The International Federation of Gynecology and Obstetrics</td>
</tr>
<tr>
<td>FRP</td>
<td>False-positive rate</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>Hb</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>Hematoxylin and eosin</td>
</tr>
<tr>
<td>ICH GCP</td>
<td>International Conference of Harmonisation-Good Clinical Practice</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>ICTSA</td>
<td>International Clinical Trial Site Agreement</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>ISF</td>
<td>Investigator Site File</td>
</tr>
<tr>
<td>ITC</td>
<td>Individual Tumour Cells</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
</tr>
<tr>
<td>LND</td>
<td>Lymph Node Dissection</td>
</tr>
<tr>
<td>LVM</td>
<td>Low Volume Micro-Metastases</td>
</tr>
<tr>
<td>LVSI</td>
<td>Lymphovascular Space Invasion</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Image</td>
</tr>
<tr>
<td>NCRI</td>
<td>National Cancer Research Institute</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service (UK)</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression Free Survival</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Plts</td>
<td>Platelets</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient Reported Outcome</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-Adjusted Life Year</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research &amp; Development</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>RSI</td>
<td>Reference Safety Information</td>
</tr>
<tr>
<td>RUSAR</td>
<td>Related and Unexpected Serious Adverse Reactions</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SLN</td>
<td>Sentinel Lymph Node</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>UCL CTC</td>
<td>CR UK and UCL Cancer Trials Centre</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
</tbody>
</table>
APPENDIX 2: QUALITY OF LIFE SUB-STUDY

List of Collaborators
Dr. Kristina Lindemann, NHMRC Clinical Trials Centre, University of Sydney
A/Prof. Alison Brand, Department of Gynecological Oncology, Westmead Hospital, Westmead and Sydney Medical School, University of Sydney
Rebecca Mercieca-Bebber, School of Psychology and Sydney Medical School, University of Sydney
Prof. Madeleine King, Cancer Australia Chair in Cancer Quality of Life, School of Psychology and Sydney Medical School, University of Sydney

Background: Quality of Life
Patient-reported outcomes (PROs) provide valuable information about the impact of endometrial cancer and its treatment on patients. Given that endometrial cancer is the fourth most common female cancer and that five-year survival rates are reasonably high, PROs are an important consideration in the care of endometrial cancer patients. Despite this, few RCTs have informatively reported PROs in this patient group (1). Treatment for endometrial cancer usually involves surgery (hysterectomy, bilateral salpingo-oophorectomy, with or without lymphadenectomy), followed by adjuvant treatment with chemotherapy and/or radiotherapy for high-risk disease. Each of those treatment modalities will come with specific treatment-related side effects and recovery time, with probable impacts on quality of life.

Patient reported outcome evidence on lymphadenectomy is limited. The two randomised trials on the role of lymphadenectomy in endometrial cancer did not sufficiently address quality of Life (QOL) as highlighted by a Cochrane review (2). They only reported the increased incidence of post-operative complications, mainly due to lymphoedema in the lymphadenectomy group. We are aware of only two non-randomised studies that have assessed PROs associated with lymphadenectomy (3, 4), and only one did so prospectively. It found that global QOL scores were similar between women treated with lymphadenectomy and those who did not undergo lymphadenectomy, but the lymphadenectomy group scored higher on the lymphoedema symptom scale (4). Additionally, there was wide variation among patients in the timing of PRO assessment (3, 4), and this may have diluted treatment impact on PROs and differences in PROs between groups. This underlines the need for assessment of specific PROs of clinical relevance (in contrast to global QOL/health status), and careful timing of PRO assessments.

The clinical validity of patient-reported lymphoedema measures has been demonstrated, with a prevalence of self-reported lymphoedema around 50% among endometrial cancer patients after lymphadenectomy (4-6). Yost and colleagues (5) found that presence of lymphoedema was linked to poor PROs in nearly all quality of life domains and increased medical costs. This highlights the importance of assessing PROs after lymphadenectomy. Despite the probably detrimental effect of lymphadenectomy as a surgical procedure on QOL, comprehensive surgical staging of endometrial cancer patients may also
offer benefits in PROs as it may spare node negative patients from systemic treatment, while lymph node positive patients can justifiably be treated more aggressively.

Even though the optimal adjuvant treatment still needs to be determined, all modalities have specific short- and long-term toxicities that impact PROs (7). Radiation is more commonly associated with vaginal, urological and gastrointestinal toxicity, while chemotherapy may cause haematological and gastrointestinal side effects, fatigue and neuropathy. The impact of short- and long-term toxicity of both vaginal brachytherapy and external beam radiation treatment on PROs has been extensively studied in the PORTEC trials (8-10). Short-term assessments of PROs after sequential chemoradiation have also been reported (11), but only in a non-randomised study, while the results from current randomised clinical trials (i.e. GOG0258) are still pending.

STATEC will explore the tradeoff between the impact of lymphadenectomy followed by tailored adjuvant treatment and no lymphadenectomy followed by adjuvant treatment given to all patients due to unknown lymph node status. A key secondary endpoint of the STATEC trial is to assess the impact of more extensive surgery, i.e. lymphadenectomy, versus less extensive surgery, i.e. no lymphadenectomy but more systemic adjuvant treatment (to include chemotherapy +/- pelvic external beam radiotherapy) on key PROs.

**PRO objectives**

Please refer to the main protocol for details of the trial objectives (section 3.1) and the related statistics (section 17.2.4).

**Methods**

**Inclusion criteria**

All patients enrolled in STATEC will participate in the PRO study, provided they are willing and able to self-complete PRO Questionnaires in the most common languages in the countries recruiting to STATEC, and provided the questionnaires are available in authorised translations.

**Patient-reported outcome measures (PROs)**

The European Organization for Research and Treatment of Cancer (EORTC) Core questionnaire (QLQ-C30) (12), the EORTC endometrial cancer module (QLQ-EN24) and a subset of additional, relevant items from the EORTC PRO item bank will be used to assess key quality of life outcomes in endometrial cancer. The QLQ-C30 and QLQ-EN24 were chosen on the basis of their coverage of relevant domains for endometrial cancer patients and their reliability and validity.

The EORTC QLQ-C30 (12) is a cancer-specific, quality of life questionnaire with 30 items, which summarize as five core functional domains (physical, cognitive, emotional, social and role functioning), a global health status/quality of life scale, three symptom scales (pain, fatigue and nausea/vomiting), and six single items assessing additional symptoms and perceived financial impact.
Key to this study are the physical, social and role functioning domains and the fatigue, pain, appetite loss, constipation and diarrhoea symptom scales.

The EORTC endometrial cancer module (EN24) (13) includes 24 items with five multi-item scales (lymphoedema, urological symptoms, gastrointestinal symptoms, poor body image and sexual/vaginal problems) and eight single-item scales (sexual interest, sexual activity, sexual enjoyment, pain in back and pelvis, tingling/numbness, muscular pain, hair loss, taste changes). Key to this study are the lymphoedema, urological symptoms, gastrointestinal symptoms, tingling/numbness, hair loss, taste change domains. For participants who are sexually active, we will also explore the impact of treatment on the sexual function scales.

Some issues relevant to this patient group are not addressed by EORTC QLQ-C30 and EN24. Additional items from the EORTC item pool have hence been selected to ensure these issues are assessed, rather than selecting additional questionnaires, in order to limit patient-burden and repetition of questions. Additional items include the attitude to disease and treatment subscale (items 52-54) from the ovarian cancer module (QLQ-OV28) (14); three items (item 41, 43, 44) from the cervical cancer module (QLQ-CX24) to measure vaginal symptoms and hot flushes; and two items (items 39 and 40) from the prostate cancer module (QLQ-PR25) to measure daily activities limited by urinary problems and daily activities limited by bowel problems.

Self-reported lymphoedema will be assessed with a 13-item Self-report lower-extremity lymphoedema screening questionnaire - a brief, easy to complete and content valid tool developed by Yost et al. (15). This screening tool for identifying women with lower extremity lymphoedema (LEL) addresses absolute signs or symptoms of LEL in women. It was chosen based on its rigorous psychometric development, clinical appropriateness to our sample and content validity. Both underweight and overweight women were involved in the development study, which is important for the present study as we anticipate that a high proportion of the sample may be overweight.

**PRO assessment schedule – please see Tables 1 and 2 in main protocol for list of time points where QOL completion is required**

PRO assessments are expected from all patients alive and enrolled in the study, unless they specifically withdraw their consent for this.

**Administration of questionnaires**

The questionnaires will be distributed by the study personnel when the patient attends clinic, before seeing their clinician. Patients will be asked to complete the paper-based questionnaires. The study personnel (e.g. site coordinator, site nurse) will also be responsible for collecting the completed questionnaire. Study personnel will be asked to review questionnaires for completeness while the patient is still at the clinic and will invite participants to complete any missed questionnaire items at that time. Participants may refuse to complete questionnaires at any time-point if they wish. Study personnel should record the reason for refusal, or any other reason for missing PRO data. Completed questionnaires will be sent to the relevant County Coordinating Centre who
will then forward to the Cancer Research UK and UCL Cancer Trials Centre (UCL CTC) for entry onto the eCRF.

**Statistical analysis of PROs**

A summary of planned PRO analyses is presented here. A detailed statistical analysis plan will be developed. For each scale, all patients with a valid baseline and at least one follow-up PRO questionnaire will be included in the analysis.

PRO objective 1: Descriptive statistics and line graphs will be used to describe the average trajectory of patients in each trial arm over the course of the study for the following questionnaires and scales:

- **EORTC QLQ-C30**: Physical social and role functioning. Symptoms scales: Fatigue, pain, appetite loss, constipation and diarrhea.
- **EORTC QLQ-EN24**: Lymphoedema, urological symptoms, gastrointestinal symptoms, tingling/numbness, hair loss, taste change.
- **EORTC Item Bank**: Attitude to disease/treatment, vaginal bleeding, vaginal dryness/soreness, hot flashes, daily activities limited by urinary problems, daily activities limited by gastrointestinal problems.
- **Self-report lower extremity lymphoedema screening questionnaire**: Total score with a cut off of 5 for prevalent lymphoedema

PRO objective 2: Generalised estimating equations will be used to assess treatment effects of interest stated for this objective.

PRO objective 3: For pre-specified EORTC scales, the proportion of participants reporting ‘quite a bit’ and ‘very much’ responses will be described for each treatment group, at end of adjuvant treatment, 9 months, 12 months, 16 months and 2 years, 3 years, 4 years and 5 years.

PRO objective 4: For pre-specified symptoms, Spearman r correlations will be calculated between PRO and CTCAE scores. As the PRO scales and the CTCAE categories are not directly comparable, cross-tabulations will also be used to explore the nature of their relationship.

PRO objective 5: Spearman r correlation will also be calculated for self-report lower extremity lymphoedema screening questionnaire total score and leg circumference measures.

**Power and PRO sample size**

The trial is powered for the primary endpoint, with a sample size of 2000. This will provide ample power for the PRO analysis, even after adjusting for multiple PRO domains. For example, in relation to objective 2, 800 participants per trial arm (allowing for approximately 20% drop-out), and alpha of 0.0025 (Bonferroni adjustment allowing for 20 PRO domains), a two-tailed test for a small effect size of .02 would have 83% power.
**Impact of missing PRO data**

PRO completion rates, defined as the number of patients still on trial who completed PRO assessments, divided by the number of patients still on the trial, will be calculated for each scheduled PRO assessment time point.

Baseline characteristics and baseline PRO responses of participants not included in the PRO analysis will be compared with those of participants included in PRO analyses to determine the likelihood of bias induced by their exclusion.

CoMiDa Form data will also be examined to determine reasons for missing PRO data. These will be used by trial statisticians to understand missing data mechanisms and implications for statistical analyses. They will also be summarised in publications to support valid interpretation of the potential impact of missing PRO data on results and conclusions.

**References**


APPENDIX 3: SENTINEL LYMPH NODE (SLN) SUB-STUDY

BACKGROUND

The concept of the “sentinel lymph node (SLN)” was devised over 50 years ago. The idea of the SLN is that lymph node metastases occur sequentially as lymph drains away from a tumour so that if the SLN, or first node, is negative for metastasis, then the ensuing nodes should also be negative.

In endometrial cancer (EC), the SLN technique has been investigated in a number of small-scale studies dating back to 1996. Whilst these studies are mainly of small size, a systematic review of these showed overall high detection rates for SLN in EC. Further, data from Khoury-Collado et al supports the hypothesis of the SLN concept applying to EC as their study of 266 patients showed that the SLN is positive three times more often than non-sentinel nodes in EC.

Whilst the potential for the use of SLN biopsy is widely recognised internationally, there is ongoing debate about whether SLN biopsy alone can be used to replace formal full lymphadenectomy in the staging of EC patients. Whilst the risk of false negatives is low in low risk EC, Ballester et al, who undertook a prospective analysis of SLN biopsy followed by completion lymphadenectomy, found a false negative rate of 18% in patients with high risk EC whereas the NPV for low and intermediate risk EC was 100%.

The STATEC trial concept offers an unparalleled opportunity to prospectively evaluate the role of sentinel lymph node biopsy in the management of high-risk EC patients. Whilst the primary endpoint of the main trial is to determine the clinical effectiveness of adjuvant therapy given to all un-staged high risk patients compared to node negative (staged) cases, the SLN sub-study will determine whether sentinel node biopsy is as accurate as systematic node dissection. An additional aim of the sub-study is to evaluate whether SLN status is prognostic in terms of survival. Further, STATEC will allow the modelling of patient relapse and survival based on low volume micro-metastatic (LVM) and individual tumour cell (ITC) status, the significance of which is not currently understood.

Systematic review of the literature in relation to SLN methodology has principally described the use of two agents in SLN detection in EC: i) 99mTc-labeled nano-colloid and ii) blue dye. However, data supporting Indo Cyanine Green as a superior alternative to blue dye is becoming available.

In addition to the agent(s) used to detect SLN, the site of injection has also been investigated. Three methods have been evaluated: i) intra-cervical injection ii) intra-myometrial (hysteroscopic) injection and iii) laparoscopic “sub-serosal” injection. In the meta-analysis of Kang at al, the detection rate decreased when intra-cervical injection method was not used, although the correlation did not reach statistical significance. Kang et al therefore concluded...
that cervical injection was not inferior to other methods. These authors also stated that ‘sub-serosal injection only’ should be avoided because it decreased the sensitivity of SLN biopsy.

Over the last few years, as surgeons have developed the SLN technique with regard to simplifying its use, data have been reported demonstrating high and acceptable SLN detection rates in EC using either single agent blue dyes’ or indocyanine green (ICG) injected in to the cervix at the time of surgery \textsuperscript{7,8,10,11}. This does not appear to be at the expense of efficacy in detecting SLNs. Further, this approach is more patient friendly and resource sparing. Additionally, comparative studies suggest that ICG alone is more effective at SLN detection than blue dye alone\textsuperscript{8,11,12}. There is, therefore, widespread variation in practice internationally around agents of preference in SLN detection in EC.

We aim to determine sensitivity, false positive rates and false-negative ratio of the SN procedure compared to the gold standard of LND. There should be enough patients within the main STATEC trial for the SLN sub-study. Table 1 shows the width of the 95% confidence interval for the sensitivity of sentinel node testing, for various assumptions about (i) number of recruited patients, (ii) % of these who have metastatic node chains, and (iii) sensitivity of 60 to 90%. For example, if there are 300 patients in total who have cervical blue dye+99mTc, and 60 of these (i.e. 20%) have metastatic node chains, then the corresponding 95% CI margin would range from ±7% to ±12%, for sensitivities between 60 and 90%. The ±12% margin is acceptable.

Table 1. Width of 95% CI for sensitivities ranging from 60 to 90%, according to number of patients and whether the percentage who have metastatic node chains is 20 or 50%

<table>
<thead>
<tr>
<th>Total number recruited:</th>
<th>200</th>
<th>250</th>
<th>275</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
<th>700</th>
<th>800</th>
<th>900</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% of the total have metastatic node chains</td>
<td>±9-15%</td>
<td>±8-14%</td>
<td>±3-13%</td>
<td>±7-12%</td>
<td>±6-11%</td>
<td>±6-10%</td>
<td>±5-9%</td>
<td>±5-8%</td>
<td>±5-8%</td>
<td>±4-7%</td>
<td>±4-7%</td>
</tr>
<tr>
<td>50% of the total have metastatic node chains</td>
<td>±6-10%</td>
<td>±5-9%</td>
<td>±5-8%</td>
<td>±4-7%</td>
<td>±4-6%</td>
<td>±3-6%</td>
<td>±3-5%</td>
<td>±3-5%</td>
<td>±3-4%</td>
<td>±3-4%</td>
<td>±3-4%</td>
</tr>
</tbody>
</table>

Recent data comparing ICG and blue dye, albeit with small numbers of patients and mainly low risk EC, has shown that ICG is superior to blue dye and that adding blue to ICG adds no additional value\textsuperscript{8}. On the basis of data showing the superiority of ICG over blue dye, this is the preferred single agent dye for STATEC\textsuperscript{3,7,8}.
The main platforms that will be used in STATEC to perform hysterectomy and lymphadenectomy internationally will be i) laparoscopic and ii) robotic. Many sites with the da Vinci platform will have access to “Firefly” which allows visualization of ICG. There is also a laparoscopic platform now available for ICG (Pinpoint® Endoscopic Fluorescence Imaging System (Pinpoint®, Novadaq Technologies, Bonita Springs, F). This will bring wider application of the ICG technique to those with these laparoscopic systems. Where a site feels that they would like to use the 99m-Tc detection technique, this will be allowed in combination with blue dye or ICG.

Kang et al in their meta-analysis from 2009 found that sub serosal injection reduced sensitivity of the SLN technique if used alone without an alternative technique\(^2\). Thus the STATEC SLN sub-study proposes to allow the following techniques

i) Cervical blue dye or ICG  
ii) Cervical blue dye or ICG plus cervical 99mTc  
iii) Cervical blue dye or ICG plus cervical 99mTc plus sub-serosal blue dye or ICG

In order to encourage uptake of the SLN technique, for sites wishing to participate in the SLN sub-study within STATEC, there is no requirement for previous experience in SLN methodology and neither is there a proposal for a set number of learning curve cases.

**SLN DETECTION AGENTS**

**Coloured Dye**

If a site has not used the SLN technique before, we would recommend starting with Patent Blue unless the site has the ability to utilise ICG via Pinpoint or the robot. However, the following coloured dyes may be used:

- Patent Blue V ® 2.5% (Bleu Patente V; Guerbet Laboratory, Aulnay-sous-Bois, France) – preferred blue dye
- Isosulfan (Lymphazurin® 1%, Tyco Healthcare, Norwalk, CT)
- Methylene Blue (Methylene Blue 1%, American Regent, Inc. Shirley, NY),
- ICG (Indocyanine green, Akorn USA)

**Cervical Injection of ICG/Blue Dye**

ICG is allowed with or without 99m-Tc nano-colloid. For cervical injection of 99m-Tc nano-colloid, see below. ICG is available in 25 mg bottles as a dry powder. To reconstitute ICG in solution, mix 20 ml of sterile water into the ICG bottle to get a 1.25 mg/ml dose, draw the ICG dye into a syringe and inject ICG directly into the cervix at the 3 and 9 o’clock position, one quarter of the total volume superficially (2-3 mm depth) and one quarter deep (1-2 cm) on each side. It is recommended that the injection is undertaken very slowly to prevent extravasation of dye into the uterine vasculature. The total volume of ICG recommended is between 1 and 4 ml in total the injection method into the cervix.
is similar for the blue dyes, which come pre-mixed in solution. For example, Patent Blue V comes pre mixed in solution to a total of 2 ml. Therefore, 0.5 ml would be injected at 2-3 mm depth and at 1-2 cm depth at 3 o’clock and 9 o’clock respectively.

**Serosal Injection of ICG/Blue Dye**

Serosal injection of either ICG or Blue dye can be undertaken as part of the method allowed for STATEC as described in (iii) above. Injection is undertaken at the time of surgery either at open procedure or laparoscopically. The total volume of the dye to be used is injected into the middle of the fundus at a depth of 1-4 cm. It is recommended that the injection is undertaken very slowly to prevent extravasation of dye into the uterine vasculature and down into the fallopian tubes. If serosal dye injection technique is used, then it is mandatory for the patient to have either a long or short protocol 99m-Tc non-colloid injection to the cervix before procedure as described in the next section.

**99m-Tc nano-colloid**

The afternoon before the operation, or on the morning of the day of the operation, a total of 30 – 100 MBq (depending on the local situation but primarily on the planned interval between injection and surgery and also on the sensitivity of the intraoperative gamma probe as determined in discussion with local medical physics colleagues) 99m-Tc-labeled nano-colloid (e.g. Solco Nuclear, Birsfelden, Switzerland) with a particle size < 80 nm is injected intradermally in 4 quadrants at 1-3 mm depth (each 0.5 – 1 ml of 99mTc-labeled nanocolloid) of the cervix at 12, 3, 6 and 9 o’clock using a 25 gauge spinal needle, 3.5 inches long.

Anterior scintographic images are then obtained using a gamma camera with a low energy high-resolution collimator. Within 5 minutes of radio-colloid injection, dynamic imaging is started (30 second frames for about 30 minutes) A further anterior static image is obtained after approximately 2 hours (In order to facilitate anatomical interpretation of the delayed image, transmission scanning may be done simultaneously using the 120 keV gamma rays of a 57Co flood source) SPECT CT is not required.

The first appearing persistent focal accumulation is considered to be a sentinel node, especially when a direct connection from the injection site to the sentinel node is visible on the dynamic sequence. The lympho-scintograph will be made available to the surgeon prior to the operative procedure.

**SURGICAL PROTOCOL**

After the cervical injection of dye, the patient is prepped and draped in the usual sterile fashion. The procedure is continued as planned either through laparoscopy, robotics, or laparotomy. The cervical injection can also be performed after the patient is prepped and draped if desired.

The surgical procedure starts with localisation and removal of the sentinel node(s). The anatomic locations of SLN are noted. A gamma probe may be
used to locate the sentinel lymph node (as an area of greatest radioactivity when compared to background tissue). A sentinel node excision biopsy is then performed under directional guidance from the gamma probe and also by dissection of the dye-stained lymphatic vessels.

Following its removal, the SLN is moved away from the surgical field (away from background counts within the patient), and the gamma probe is used to confirm that the SLN removed is indeed radioactive (“hot”) The extracorporeal count-rate should be broadly concordant with the counts obtained in vivo. The surgical site is then re-examined with the gamma probe to see if there are any remaining “hot” nodes, which should be excised as additional sentinel nodes.

All coloured or hot nodes are to be considered sentinel. If a coloured channel leads directly to a lymph node but the lymph node itself is not coloured it should still be considered sentinel. All mapped coloured nodes are removed separately, labelled based on anatomic location, and sent to the specialist gynaecological oncology pathologist as SLN.

The SLNs should not be sent for a frozen-section analysis. If the sentinel node is suspicious, the surgeon should continue the surgery as indicated by the trial randomisation.

Hysterectomy, removal of adnexae, and pelvic and para aortic lymphadenectomy must follow the SLN mapping procedure. The SLN identification and removal is performed first. The completion lymphadenectomy is performed either prior to or after the hysterectomy. Lymph nodes from the lymphadenectomy are anatomically labelled according to the table shown in the manual of surgery and pathology for STATEC. It should be noted that the proximal obturator nodes and the internal iliac nodes are anatomically difficult to distinguish and frequently overlap. The assignment of SLN to internal iliac versus obturator is left up to the surgeon removing the SLN, but in general, proximal obturator nodes overlying the internal iliac vessels are considered internal iliac and the more distal obturator nodes ventral to or surrounding the obturator nerve are considered obturator. The enclosed table can be used to record where SLN nodes are detected and subsequent SLN and non-SLN histological outcomes.

**SLN PROCESSING INCLUDING PATHOLOGY**

All SLN removed will be subjected to enhanced pathology following routine H&E stained section. Non-SLN will undergo routine pathology. If the SLN is the only positive node after total node analysis following full lymphadenectomy, only the presence of metastases visible on routine H&E examination will be used to direct post-operative adjuvant therapy according to the STATEC protocol.

Enhanced pathology for each SLN entails: the node is sliced perpendicular to the long axis in 2-3 mm slices. If the SLN is negative on initial H&E staining an ultrastaging procedure is carried out. Ultrastaging re-evaluates the presumed negative SLN at two additional levels, 50 µm apart, with an extra H&E stained
slide and immunohistochemistry (IHC) using the anti-cytokeratin AE1:AE3 [ref: Gynecol Oncol. 2013 Dec; 131(3)].

In determining adjuvant treatment, the sentinel lymph node will be regarded as positive if there is disease visible on the routine H&E stained section. If disease is only seen on enhanced pathology then this will not be regarded as a positive result with regard to adjuvant treatment.
<table>
<thead>
<tr>
<th>Site</th>
<th>No. SLN Nodes Detected</th>
<th>No. SLN Nodes Metastatic</th>
<th>No. SLN Nodes with MM</th>
<th>No. SLN Nodes with LVM</th>
<th>No. SLN Nodes with ITC</th>
<th>No. SLN Nodes Extracapsular Extension</th>
<th>No. Non SLN Nodes Detected</th>
<th>No. Non SLN Nodes with MM</th>
<th>No. Non SLN Nodes with LVM</th>
<th>No. Non SLN Nodes with Extracapsular Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parametrical Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parametrical Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obturator Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obturator Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal Iliac Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal Iliac Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External Iliac Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External Iliac Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Iliac Distal Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Iliac Distal Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Iliac Proximal Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Iliac Proximal Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presacral Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presacral Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Aortic Left (below IMA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Aortic Right (below IMA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher Aortic Left (above IMA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher Aortic Right (above IMA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic NOS Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic NOS Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic NOS Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic NOS Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (specify)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MM=macro-metastases >2mm  
LVM= low volume metastases 0.2mm-2.0mm  
ITC=individual tumour cells detected by cytokeratin IHC
REFERENCES


APPENDIX 4: ADJUVANT TREATMENT REGIMENS

The list of standard recommendations for adjuvant treatment is provided in the Adjuvant Treatment Guidance Document.

During setup, each site must indicate what adjuvant treatment they intend to use for:

a) Arm 1 node positive and Arm 2 patients, and
b) Arm 1 node negative patients.
APPENDIX 5: EXPECTED SURGICAL ADVERSE EVENTS

The following adverse events, to be reported according to CTCAE v4.03, are associated with hysterectomy, bilateral salpingo-oophorectomy (BSO) and lymphadenectomy and will be considered expected for these treatments. This list will serve as reference safety information, has been agreed by the TMG and is derived from the following references:


   The aforementioned paper lists all observed intraoperative (143/2948, lowest incidence 0.03%) and postoperative (453/1462, lowest incidence 0.1%) surgical adverse events occurring in surgery for gynaecological cancers.

2. Hysterectomy Educational Resources and Services (HERS) Foundation. Adverse Effects Data, reported by 1,000 women who responded to HERS Questionnaire. Chart 1: Responses from all 1,000 women whose uterus was removed with or without removal of their ovaries. http://www.hersfoundation.com/effects.html

   The lowest incidence of an expected adverse event derived from the aforementioned chart is 0.2% (stroke).
<table>
<thead>
<tr>
<th>INTRAOPERATIVE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>Verbatim term</td>
<td>CTCAE term (System Organ Class)</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>Ventricular arrhythmia (Cardiac Disorders)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>Cardiac arrest (Cardiac Disorders)</td>
</tr>
<tr>
<td>Immune system</td>
<td></td>
</tr>
<tr>
<td>Verbatim term</td>
<td>CTCAE term (System Organ Class)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>Allergic reaction (Immune system disorders)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Anaphylaxis (Immune system disorders)</td>
</tr>
<tr>
<td>Injury</td>
<td></td>
</tr>
<tr>
<td>Verbatim term</td>
<td>CTCAE term (System Organ Class)</td>
</tr>
<tr>
<td>Perforation of uterus</td>
<td>Uterine perforation (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Tear at delivery of uterus</td>
<td>Intraoperative reproductive tract injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Injury to major artery e.g. iliacs, aorta</td>
<td>Intraoperative arterial injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Injury to major vein e.g. inferior vena cava</td>
<td>Intraoperative venous injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Accidental injury involving complete penetration into the stomach</td>
<td>Intraoperative gastrointestinal injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Accidental injury involving complete penetration into the small bowel</td>
<td>Intraoperative gastrointestinal injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Injury</td>
<td>Verbatim term</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Accidental injury involving complete penetration into the large bowel</td>
<td>Intraoperative gastrointestinal injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Laceration of liver due to penetration</td>
<td>Intraoperative hepatobiliary injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Laceration of gallbladder due to penetration</td>
<td>Intraoperative hepatobiliary injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Laceration of spleen due to penetration</td>
<td>Intraoperative splenic injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Laceration of diaphragm due to penetration</td>
<td>Intraoperative musculoskeletal injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Nerve injury e.g.</td>
<td>Intraoperative neurological injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>- Obturator</td>
<td></td>
</tr>
<tr>
<td>- Genitofemoral</td>
<td></td>
</tr>
<tr>
<td>- Parasympathetic leading to warm foot</td>
<td></td>
</tr>
<tr>
<td>Bladder injury e.g. accidental bladder injury (full thickness)</td>
<td>Intraoperative urinary injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Ureteric injury e.g.</td>
<td>Intraoperative urinary injury (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>- Ligation</td>
<td></td>
</tr>
<tr>
<td>- Transection</td>
<td></td>
</tr>
<tr>
<td>- Diathermy burn</td>
<td></td>
</tr>
<tr>
<td>Haemorrhage – estimated blood loss &gt; 2.5 L</td>
<td>Intraoperative hemorrhage (Injury, poisoning and procedural complications)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>CTCAE term (System Organ Class)</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Aspiration (Respiratory, thoracic and mediastinal disorders)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Pneumothorax (Respiratory, thoracic and mediastinal disorders)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Pulmonary edema (Respiratory, thoracic and mediastinal disorders)</td>
</tr>
<tr>
<td>POST-OPERATIVE</td>
<td>Verbatim term</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Angina or Chest pain - cardiac</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Cardiac failure</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Bowel perforation</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Gastrointestinal (cont.)</td>
<td>Verbatim term</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td>Enterocutaneous fistula</td>
</tr>
<tr>
<td></td>
<td>Enterovesical fistula</td>
</tr>
<tr>
<td></td>
<td>Gastric fistula</td>
</tr>
<tr>
<td></td>
<td>Large bowel fistula</td>
</tr>
<tr>
<td></td>
<td>Small bowel fistula</td>
</tr>
<tr>
<td></td>
<td>Faecal incontinence or urgency</td>
</tr>
<tr>
<td></td>
<td>Ileus complication</td>
</tr>
<tr>
<td></td>
<td>Large bowel obstruction</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Small bowel obstruction</td>
</tr>
<tr>
<td>General</td>
<td>CTCAE term (System Organ Class)</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>Verbatim term</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>Non-cardiac chest pain</td>
</tr>
<tr>
<td></td>
<td>(General disorders and administration site conditions)</td>
</tr>
<tr>
<td>Fever / pyrexia ≤ 48 hours after surgery</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>(General disorders and administration site conditions)</td>
</tr>
<tr>
<td>Pain e.g. sternum</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>(General disorders and administration site conditions)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Verbatim term</td>
<td>CTCAE term (System Organ Class)</td>
</tr>
<tr>
<td>Abdominal abscess</td>
<td>Infections and infestations - Other, specify (Infections and infestations)</td>
</tr>
<tr>
<td>Bladder infection</td>
<td>Bladder infection</td>
</tr>
<tr>
<td></td>
<td>(Infections and infestations)</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Infections and infestations - Other, specify (Infections and infestations)</td>
</tr>
<tr>
<td>Kidney infection</td>
<td>Kidney infection</td>
</tr>
<tr>
<td></td>
<td>(Infections and infestations)</td>
</tr>
<tr>
<td>MRSA</td>
<td>Infections and infestations - Other, specify (Infections and infestations)</td>
</tr>
<tr>
<td>Pelvic abscess</td>
<td>Infections and infestations - Other, specify (Infections and infestations)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>Peritoneal infection</td>
</tr>
<tr>
<td></td>
<td>(Infections and infestations)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>Phlebitis</td>
</tr>
<tr>
<td></td>
<td>(Infections and infestations)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>(Infections and infestations)</td>
</tr>
<tr>
<td>Infections and infestations (cont.)</td>
<td>Verbatim term</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Wound infection</td>
<td>Wound infection</td>
</tr>
<tr>
<td>Injury</td>
<td>Anastomotic leak – small bowel</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>Anastomotic leak – large bowel</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>Damage to other internal organs or structures e.g. ureter</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Hernia</td>
<td>Hernia</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>Primary haemorrhage – i.e. &lt; 24 hours after surgery</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>Secondary haemorrhage – i.e. &gt; 24 hours after surgery</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound breakdown</td>
<td>Wound breakdown</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Superficial – skin and subcutaneous tissue</td>
</tr>
<tr>
<td></td>
<td>- Deep – involving fascia / muscle</td>
</tr>
<tr>
<td></td>
<td>- Burst abdomen requiring repair under anaesthesia</td>
</tr>
<tr>
<td>Neurological</td>
<td>CTCAE term</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Verbatim term</td>
<td>(System Organ Class)</td>
</tr>
<tr>
<td>Nerve palsy</td>
<td>Nervous system disorders - Other, specify</td>
</tr>
<tr>
<td></td>
<td>(Nervous system disorders)</td>
</tr>
<tr>
<td>Numbness</td>
<td>Nervous system disorders - Other, specify</td>
</tr>
<tr>
<td></td>
<td>(Nervous system disorders)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>Paresthesia</td>
</tr>
<tr>
<td></td>
<td>(Nervous system disorders)</td>
</tr>
<tr>
<td>Stroke</td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>(Nervous system disorders)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>CTCAE term</td>
</tr>
<tr>
<td>Verbatim term</td>
<td>(System Organ Class)</td>
</tr>
<tr>
<td>Delirium</td>
<td>Delirium</td>
</tr>
<tr>
<td></td>
<td>(Psychiatric disorders)</td>
</tr>
<tr>
<td>Depression</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>(Psychiatric disorders)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Psychosis</td>
</tr>
<tr>
<td></td>
<td>(Psychiatric disorders)</td>
</tr>
<tr>
<td>Renal and urinary</td>
<td>CTCAE term</td>
</tr>
<tr>
<td>Verbatim term</td>
<td>(System Organ Class)</td>
</tr>
<tr>
<td>Bladder perforation</td>
<td>Bladder perforation</td>
</tr>
<tr>
<td></td>
<td>(Renal and urinary disorders)</td>
</tr>
<tr>
<td>Bladder prolapse</td>
<td>Renal and urinary disorders – Other, specify</td>
</tr>
<tr>
<td></td>
<td>(Renal and urinary disorders)</td>
</tr>
</tbody>
</table>
### Renal and urinary (cont.)

<table>
<thead>
<tr>
<th>Verbatim term</th>
<th>CTCAE term</th>
<th>(System Organ Class)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased urination</td>
<td>Urinary frequency</td>
<td>(Renal and urinary disorders)</td>
</tr>
<tr>
<td>Urinary fistula</td>
<td>Urinary fistula</td>
<td>(Renal and urinary disorders)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Urinary incontinence</td>
<td>(Renal and urinary disorders)</td>
</tr>
<tr>
<td>Urinary obstruction</td>
<td>Urinary tract obstruction</td>
<td>(Renal and urinary disorders)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Urinary retention</td>
<td>(Renal and urinary disorders)</td>
</tr>
<tr>
<td>Urge / stress to urinate or urinary urgency</td>
<td>Urinary urgency</td>
<td>(Renal and urinary disorders)</td>
</tr>
</tbody>
</table>

### Reproductive

<table>
<thead>
<tr>
<th>Verbatim term</th>
<th>CTCAE term</th>
<th>(System Organ Class)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovaginal fistula</td>
<td>Vaginal fistula</td>
<td>(Reproductive system and breast disorders)</td>
</tr>
<tr>
<td>Vesicovaginal fistula</td>
<td>Vaginal fistula</td>
<td>(Reproductive system and breast disorders)</td>
</tr>
<tr>
<td>Ureterovaginal fistula</td>
<td>Vaginal fistula</td>
<td>(Reproductive system and breast disorders)</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>Vaginal haemorrhage</td>
<td>(Reproductive system and breast disorders)</td>
</tr>
<tr>
<td>Vaginal prolapse</td>
<td>Reproductive system and breast disorders</td>
<td>– Other, specify</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Reproductive system and breast disorders)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Verbatim term</td>
<td>CTCAE term</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(System Organ Class)</td>
</tr>
<tr>
<td>Asthma</td>
<td>Respiratory, thoracic and mediastinal disorders – Other, specify</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
</tr>
<tr>
<td></td>
<td>(Respiratory, thoracic and mediastinal disorders)</td>
<td></td>
</tr>
<tr>
<td>Atelectasis</td>
<td>Atelectasis</td>
<td>Atelectasis (Respiratory, thoracic and mediastinal disorders)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Pleural effusion</td>
<td>Pleural effusion (Respiratory, thoracic and mediastinal disorders)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Aspiration</td>
<td>Aspiration (Respiratory, thoracic and mediastinal disorders)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Pneumothorax</td>
<td>Pneumothorax (Respiratory, thoracic and mediastinal disorders)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Pulmonary edema</td>
<td>Pulmonary edema (Respiratory, thoracic and mediastinal disorders)</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood clot in leg</td>
<td>Thromboembolic event</td>
<td>Thromboembolic event (Vascular disorders)</td>
</tr>
<tr>
<td></td>
<td>(Vascular disorders)</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>Thromboembolic event</td>
<td>Thromboembolic event (Vascular disorders)</td>
</tr>
<tr>
<td></td>
<td>(Vascular disorders)</td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>Hematoma</td>
<td>Hematoma (Vascular disorders)</td>
</tr>
<tr>
<td>Hypotension or low blood pressure</td>
<td>Hypotension</td>
<td>Hypotension (Vascular disorders)</td>
</tr>
<tr>
<td></td>
<td>(Vascular disorders)</td>
<td></td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>Lymphedema</td>
<td>Lymphedema (Vascular disorders)</td>
</tr>
<tr>
<td></td>
<td>(Vascular disorders)</td>
<td></td>
</tr>
<tr>
<td>Vascular (cont.)</td>
<td>Verbatim term</td>
<td>Verbatim term</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td></td>
<td>Lymphocyst / Lymphocele</td>
<td>Lymphocele</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Vascular disorders)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
<td>Thromboembolic event</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Vascular disorders)</td>
</tr>
</tbody>
</table>
### APPENDIX 6: FIGO STAGING FOR ENDOMETRIAL CANCER, 2009

<table>
<thead>
<tr>
<th>FIGO STAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
</tr>
<tr>
<td>1B</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>IIIA</td>
</tr>
<tr>
<td>IIIB</td>
</tr>
<tr>
<td>IIIC1</td>
</tr>
<tr>
<td>IIIC2</td>
</tr>
<tr>
<td>IVA</td>
</tr>
<tr>
<td>IVB</td>
</tr>
</tbody>
</table>

_FIGO Committee on gynaecological oncology. Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. Int J Gynaecol Obstet 2009;105(2):103-4_
APPENDIX 7: FIGO GRADING FOR ENDOMETRIAL CANCER, 1988

Histopathology – Degree of Differentiation

Cases of carcinoma of the corpus should be classified (or graded) according to the degree of histologic differentiation, as follows:

G1 = 5% or less of a nonsquamous or nonmorular solid growth pattern
G2 = 6% - 50% of a nonsquamous or nonmorular solid growth pattern
G3 = More than 50% of a nonsquamous or nonmorular solid growth pattern

Notes on Pathologic Grading

1. Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or grade 2 tumor by 1
2. In serous adenocarcinomas, clear-cell adenocarcinomas, and squamous carcinomas, nuclear grading takes precedence.
3. Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

APPENDIX 8: ECOG PERFORMANCE STATUS

<table>
<thead>
<tr>
<th>GRADE</th>
<th>ECOG PERFORMANCE STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any selfcare; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

## APPENDIX 9: PROTOCOL VERSION HISTORY

<table>
<thead>
<tr>
<th>Protocol:</th>
<th>Amendments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version no.</td>
<td>Date</td>
</tr>
<tr>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1.1</td>
<td>18oct16</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>13dec16</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>