The RACC trial - Robot Assisted Approach to Cervical Cancer

A multi-centre randomised non-inferiority trial of robot assisted laparoscopic surgery versus laparotomy in women with early stage cervical cancer

Protocol identification number: RACC Version 1.0

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**SYNOPSIS**

<table>
<thead>
<tr>
<th>Protocol Title</th>
<th>RACC- Robot assisted Approach to Cervical Cancer</th>
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<tbody>
<tr>
<td>Indication</td>
<td>Participants have operable early stage cervical cancer.</td>
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<tr>
<td>Primary objective</td>
<td>To investigate the oncologic safety of robot-assisted laparoscopic surgery as compared to standard laparotomy.</td>
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<td>Secondary objectives</td>
<td>To evaluate intra and postoperative outcomes, overall survival, diagnostic accuracy of sentinel lymph node biopsy, patient reported quality of life including lymphedema and health care costs.</td>
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<tr>
<td>Study Design</td>
<td>Randomised controlled non-inferiority trial</td>
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<tr>
<td>Planned sample size</td>
<td>800 women</td>
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**Inclusion criteria**
- Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adeno-squamous carcinoma of the uterine cervix;
- Women with histologically confirmed FIGO stage IB (IB3 excluded) and IIA1 disease
- Women undergoing either a Type B or C radical hysterectomy according to Querleu Morrow classification
- ECOG Performance Status of 0, 1 or 2
- Patient must be suitable candidates for surgery.
- Patients who have signed an approved Informed Consent
- Age > 18 years

**Exclusion criteria**
- Any histology other than adenocarcinoma, squamous cell carcinoma or adeno-squamous carcinoma of the uterine cervix
- Tumor size greater than 4 cm
- FIGO stage II-IV (except IIA1)
- Women with a history of pelvic or abdominal radiotherapy
- Women who are pregnant
- Women with contraindications to surgery
- Women with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2cm; or histologically positive lymph nodes
- Serious concomitant systemic disorders incompatible with surgery or study (at the discretion of the investigator)
- Women unable to withstand prolonged lithotomy and steep Trendelenburg position
- Women with secondary invasive neoplasm in the last 5 years (except non-melanoma skin cancer, breast cancer T1 N0 M0 grade 1 or 2 without any signs of recurrence or activity)
- Women with iodine allergy cannot participate in the sentinel node part of the trial (not an exclusion criteria for the primary outcome)
<table>
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<tr>
<th>Primary outcome</th>
<th>Recurrence free survival</th>
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| **Secondary outcomes** | • Overall survival  
• Health related quality of life including lymphoedema, bladder and sexual dysfunction  
• Intraoperative complications  
• Postoperative complications  
• Diagnostic accuracy of the pelvic sentinel lymph node concept  
• Health care costs |
| **Standard treatment** | Radical hysterectomy and pelvic lymphadenectomy by laparotomy |
| **Experimental treatment** | Robot-assisted laparoscopic radical hysterectomy and pelvic lymphadenectomy |
| **Duration of study including follow up** | 8 years (inclusion 5 years and follow-up 3 years) |
### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CC</td>
<td>Cervical cancer</td>
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<tr>
<td>HPV</td>
<td>Human papilloma virus</td>
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<td>FIGO</td>
<td>International Federation of Gynecology and Obstetrics</td>
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<td>LVSI</td>
<td>Lympho-vascular space invasion</td>
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<td>OS</td>
<td>Overall survival</td>
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<td>DFS</td>
<td>Disease free survival</td>
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<tr>
<td>EBRT</td>
<td>External beam radiation therapy</td>
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<td>ESGO</td>
<td>European Society of Gynaecological Oncology</td>
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<tr>
<td>TMMR</td>
<td>Total Mesometrial Resection</td>
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<tr>
<td>LS</td>
<td>Laparoscopy</td>
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<tr>
<td>TLRH</td>
<td>Total laparoscopic radical hysterectomy</td>
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<tr>
<td>PLND</td>
<td>Pelvic lymph node dissection/lymphadenectomy</td>
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<tr>
<td>PALND</td>
<td>Paraaortic lymph node dissection/lymphadenectomy</td>
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<tr>
<td>US FDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>RALS</td>
<td>Robot-assisted laparoscopic surgery</td>
</tr>
<tr>
<td>OT</td>
<td>Operation time</td>
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<tr>
<td>LT</td>
<td>Laparotomy</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>NCDB</td>
<td>National Cancer Database</td>
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<td>MIS</td>
<td>Minimally invasive surgery</td>
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<tr>
<td>SGO</td>
<td>Society of Gynecologic Oncologists</td>
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<tr>
<td>LACC</td>
<td>Laparoscopic Approach to Cervical Cancer</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>CO$_2$</td>
<td>Carbon dioxide</td>
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<tr>
<td>SQRGC</td>
<td>Swedish Quality Registry for Gynecologic Cancer</td>
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<tr>
<td>SNB</td>
<td>Sentinel node biopsy concept</td>
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<td>SLN</td>
<td>Sentinel lymph node</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
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<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
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<tr>
<td>ICG</td>
<td>Indocyanine Green</td>
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<tr>
<td>UPP</td>
<td>Upper paracervical pathway</td>
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<tr>
<td>LPP</td>
<td>Lower paracervical pathway</td>
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<tr>
<td>H&amp;E</td>
<td>Hematoxylin and eosin</td>
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<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
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<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
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<tr>
<td>QLQ</td>
<td>Quality of Life Questionnaire</td>
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<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
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<tr>
<td>RFS</td>
<td>Recurrence free survival</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
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<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
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1 WHY THIS TRIAL IS NEEDED

FIGO staging in this chapter refers to staging manual before the latest revision in 2018.

1.1 BACKGROUND

Cancer of the uterine cervix is the fourth leading cause of cancer deaths in women and the fourth most common cancer in females worldwide, affecting 500 000 women annually.\(^1\) In many developing countries, cervical cancer (CC) is the leading cause of cancer death and also the most commonly diagnosed cancer. In the industrialized world, the incidence and mortality is considerably lower, mainly as a result of effective screening programs where precancerous lesions are diagnosed and treated but also due to effective treatment.\(^2,3\) In the Nordic countries, 1390 women are diagnosed annually and the incidence is rising.\(^4\) In Sweden, 550 new cases of cervical cancer are diagnosed annually with a median age at diagnoses of 48 years with the highest incidence at ages 40 and 70.\(^5\)

The presence of Human papillomavirus (HPV) infection is necessary but not sufficient in the carcinogenesis leading to cervical cancer.\(^6\) Synchronous sexually transmitted disease, immunosuppression (e.g HIV infection), long term use of oral contraceptives, high number of live births, smoking and increased number of sexual male partners are all factors associated with cervical carcinoma.\(^7,8\)

**Staging**

Staging of cervical cancer according to the International Federation of Obstetrics and Gynaecology (FIGO) and was clinical until October 2018.\(^9\) However, it has been demonstrated that clinical FIGO staging underestimates disease stage in 15-30% and 40% of women with early and advanced stage disease respectively as compared to surgical staging.\(^10-12\) In the revised FIGO staging manual, imaging and histopathological evaluation may be included.\(^13\) The latest FIGO staging is available in Appendix 16.1.

**Prognosis**

The total 5-year relative survival in the Nordic countries ranges between 58-67%.\(^4\) Stage of disease at diagnosis strongly correlates to prognosis. In Sweden, 57% of women are diagnosed in early stage (stage ≤ IB1) of disease with a 5-year overall survival (OS) of >90%.\(^14\) However, presence of lymph node metastasis deteriorates prognosis with a reported 75% overall 5-year survival.\(^15,16\) Lymphatic or vascular space invasion (LVSI) of tumour, depth of tumour invasion
in the cervical stroma and size of tumour are also unfavorable prognostic factors. $^{17-19}$

**Treatment**

Treatment of CC consists of surgery, radiotherapy and chemotherapy alone or in different combinations. Traditionally, surgery constitutes primary treatment of early stage tumors with or without adjuvant treatment depending on prognostic factors. Advanced stage tumors are treated with primary radiotherapy with concomitant chemotherapy. $^{20,21}$

1.1.1 Surgical Treatment

Ernst Wertheim described the radical hysterectomy with excision of parametria and pelvic lymph node removal in 1912, the procedure resulted in high mortality and morbidity. $^{22}$ Four decades later, Joe Vincent Meigs modified the procedure with parametrial resection to the pelvic side wall with addition of systematic pelvic lymph node dissection. $^{23}$ In addition to a very low operative mortality, a 90% and 63% 5-year overall survival was demonstrated for stage I and stage II respectively. Piver et al further modified the procedure in an attempt to further reduce morbidity and also classified the extent of the procedure (class I; removal of paracervical tissue including uterine vessels without dissecting into cervical tissue or mobilization of the ureter, class II; uterine artery is resected medially to the ureter after its mobilization, class III; uterine artery resected at its origin from the internal iliac artery). $^{24}$ The less radical surgical approach was further investigated with reassuring survival and reduced morbidity. $^{25,26}$ Landoni et al randomised 243 women with stage IB1 and IIA cervical cancer to either Piver class II or III radical hysterectomy. $^{18}$ There was no difference in 5-year OS (81 vs 77%) or disease free survival (DFS) (75 vs 73%) but less late morbidity was reported in the Piver class II group (13 vs 28% p=0.1). The proportion of patients who received adjuvant external beam radiation therapy (EBRT) was high but balanced (54 vs 55%).

There are other classifications of radical hysterectomy that have been proposed like the nerve sparing technique originating from Japan $^{27,28}$ that has further complicated the nomenclature of anatomic structures involved. In order to simplify classification, Querleu and Morrow proposed a system with four types of radical hysterectomy regardless of operation modality (type A-D) and in addition, a common nomenclature of the anatomic structures surrounding the uterine cervix. They describe type A being the least radical with only minimal paracervical tissue dissection and D being the most radical laterally and dorsally. $^{29,30}$ This system has gained substantial popularity. The trend has been towards less radical surgery in stage IA disease, where simple hysterectomy and sentinel node is now according to the
European Society of Gynaecological Oncology (ESGO) guidelines accepted instead of complete lymph node dissection with exception where LVSI is present. Further data on a less radical approach for low-volume disease can be expected once the international SHAPE trial is completed (ClinicalTrials.gov Identifier: NCT01658930).

In 2009, Hockel et al presented a novel surgical technique based on resection of embryological compartments, the Total Meso Metrial Resection (TMMR), where the lymphadenectomy described was very radical in contrast to a less radical hysterectomy. In his study 212 women with stage IB1-IIB cervical cancer were prospectively followed after surgery with TMMR without adjuvant treatment. The 5-year OS and DFS was 96 vs 94% respectively despite omitting adjuvant treatment, which is exceptional. The results have yet to be reproduced.

In summary, despite efforts of standardizing surgery for patients with cervical cancer during the last decades, the anatomic-surgical definition of radical hysterectomy remains a challenge for the surgeon. However, there is consensus in the western world that surgery is gold standard treatment for early stage disease (≤ IB1 + IIA1) and radiation with concomitant chemotherapy for advanced stages ≥ IB2 (except IIA1). In Sweden, radical hysterectomy type B according to Querleu-Morrows classification is recommended for patients with stage IA2 with LVSI, type B or C for stage IB1 (type B or C) and type C for stage IIA.

1.1.2 Minimally invasive surgery

In the 1990’s the first experiences with laparoscopic (LS) radical hysterectomy (TLRH) with pelvic (PLND) and paraaortic lymphadenectomy (PALND) were published. Despite promise of possible advantages, LS for cervical cancer did not gain strong acceptance.

The United States Food and Drug administration (U.S. FDA) approved robot-assisted laparoscopic surgery (RALS) for gynecologic procedures in 2005. RALS offers the three-dimensional magnification vision, dexterity and possibly shorter learning curve and favorable ergonomics. Shortly after introduction, the first case-report was published describing the feasibility of RALS to perform a Piver class III radical hysterectomy. The uptake of RALS has been dramatic and observational studies have demonstrated that RALS is associated with shorter hospital stay, less blood loss and acceptable operation time (OT). Furthermore, compared to conventional laparoscopy, OT is significantly shorter with RALS.
Most observational studies on oncologic outcomes after RALS seem reassuring with no apparent differences in comparison with laparotomy (LT).\textsuperscript{43-46} However, in 2018, population-based data were presented from the United States (US) National Cancer Database (NCDB), demonstrating inferior survival in women treated with minimally invasive surgery (MIS). Based on almost 2000 treated women, Margul \textit{et al} showed that women with tumours larger than 2 cm had a significantly decreased 5-year OS 81% (95% CI 76%-87%) when operated by MIS vs 91% (95% CI 88%-94%) by LT. Similar outcomes were earlier presented at the Society of Gynecologic Oncologists (SGO) meeting, March 2018, with a HR for death at 1.48 (1.10-1.98) for women operated with MIS.\textsuperscript{47} At the same meeting, the preliminary results from the LACC-trial (Laparoscopic Approach to Cervical Cancer) were presented. The LACC-trial, a multi-centre non-inferiority randomised controlled trial, started recruitment in 2008. The study was prematurely closed by the Data safety monitoring committee in 2017 before reaching the planned accrual of 740 women. The final study population comprised 631 women with stage I cervical cancer, treated either by MIS (n=319) or laparotomy (n=312).\textsuperscript{48} In the MIS group, the majority of patients (84%) were operated by conventional laparoscopy whereas 16% by RALS. There were no differences in tumor size, histology, adjuvant treatment or patient characteristics. However, after a median follow up of 30 months, MIS was inferior to LT in DFS, with a hazard ratio (HR) of 3.7 (95% CI 1.63-8.58) $p=0.002$ for recurrence and 6 (95% CI 1.77-20.3) $p=0.004$ for OS. The authors speculate that the use of intra-uterine manipulators, intracorporeal colpotomy and effects of the carbon dioxide (CO\textsubscript{2}) gas may account for the negative findings.

In response to the unexpected LACC outcomes, a population based, nation-wide analysis based on data from the Swedish Quality Register for Gynecologic Cancer (SQRGC), was conducted. Preliminary results demonstrate equal OS and DFS in women operated by RALS or LT between 2011-2017. The DFS of 87\% for robotic surgery is in fact identical to the DFS in MIS arm of the LACC trial while the DFS for laparotomy group was 84\%, both had a median follow up time of 44 months.\textsuperscript{14}

\subsection{Sentinel lymph node biopsy}

The sentinel node biopsy concept (SNB) is well established in the surgical management of several malignancies including breast and vulvar cancer, with sufficient information gained on lymph node status for clinical decision making but with less morbidity.\textsuperscript{49-51 52}
Pelvic lymphadenectomy in cervical cancer is an extensive diagnostic procedure with risk of lasting morbidity. It is estimated that 15% of women surgically treated for early stage disease have metastasis in the pelvic lymph nodes. These women are subjected to additional adjuvant EBRT with substantially increased morbidity. Undoubtedly, replacing PLND with SNB in cervical cancer would decrease morbidity.

Traditionally, radiotracers (Technetium) with or without augmentation of blue dye have been used for SNB. In patients with early stage CC, the reported detection rate of sentinel lymph nodes (SLN) with blue dye only is unsatisfactory. However, when Technetium tracer is added, single center cohort studies suggest a unilateral detection from 75-100% and bilateral detection rate 66-72%, sensitivity reported 83-87% and a negative predictive value (NPV) of 95-97%. Moreover, ultrastaging of SLN enhances detection of metastases with an increase of micro-metastases and isolated tumour cells.

The SENTICOL I multicenter cohort study, followed 139 women with early CC subjected to SNB (blue dye and technetium as tracer) by laparoscopy prospectively. A sensitivity and negative predictive value (NPV) of 92 and 98% respectively was demonstrated. Moreover, the bilateral detection rate was 77%. The SENTICOL II randomised 200 women with early stage CC to either PLND or SNB only with aim of evaluating postoperative short and long term complications. A significantly decreased morbidity in favour of SNB only was demonstrated, though final publication is awaited.

In the most recent ESGO guidelines on cervical cancer, SNB is recommended in stage IA without LVSI. There are small studies suggesting a high diagnostic accuracy of SNB even in larger tumors.

The SENTICOL III RCT (ClinicalTrials.gov Identifier: NCT03386734), will start accrual this year with the aim to investigate the oncologic safety of SNB only vs PLND with 3-year DFS as primary outcome. The SENTIX cohort study (ClinicalTrials.gov Identifier: NCT02494063), with ongoing prospective accrual of women with stage ≤ IB1 CC, aims to investigate the 2-year recurrence rate of women subjected to SNB only.

Indocyanine green (ICG), primarily used in MIS with near infra-red camera for detection, has been demonstrated to be superior in small series of patients with cervical cancer both regarding diagnostic accuracy and detection rate. Larger prospective studies on ICG with near
infrared fluorescence detection in patients with CC are lacking. Furthermore, the optimal dose and number of injections sites for ICG has not yet been established.

1.2 RATIONALE FOR STUDY

The standard surgical treatment for early stage cervical cancer is radical hysterectomy with pelvic lymphadenectomy. During the past decade, RALS has replaced the open approach in the Nordic countries. The implementation of RALS has fundamentally changed Nordic health care with significant effects on infrastructure, health economy and surgical training. Novel technologies incorporated in the robotic platform enables improved lymph node assessment. The unexpected results from the LACC trial suggest that MIS no longer can be considered safe for the surgical management of early stage cervical cancer. However, these outcomes contrast with nationwide, population-based data demonstrating equal outcomes between women treated with RALS or laparotomy.

The LACC trial has several important limitations:

- More than 80% of women in the MIS arm were treated with conventional laparoscopy. In the Nordic countries, conventional laparoscopy never gained acceptance and laparotomy remained the primary modality until the introduction of RALS. Whether RALS would result in different outcomes remains to be demonstrated.

- The LACC trial recruited participants from 33 centers worldwide during nine years. Although the protocol required accreditation of participating surgeons, internal validity can be questioned. This is supported by the fact that all recurrences in MIS arm were concentrated to 13 centers. In the Nordic countries, cervical cancer treatment is centralised to tertiary referral centers (university hospitals), resulting in high-volume centers. In addition, radical hysterectomy is restricted to a limited number of sub-specialised surgeons.

- The LACC trial allowed any type of uterine manipulators, including intra-uterine devices. In the Nordic countries, only different types of vaginal probes (to delineate the fornices) are being used.
Taken together, the LACC trial does not reflect current practice in the Nordic countries. The health care systems have gradually been adapted to RALS and the perceived safety is supported by Nordic population-based studies. However, the LACC trial is currently the only RCT exploring the safety of MIS and to establish the safety of current practice, a new RCT is needed. Given the excellent outcomes in the open arm in the LACC trial, it is unlikely that RALS can generate superior outcomes. It is therefore reasonable to design a new RCT as a non-inferiority trial.

2 STUDY OBJECTIVES

2.1 HYPOTHESIS
Robot-assisted laparoscopic radical hysterectomy with pelvic lymphadenectomy is non-inferior to laparotomy in recurrence free survival with the advantage of shorter hospital stay, postoperative complications and lower health care costs in a public health care system.

2.2 PRIMARY OBJECTIVE
The less invasive surgical modality, robot assisted laparoscopic surgery, has become standard of care in the Nordic countries for treatment of early stage cervical cancer without any trial supporting its safety or superiority over laparotomy. This trial aims to compare the oncologic safety of RALS to conventional laparotomy.

2.3 SECONDARY OBJECTIVES
To evaluate overall survival, intra- (including validation of proposed intraoperative classifications) and postoperative outcomes 30 days after surgery, health care costs, quality of life and lymphoedema and the diagnostic accuracy of pelvic sentinel lymph node biopsy concept in women with early stage cervical cancer.

2.4 PRIMARY OUTCOME MEASURE
5-year recurrence-free survival

2.4.1 Definition of primary outcome measure
Recurrence-free survival time (RFS) is defined as the time-interval between the date of randomisation and the date of recurrence or to the date of death (according to STEEP\textsuperscript{67}). For recurrence-free patients still alive, RFS time is calculated from the date of randomisation to the date of last clinical visit.

A clinical or by imaging suspicion of recurrence of disease has to be verified by histopathological assessment.

The date of biopsy will be the date of recurrence (or date of death).

2.4.1.1 Local recurrence
Vaginal or pelvic side-wall (including nodal recurrence)

2.4.1.2 Distant recurrence
Extra-pelvic lymph nodes, port site metastases, parenchymatous organ, carcinomatosis, bone metastases

2.5 SECONDARY OUTCOME MEASURES

- Overall survival
- Health related quality of life including lymphoedema
- Intraoperative complications
- Postoperative 30 complications
- Diagnostic accuracy of the pelvic sentinel lymph node concept
- Health care costs

2.5.1 Definition of secondary outcome measures

Overall survival (OS): Survival time is calculated from the date of randomisation to the date of death (due to any cause), or for patients still alive to the date of last clinical follow-up or contact.
Health related quality of life (HRQoL): will be assessed by questionnaires completed by study participants preferably as electronical patient reported outcome measures or during the clinic visit (by manually filling in forms, by accessible computer or by mail). The assessments are performed before randomisation (baseline), 1 month, 6 months, 1 year, 2 years and 5 years after surgery. Questionnaires comprise the EORTC QLQ-30, QLQ-CX24 and Eq5D-3L (see Appendix 16.8).

Intraoperative complications: Defined according to Kaafarani et al and the CLASSIC classification (see Appendix 16.4).

Postoperative 30 day complications: According to the Clavien-Dindo classifications (see Appendix 16.2)

Diagnostic accuracy of the pelvic sentinel lymph node concept: Sensitivity and negative predictive value of the sentinel lymph node specimen (in mapped women) and the sentinel lymph node algorithm. In addition, the uni and bilateral mapping rate.

Health care costs: At the discretion of the chair of the sub-committee on health care costs. Direct costs will be used by assessing internal accounting and billing systems within the hospitals. We will also measure the quality-adjusted life years (QALYs) gained with the intervention and use this to undertake a cost-utility analysis. The QALY calculations will be based on health status measures for trial participants, with valuations of changes in health status and quality of life based on the EQ-5D.
3 STUDY DESIGN

Randomised controlled non-inferiority trial.

3.1 STUDY SCHEMA

Cervical cancer patients assessed for eligibility; FIGO stage IB (IB2 excluded), IIA1

Meeting all inclusion criteria
Informed written consent, baseline assessments
HRQoL before randomisation

RANDOMISATION 1:1

Robot assisted laparoscopic surgery
(Experimental)

Laparotomy
(Control)

Do not wish to participate/do not meet inclusion/exclusion criteria:
Screening log, excluded

Adjuvant treatment as per national guidelines and indication

Study specific follow-up

Visits:
1 month after surgery
6 months after surgery
1 year after surgery
2 years after surgery
3 years after surgery
5 years after surgery

Assessment:
lymphoedema, recurrence and HRQoL

Follow-up according to national guidelines

1 Including postoperative complications.
2 Including collection of blood for biobank if participation in the translational part of the RACC trial.
3 Including possible adjuvant treatment.
* Only evaluation of recurrence.
### 3.2 SCHEDULE OF EVENTS TABLE

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Enrolment/Baseline</th>
<th>Enrolment*</th>
<th>Surgery</th>
<th>Clinical visit 1-month after surgery</th>
<th>Clinical visit 6-months after surgery</th>
<th>Clinical visit 1-year after surgery</th>
<th>Clinical visit 2-years after surgery</th>
<th>Clinical visit 3-years after surgery</th>
<th>Clinical visit 5-years after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent oral and written</td>
<td>X</td>
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<td></td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Randomisation</td>
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<td></td>
<td></td>
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<tr>
<td>Record surgical procedure performed and localization of sentinel lymph node</td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Record per-operative complications*</td>
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<td>Length of stay</td>
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<tr>
<td>Record 30 day post-operative complications*</td>
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<td>Record final pathology</td>
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<td></td>
</tr>
<tr>
<td>Record adjuvant treatment</td>
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<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Collection of blood for biobank</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of wet smear from cervix (Thin-prep)*</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*EORTC-QLQ-C30 + CX24, Eq5D-3L. According to Classic and Kaafarani see Appendix 16.4. According to Clavien-Dindo classification, by review of hospital charts, contact with patient at visit or per telephone, see Appendix 16.2. Not mandatory for participating centers outside Sweden. Lymphatic side effects according to the CTCAE 3.0, see Appendix 16.2 and LYMQOL Questionnaire, see Appendix 16.10 may only be used by centres in which the questionnaire’s translation has been validated. Randomisation only after completed quality of life questionnaires.
4 STUDY ENROLLMENT

4.1 SCREENING PROCEDURE AND PARTICIPANT IDENTIFICATION

All women with histologically proven cervical cancer, FIGO stage IB (IB3 excluded), IIA1 can undergo screening for this trial and will be documented in a screening log. After obtaining oral and written informed consent, patients will be registered and randomised. Registration data has to be entered to an electronic Case Report Form (eCRF).

4.2 INCLUSION CRITERIA

- Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adeno-squamous carcinoma of the uterine cervix;
- Women with histologically confirmed FIGO stage IB (IB3 excluded) and IIA1 disease
- Women undergoing either a Type B or C radical hysterectomy according to Querleu Morrow classification
- ECOG Performance Status of 0, 1 or 2
- Patient must be suitable for surgery.
- Patients who have signed an approved Informed Consent
- Age > 18 years

4.3 EXCLUSION CRITERIA

- Any histology other than adenocarcinoma, squamous cell carcinoma or adeno-squamous carcinoma of the uterine cervix
- Tumor size greater than 4 cm, estimated by either magnetic resonance imaging (MRI) or clinical examination
- FIGO stage II-IV (except IIA1)
- Women with a history of pelvic or abdominal radiotherapy
- Women who are pregnant
- Women with contraindications to surgery
- Women with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2cm; or histologically positive lymph nodes
- Serious concomitant systemic disorders incompatible with surgery or study (at the discretion of the investigator)
- Women unable to withstand prolonged lithotomy and steep Trendelenburg position
- Women with secondary invasive neoplasm in the last 5 years (except non-melanoma skin cancer, breast cancer T1 N0 M0 grade 1 or 2 without any signs of recurrence or activity)
Women with iodine allergy cannot be part of the sentinel node part of the trial but are allowed randomisation as to the primary outcome.

4.4 RANDOMISATION
After verification of eligibility, signed informed written consent and baseline HRQoL questionnaires completed, patients will be randomised to either robot assisted laparoscopic surgery or laparotomy by equal allocation, 1:1. The randomisation procedure will be pre-stratified for participating centre.

Randomisation will be performed centrally by the Clinical Trials Unit at Center for Clinical Cancer Studies, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden. Randomisation will only be performed if the investigator confirms completed baseline HRQoL questionnaires. All inclusion criteria and no exclusion criteria must be met. At the time of inclusion, inclusion and exclusion criteria are entered into the randomization/registration application, which is a web-based instrument (ALEA). Username and password are required to log in; each investigator authorized to register patients has a personal login user name and password. If all criteria are met, patients are registered, and the allocated patient number is recorded in the patients‘ medical file.

4.5 DEFINITION END OF TRIAL
The study will end when all patients enrolled in trial have been followed for 5 years, died, withdrawn consent or are lost to follow-up. The trial steering committe may end enrolment at any time if it is deemed that this is in the best interest of the patients.
5 STUDY TREATMENT

The surgical procedure between treatment arms do not differ except for which surgical modality (RALS or LT). If results from ongoing studies (e.g. SHAPE study, ClinicalTrials.gov Identifier: NCT01658930) is presented during the course of the RACC study the surgical procedure might be altered but remains the same in both treatment arms. An amendment to protocol will then be made after decision by the Trial Steering Committee.

5.1 EXPERIMENTAL TREATMENT

- Radical hysterectomy, Type B or C according to the Querleu Morrow classification, (± salpingoophorectomy, ± salpingectomy) with pelvic lymphadenectomy after pelvic sentinel lymph node mapping and biopsy (± paraaortic lymphadenectomy at the institutions discretion) by robot-assisted laparoscopic surgery.

5.2 STANDARD/CONTROL TREATMENT

- Radical hysterectomy, Type B or C radical hysterectomy according to Querleu Morrow classification, (± salpingoophorectomy, ± salpingectomy) with pelvic lymphadenectomy after pelvic sentinel lymph node mapping and biopsy (± paraaortic lymphadenectomy at the institutions discretion) by laparotomy.
5.3 SURGICAL PROCEDURE

The surgery starts with injection of tracer in the uterine cervix and SLN biopsy (as defined in 5.4). _For RALS, an intrauterine manipulator is not allowed._ A vaginal probe/manipulator to delineate the vaginal fornices is allowed.

The abdomen is then entered at the discretion of the surgeon, the salpinx is closed by coagulation. After extirpation of the sentinel nodes the pelvic lymphadenectomy is performed followed by the radical hysterectomy. In case of leaving the ovaries in situ it is recommended that the salpinges are extirpated.

If surgery is performed by RALS the lymph nodes are retrieved via endo-catch or other specimen retrieval bags and the hysterectomy specimen is retrieved via the vagina.

Closure of the vagina before colpotomy is recommended but not mandatory.

5.3.1 Definition of radical hysterectomy

The extent of radicality according to the Querleu & Morrow classification should be based on tumor characteristics and national guidelines. The following types (Table 1) of radical hysterectomy is allowed in the trial. 30,68

Table 1

<table>
<thead>
<tr>
<th>Type</th>
<th>Lateral parametrium</th>
<th>Ventral parametrium</th>
<th>Dorsal parametrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>At the ureter</td>
<td>Partial excision of the vesicouterine ligament</td>
<td>Partial resection of the rectouterine-rectovaginal ligament and uterosacral peritoneal fold</td>
</tr>
<tr>
<td>B2</td>
<td>Identical to B1 plus paracervical lymphadenectomy without resection of vascular/nerve structures</td>
<td>Partial excision of the vesicouterine ligament</td>
<td>Partial resection of the rectouterine-rectovaginal ligament and uterosacral peritoneal fold</td>
</tr>
<tr>
<td>C1</td>
<td>At the iliac vessels transversally, caudal part is preserved</td>
<td>Excision of the vesicouterine ligament at the bladder. Proximal part of the vesicovaginal ligament</td>
<td>At the rectum (hypogastric nerve is dissected and spared)</td>
</tr>
</tbody>
</table>
5.3.2 Definition and anatomical boundaries for pelvic (and paraaortic) lymphadenectomy

Pelvic lymphadenectomy is defined as resection of all fatty tissue and lymph nodes in lymph node compartment 1 to 4, See Table 2.

Table 2

<table>
<thead>
<tr>
<th>Lymph node compartment</th>
<th>Cephalad limit</th>
<th>Lateral limit</th>
<th>Caudad limit</th>
<th>Medial limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>External iliac area</td>
<td>Bifurcation of external and internal iliac artery</td>
<td>Genitofemoral nerve</td>
<td>Cloquet's lymph node</td>
<td>External iliac vein</td>
</tr>
<tr>
<td>Obturator fossa</td>
<td>Internal iliac vein</td>
<td>Iliopsoas muscle</td>
<td>Os pubis, obturator nerve</td>
<td>Obliterated umbilical artery</td>
</tr>
<tr>
<td>Common iliac</td>
<td>Aortic bifurcation</td>
<td>Genitofemoral nerve</td>
<td>Bifurcation of external and internal iliac artery</td>
<td>Common iliac artery</td>
</tr>
<tr>
<td>Pre-sacral</td>
<td>Aortic bifurcation</td>
<td>Common iliac artery</td>
<td>Lower promontory</td>
<td>Hypogastric nerve (as distinction between right and left)</td>
</tr>
<tr>
<td>Lower paraaortic</td>
<td>Inferior mesenteric artery</td>
<td>Ureter</td>
<td>Aortic bifurcation</td>
<td></td>
</tr>
<tr>
<td>Higher paraaortic</td>
<td>Left renal vein</td>
<td>Ureter</td>
<td>Inferior mesenteric artery</td>
<td></td>
</tr>
</tbody>
</table>

5.3.2.1 Labelling of lymph node specimens for histopathology review

- Right pelvis: External iliac, obturator fossa, common iliac
- Left pelvis: External iliac, obturator fossa, common iliac
- Pre-sacral: Left, Right
- (Lymph nodes above the inferior mesenteric artery (higher paraaortic))
- (Lymph nodes below the inferior mesenteric artery (lower paraaortic))

The specimens are sent to for histopathological review labelled according to Appendix 16.5.
5.4 SENTINEL NODE BIOPSY

5.4.1 Surgical procedure

The abdominal part of the procedure starts with identification and extirpation of the sentinel lymph nodes. The sentinel lymph node biopsy procedure is described as follows and below must be adhered to. The description is applicable for both randomisation arms.

Injection of tracer in the uterine cervix, for details on dilution, dose and injection of ICG, see Appendix 16.6. For women randomised to RALS, a fornix presenter without an intracervical device is then adapted around the cervix. After entering the abdomen fluorescence imaging using the FireFly® Mode is utilized. The transperitoneal display of afferent lymphatic pathways from the uterine cervix is to be identified bilaterally. The two pathways comprise the upper paracervical pathway (UPP) (along the uterine artery to the external and obturator nodes, continuing lateral to the common iliac artery to the inframesenteric paraaortic nodes) and the lower paracervical pathway (LPP) (medial to the internal iliac artery to the internal iliac and presacral nodes and continuing medial to the common iliac artery to the inframesenteric paraaortic area) according to Geppert et al̆⁶⁹, see Figure 1.
If a pathway is not visualized through the peritoneum, the avascular presacral, paravesical and pararectal planes are opened, keeping the lymphatic vessels intact. In case of non-display in any pathway after 10 minutes, an ipsilateral re-injection at 3 or 9 o’clock of 0,25ml of the ICG-solution is performed if ICG is used. Display of pathways after the first and if needed the second injection is registered in the study case report form. A **SLN type 1** is defined as the juxta-uterine ICG/tracer positive node with an afferent ICG positive lymph vessel in the UPP and LPP respectively on each pelvic sidewall with the potential of parallel lymphatics in the UPP to the external, common iliac and obturator areas. In case of an ICG positive pathway with no ICG positive nodes, the node draining the ICG positive lymphatic channel was defined as **SLN type 2**.

Nodes macroscopically suspect of metastatic disease are defined as **SLN macro** regardless of ICG uptake although ICG positivity or negativity is noted in the study file. *These nodes are allowed to be sent for frozen section as per usual.* To avoid visual obstruction by ICG-leaking, SLNs is first removed along the LPP, see Figure 1.
The positions and types of SLNs are graphically illustrated by the surgeons during surgery on an anatomical chart. Following identification and removal of SLNs, a pelvic lymphadenectomy is then performed. (see Appendix 16.5)

*Frozen section of the sentinel lymph nodes during surgery is not allowed.*

The sentinel lymph node specimens are labelled and sent for histopathological review according to Appendix 16.5

New methodologies that may be introduced as routine procedure during the course of the study are also permitted, provided that the reliability is proven. Approval of new methods can only be granted by the study steering committee (coordinating investigators and trial steering committee).

In the laparotomy group a robotic endoscope with fluorescence imaging using the FireFly® Mode is utilized in the same manner as in the RALS group. If suffice funding is granted for the RACC trial, it is the aim of the coordinating investigator to provide each participating site with an Xi light weight robotic endoscope for this purpose only during the course of the RACC trial. If a participating centre have access to near infra-red endoscope for traditional laparoscopy, they are of course allowed.

### 5.4.2 Sentinel lymph node algorithm

The sentinel lymph node algorithm includes;

- Assessment of the UPP and LPP in both hemi-pelvises
- Reinjection of ICG tracer, if used, in the uterine cervix in case of uni- or bilateral non-display.
- Resection of all macroscopic suspicious lymph nodes regardless of mapping success or not.
5.4.3 If sentinel lymph node mapping fails

To avoid uneven distribution of ultrastaging between the treatment arms due to possible higher mapping rate of sentinel lymph nodes in any of the arms and thus possible uneven detection of micro-metastases, it is of utmost importance that below is adhered to.

In case of uni or bilateral mapping failure, “sampling” of lymph nodes in the previously most commonly described anatomic-topographic location of sentinel lymph nodes is performed, either uni or bilaterally\(^{61,70}\). Unpublished data from Persson and colleagues (Lund, Sweden) utilising ICG as tracer for detection of SLN is the basis of the anatomic locations that should be “sampled” in the RACC trial, see Figure 3.

The “sampled” lymph nodes are labelled as **SLN-sampling** and graphically illustrated by the surgeons during surgery on an anatomical chart just as the other sentinel lymph nodes (Appendix 16.7) and are also subjected to ultrastaging.

**Positions of SLN in cervical cancer following cervical injection of ICG**

![Figure 2](image-url)
5.4.4 Schema for sentinel node biopsy

Sentinel node biopsy

Injection ICG in uterine cervix

Enter abdomen evaluate transperitoneal display of afferent lymphatic vessels
Open the pelvic retroperitoneal surgical spaces

Display of tracer bilaterally

Non-Display tracer uni-/bilaterally

Reinjection of ICG according to protocol

Sentinel node sampling according to protocol

Non-Display ICG uni-/bilaterally

Send Sentinel Lymph Nodes for histopathological review with predefined labels according to protocol

CONVENTIONAL HISTOPATHOLOGICAL EXAMINATION

ULTRASTAGING

Pathology report and definition of lymph node metastases according to protocol
5.5 ADJUVANT TREATMENT

It is of utmost importance that adjuvant treatment is adhered to according to national or institutional guidelines, each participating centre will disclose indication for and schema of adjuvant treatment in the site identification and quality assessment form (see Appendix 16.7). Patients enrolled in the RACC trial can be enrolled in other trials on adjuvant medical oncologic treatment. However, it is crucial, that these protocols are open for ALL patients from both treatment arms.

6 EVALUATION OF HISTOPATHOLOGY

6.1 HYSTERECTOMY SPECIMEN

Hysterectomy specimens will be received and cut in accordance to the clinical routine at each of the participating centres. No adjustment of routine specimen management is required for the trial.

6.2 LYMPH NODES SPECIMENS

6.2.1 Non-sentinel lymph nodes

All macroscopically identified lymphoid tissue is embedded and, if the minimum thickness exceeds 3 mm, bisected and stained for hematoxylin and eosin (H&E).

6.2.2 Sentinel lymph nodes

All macroscopically identified lymphoid tissue is embedded and bisected if the minimum thickness exceeded 3 mm and stained for H&E, if negative for metastasis, ultrastaging is performed.

Ultrastaging using H&E staining is performed in five sections at three different levels, 200 \( \mu \text{m} \) apart, if the maximum diameter of the sentinel node tissue exceeded 1 mm. Immunohistochemistry (IHC) with staining for a cytokeratin marker, (for example pan-cytokeratin, cytokeratin MNF 116, AE1/AE3) is performed on the last, deepest level.
6.2.3 Definition of lymph node metastases

- Macro-metastases = tumour greater than 2.0 mm in diameter.
- Micro-metastases = tumour cell aggregates between 0.2 and 2.0 mm in diameter.
- Isolated tumour cells = individual tumour cells or aggregates that are less than 0.2 mm in diameter, usually detected by immunohistochemistry and less than 200 cells. *(e.g. if less than 0.2 mm but more than 200 cells (or vice versa) = micro metastases).*
- Tumour absent – no tumour cells identified in H&E (or immunohistochemically, if applicable) stained sections.

The classification is according to American Joint Committee on Cancer (AJCC) staging for axillary nodes in breast cancer. ⁷¹

6.3 PATHOLOGY REPORT

6.3.1 Hysterectomy specimen

Standard parameters in cervical cancer must be reported in the pathology report. Standard pathology reporting includes current, relevant prognostic histopathologic variables such as tumor type and grade, tumor size, tumor extension, resection margin status, presence or absence of lymph vascular invasion, and status of the vaginal manchette and parametria.
6.3.2 Lymph node specimen

Number of lymph nodes and metastatic lymph nodes per anatomic station 1-4 must be reported (see 5.3.2)

Number of sentinel lymph nodes and metastatic sentinel lymph nodes per anatomic station must be reported. In the event of no identified lymph nodes in the sentinel lymph node specimen, (“empty packet”) this must be reported

6.4 QUALITY ASSURANCE HISTOPATHOLOGY

All specimens must be evaluated/re-reviewed by the local gynecologic reference pathologist before entering data in the eCRF.

7 TRANSLATIONAL RESEARCH COMPONENT

The study will include a translational research component, which will have its focus on developing and validating novel biomarkers for prediction of lymph node status, prediction of recurrence risk and evaluation of therapy response. In addition, tumour material will be prospectively collected to allow for molecular tumour characteristics to be correlated with clinically relevant endpoints. The translational studies will be performed upon prospectively collected blood (collected at several time-points during the study, see 3.2 Schedule of events table) and tumor material. In addition, tumor material removed and processed by the clinical pathology labs will be collected and analysed for biomarkers of treatment and response.

It is highly encouraged but not mandatory for participating centres outside Sweden to participate in this part of the trial.

8 QUALITY ASSURANCE OF SURGERY

8.1 PARTICIPATING CENTERS

A site quality assessment form (see Appendix 16.7) including, institutional experience with RALS, annual volume of surgical gynecologic oncology cases and cervical cancer must be completed. In addition, 10 anonymous surgery reports from both radical hysterectomies and advanced ovarian cancer primary surgeries accompanied by their histopathology reports within 24 months has to be sent to the trial steering committee for review. Moreover, surgical
variables (e.g. operation time, blood loss) and complications within 30 days after surgery according to Clavien Dindo must be reported (see Appendix 16.7). Furthermore, the infrastructure to participate in the trial must be satisfactory and data on institutional algorithm and indication for adjuvant treatment and what it constitutes must be reported. The total annual case-load of robotic procedures per site must exceed 100. In addition, the institutions ability to perform ultrastaging is considered.

If sentinel lymph node biopsy with ICG tracer is not an established procedure the Subcommittee on Sentinel lymph node biopsy and/or Trial Steering Committee will arrange on-site training.

During the study, it is at the discretion of the coordinating investigators and Trial steering committee to close centres with a higher than average rate of postoperative major complications or poor quality of surgery, from further accrual, temporarily or irrevocably after consultation with the Data Safety Monitoring Board.

8.2 PARTICIPATING SURGEONS
All included surgeons outside the primary investigating centre must be approved by the coordination investigators/s ensuring adherence to protocol. In the site identification and quality assessment form the participating surgeons experience and annual case-load will be reported for review. It is at the discretion of the coordinating investigators to select or deselect individual surgeons from participating in the trial. Audits on site or videos of procedures can be requested at the discretion of the coordinating investigators. Only surgeons stated in the Quality assessment form (see Appendix 16.7) are allowed being lead surgeons, amendments during the trial can be made.

8.2.1 Robot-assisted laparoscopic surgery
All included surgeon must have a previous experience of at least 20 radical hysterectomies and pelvic lymphadenectomies.

8.2.2 Laparotomy
All included surgeons must have a previous experience of at least 20 pelvic lymphadenectomies and an annual case load of at least 10 surgeries for advanced pelvic surgery including pelvic lymphadenectomy. Previous experience of at least 10 open radical hysterectomies is mandatory.
9 PATIENTS REPORTED OUTCOMES (PROs)

Women with early stage CC are relatively young with high chance of long-term survival. Recurrences are most prevalent within 2 years after treatment and conditional survival after 5 years is excellent. For this reason, it is of utmost importance to offer affected women the treatment that causes the least possible late side-effects. Patient reported outcome measures are used to evaluate incidence and grade of late effects related to the standard and the experimental arm. A special focus will be on late side-effects related to para-sympathetic nerve injuries, e.g. bladder and sexual dysfunction in addition to lymphoedema, physical-, emotional, and role functioning, fatigue and pain. One of the secondary aims of the RACC trial is therefore to compare patient-reported outcomes measures, i.e. patients’ HRQoL between the treatment arms in the short-, long- and term. All women included in the RACC trial will be asked to answer the questionnaires.

9.1 POINTS OF ASSESSMENT

Baseline assessment will be obtained prior to randomisation and thereafter prospectively 1 and 6 months post-surgery. Long-term effects will be assessed after 1, 2 and 5 years.

9.2 INSTRUMENTS

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30, version 3.0 (EORTC QLQ-C30) is a HRQoL instrument developed to be multidimensional in structure and self-administrative to be used in clinical cancer trials. It includes nine multi-item scales and six single item variables. The five functional scales consist of physical- (PF), role- (RF), emotional- (EF), social- (SE), and cognitive functioning (CF). Fatigue (FA), nausea/vomiting (NV) and pain (PA) comprise the three multi-item symptom scales. Additional symptoms are assessed by single items: dyspnoea (DY), sleep disturbances (SL), appetite loss (AP), constipation (CO), and diarhoea (DI). One single item scale concern financial problems related to disease and treatment. Most items are responded to on a four-point Likert scale ranging from 1 (not at all) to 4 (very much). The two items assessing global health and overall quality of life are responded to in seven categories ranging from 1 (very poor) to 7 (excellent).
The EORTC QLQ Cervical Cancer Module (CX-24) is a cervical cancer specific questionnaire developed and validated for use in women with cervical cancer. It comprises 24-items divided into four functioning scales: Body image (CXBI), sexual activity (CXSXA), sexual enjoyment (CXSXE), Sexual/vaginal functioning (CXSV); and four symptom scales: symptom experience (CXSE), lymphoedema (CXLY), peripheral neuropathy (CXPN), menopausal symptoms (CXMS), sexual worry (CXSW). The questionnaire has been validated in an international study. Completion of the questionnaire takes about 15 min. The items are responded to in the same four categories as most items in the EORTC QLQ-C30.

The generic and disease-specific EORTC questionnaires are supplemented by 10 screening items on lymphoedema in the legs, the genital- and theinguinal region. These items derive from the EORTC item bank and has been developed and validated (and translated) with the contribution of patients from the Nordic countries. These items are supplemented by the Lymphedema Quality of Life Questionnaire (LYMQOL) which is a validated condition-specific quality of life assessment tool, i.e. to be completed only if the patient report that she has lymphoedema. The LYMQOL assesses the impact of lymphoedema on several aspects of the patient's life. The LYMQOL has been forward-backward translated to several languages. LYMQOL may only be used within the RACC study by centers in which the questionnaire’s translation has been validated.

EQ-5D is a standardized non-disease specific instrument for describing and valuing HRQoL, developed by the EuroQoL group. It includes five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with three levels of responses each (no problems, some problems or extreme problems). The EQ-5D also comprises a 20cm visual analogue scale (VAS) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) on which the respondent rates the current health. The index-based score is interpreted along a continuum where 1 represents best possible health and 0 represents dead. Some health states are given a figure below zero (worse than death).

9.3 PROCEDURE
First questionnaire: Before inclusion in the study, the patient is informed orally and in writing about the HRQoL assessment. The first questionnaire is completed before information is
conveyed about to which arm the patient have been randomization.

Subsequent questionnaires will be collected in connection to the visits at the clinic/electronically/per conventional mail. The instruments will be given to the patient in the appropriate language for the site. The treating physicians will not have access to the HRQoL-forms. Completed questionnaires are always considered source document and must be filed accordingly.

10 HEALTH CARE COSTS

At the discretion of the chair of the sub-committee on health care costs.

11 STATISTICAL CONSIDERATIONS

11.1 DATA ANALYSES

11.1.1 Primary endpoint

Recurrence-free survival time will be calculated from the date of randomization to the date of local recurrence, the date of distant recurrence or date of death (any cause), whichever comes first. For event-free patients, survival time will be calculated from the date randomization to the date of last clinical follow-up.

Recurrence-free survival (RFS) will be graphically displayed as Kaplan-Meier curves. Differences in survival times will be tested using a stratified (centre) log-rank test. The effect of treatment on time to failure will be estimated using a stratified (centre) proportional hazards regression model. Results will be presented as a hazard ratio (HR) together with a 90% confidence interval (CI), which corresponds to the one-sided hypothesis. As this is the main endpoint in the study, a graph illustrating the estimated HR and 90% CI together with the non-inferiority margin (HR=1.57) will also be presented.

All analyses of RFS will be performed according to the intention-to-treat principle but may also be presented as per-protocol.
11.1.2 Secondary endpoints

Overall survival

Survival time will be calculated as the period between date of randomization to the date of death (any cause), or for patients still alive to the date of last clinical follow-up. Differences in survival times will be tested using a stratified log-rank test, and the effect of treatment on time to death will be estimated using a stratified proportional hazards regression model. Results will be presented as a hazard ratio (HR) together with a 90% confidence interval.

HRQoL

Data for the EORTC QLQ-C30/EN24 will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual. All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where;

- a high score for a symptom scale or item represents a high level of symptoms or problems
- a high score for a functional scale represents a high or healthy level of functioning
- a high score for the global health status/QoL represents high QoL.

Compliance with completing the questionnaires will be investigated at each time point to evaluate the procedure for data collection and the feasibility of the questionnaires.

The effect of treatment, time, and the treatment-time interaction will be evaluated using linear mixed-models using all available longitudinal data on each of the scale scores at the different time points. Considering multiple testing, the results from the regression analysis will be presented as mean differences together with 99% confidence intervals.

In the interpretation of the EORTC QLQ-C30, CX-24 scores and the lymphoedema items a difference of ≥5 points on the 0–100 scales will be considered clinically important. Differences of 5–9 points are considered small, those of 10–20 as moderate, and ≥20 as large. For EQ-5D published weights are available that allow for the creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction and 1 as perfect health.
Intraoperative and Post-operative complications

Post-operative complications will be presented by numbers and percentages for each treatment. Differences in post-operative outcome will be tested using Fisher’s exact test, but may also be presented as differences in proportions together with 99% confidence intervals to guard for multiple testing.

Diagnostic accuracy of the sentinel node biopsy

Assuming that 65% of participating women also participate in the sentinel node part of the trial and that 10% of participating women have lymph node metastases, at least 50 women with lymph node metastases will be recruited.

Under the null hypothesis that the sensitivity of the sentinel lymph node specimen is 85% and tested against a one-sided alternative with a desired sensitivity of at least 92.5% the study will be powered (with an alfa of 0.05 and beta 0.2) if $≥ 48$ of the 50 women with lymph node metastases are correctly identified in their sentinel lymph node. Above according to first stage of the Fleming two stage design, which might be expanded to its second stage in the final analysis \(^{79}\). Exact 95% confidence intervals and sensitivity and negative predictive values are reported and estimated by proportions.

Health care costs

At the discretion of the chair of the sub-committee on health care costs.

11.2 HYPOTHESIS

That RALS will not worsen RFS at 5 years by more than a maximum of 7.5%. Assuming a 5-year RFS of 85% for patients treated with standard treatment (radical hysterectomy and pelvic lymphadenectomy by laparotomy) this corresponds to a hazard rate of 1.57.

11.3 POWER CALCULATION

The clinical non-inferiority margin (NIM) is in this study defined as a 5-year RFS not worsened by more than 7.5%. To show that the 5-year RFS in the RACC arm is not worse than $77.5\%$ compared to the expected 5-year rate of 85% in the standard arm, the study needs to observe 127 events with a one-sided level of significance ($\alpha$) of 5% and a power (1-$\beta$) of 80%. It is estimated that with 5 years of recruitment and 3 years of follow-up, the necessary number of events will be reached if the study can recruit totally 768 patients.
The NIM at 5-years correspond to a hazard ratio ($HR_{RALS \text{ vs } \text{ Standard}}$) of 1.57. If, at the time of the statistical analysis, the upper two-sided 90% confidence interval – this corresponds to a one-sided test at the 5% level – falls below 1.57, non-inferiority will be concluded.

### 11.4 SAMPLE SIZE

Necessary sample size for this study is estimated to 768 patients, recruited during a 5-year period.

The sample size is based on an observed RFS of 85% from the Swedish Quality Register of Gynecologic Cancer (SQRGC) 2011-2017. However, the sample size ultimately depends on the true RFS in the RACC-trial. The following sensitivity analysis demonstrates the changes in sample size depending on true RFS:

<table>
<thead>
<tr>
<th>Standard RFS</th>
<th>$HR_{\text{NIM}}$</th>
<th>Experimental RFS</th>
<th>Absolute NIM</th>
<th>Total events</th>
<th>Total sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>85%</td>
<td>1.568</td>
<td>77.5%</td>
<td>7.5%</td>
<td>127</td>
<td>768</td>
</tr>
<tr>
<td>87.5%</td>
<td>1.671</td>
<td>80.0%</td>
<td>7.5%</td>
<td>97</td>
<td>712</td>
</tr>
<tr>
<td>90%</td>
<td>1.826</td>
<td>82.5%</td>
<td>7.5%</td>
<td>72</td>
<td>656</td>
</tr>
</tbody>
</table>

According to the NORDCAN database, approximately 1400 women are diagnosed with cervical cancer annually in the Nordic countries. When the RACC inclusion criteria are applied, approximately 25% are eligible for inclusion in the trial (350 women/year). With an inclusion rate of 70%, an accrual period of 4 years is reasonable.

### 11.5 INTERIM ANALYSIS AND STOPPING RULES

An independent Independent safety and monitoring committee will review the data and carry out one interim analysis 3 years after the first patient is randomized or when 300
patients have been included in the study, whichever comes first. The purpose of this interim analysis is to assess the overall failure (recurrence/death) rate, to assess the recruitment to the study and to make sure that none of the treatment groups appear to fare worse than the other. The committee may recommend terminating the study if a statistically significant (p<0.001) difference in RFS between the study groups is observed, or if the recruitment is so low that the necessary number of events is unlikely to be seen. The interim analysis is performed based on blinded data. If the committee determines that it is safe to proceed with the study, the results of the interim analysis will remain unknown to everyone except the committee members.

12 ETHICAL CONSIDERATIONS

12.1 RISK-BENEFIT CONSIDERATION

At present, two large studies have demonstrated that MIS is associated with a higher rate of recurrence and death from disease. This is clearly deeply concerning, especially since no clear cause has been established. Most industrialised countries have abandoned the open approach in favour of MIS with substantial investments in education and equipment. A return to open radical hysterectomy will dramatically affect the health care systems, especially in the Nordic countries. The centralisation of cancer care in the Nordic countries has been successful with effects on survival for several malignancies \(^{80,81} \). The use of nationwide quality registers has further improved the oncologic management and constitutes a reliable data source for research and quality improvements. The preliminary analyses from the Danish and Swedish quality registers support previous retrospective data with no difference in DFS or OS between RALS and open surgery.

Since the LACC trial demonstrated an association between MIS and disease recurrence, the risk for similar outcomes in the RACC trial cannot be neglected. However, the potential risk should be balanced against the potential benefits including the preservation of an established surgical system, improved lymph node assessment, improved quality of life and future developments within the robotic platform. An interim analysis will be performed as stated above.
This study will be conducted according to ICH-GCP, national law and guidelines and the Helsinki declaration. Before patient inclusion starts, this study protocol will be approved by an ethical review board in each country.

There is no study specific insurance for participating subjects, who are covered by the regular health-care insurance plan in their respective country.

12.2 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE
The study protocol, patient information and informed consent form will be submitted to the ethics committee for approval. The study will only commence after approval by the ethics committee. All substantial protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval before implementation. Once approved by the appropriate Independent Ethics Committee or Institutional Review Board, the investigator shall implement such Protocol modifications. Protocol modifications for urgent safety matters shall however be directly implemented.

12.3 INFORMED CONSENT AND WITHDRAWAL
Before inclusion in the study, patients will be given oral and written information of the study aims, all treatment procedures and expected and possible adverse events. They will be informed as to the strict confidentiality of their patient data, and that their medical records will be reviewed by their treating physician and study personnel only. The patient is at any time, with or without given reason free to withdraw their consent to study participation, and this choice will not affect their subsequent treatment options or care.

Written Informed Consent must be obtained from all participants before enrolment in study. The Informed Consent Form should also be signed at the same occasion by the investigator who gave the written and verbal information. The Informed Consent Form should be filed in the Investigator’s File and one copy should be given to the study participant. The study participants will consent to: participate in the study; regulatory authorities and sponsor’s representative (e.g. monitor) to gain full access to hospital records, to control the data collected in the study; recording, collecting and processing data and storing data in a database; and storing of study samples in a biobank (if the participating centre is part of the translational part of the RACC trial).
12.4 PATIENT PROTECTION AND GOOD CLINICAL PRACTICE

The responsible investigator will ensure that the study is conducted in agreement with the declaration of Helsinki and/or Swedish/National laws and regulations; whichever provides the greatest protection for the patient. The participant should be clearly informed that the data collected in the study will not identify any subject taking part in the study following the General Data Protection Regulation (GDPR) (EU 2016/679). Participating women will be treated according to the international guidelines on GCP as defined by the European Parliament (EG596/200).

12.5 SUBJECT IDENTIFICATION

Participating patients will be identified by a study specific code consisting of a two to six-digit number. This code will be used when registering the patient into the study database. The woman’s national identification number will not be entered into the database. The key to the code will be available to the investigator only.

13 SIGNIFICANCE OF STUDY

The aim of the RACC trial is to establish the safety of robot-assisted radical hysterectomy for early stage cervical cancer. Robot-assisted laparoscopy is currently the most common approach in the Nordic countries and it is of utmost importance to verify registry-based data in a prospective, randomized trial. In addition, the use of sentinel node biopsies is increasing although the accuracy and safety has not been established. The RACC trial has the potential to determine these aspects of the sentinel node concept.

14 ADMINISTRATIVE CONSIDERATIONS

14.1 FINANCING

This is an academic study sponsored by the coordinating investigator, Stockholm County Council, with no involvement of any external sponsor. The Clinical Trial Office at Center for Clinical Cancer studies, Theme Cancer, Karolinska University Hospital, Stockholm,
Sweden will coordinate the study. All central administrative expenses related to the trial (statistics, monitoring, questionnaires) are covered by research grants. The goal is to receive sufficient grants to partially or fully fund the study specific costs for each participating site. Each participating centre is free to seek financing of their own.

**14.2 PUBLICATION POLICY**

Before publication of the main oncological outcome, no other publication regarding oncological outcome on parts of the cohort can be attempted. The Coordinating investigator and study coordinator will be first and last author of the main oncologic outcome. The members of the trial steering committee must also be (co)-authors in all (other) publications. The members of each sub-committee will be authors of their respective sub-objective. The chair of each sub-committee will be first or last author and assembles the first draft of the manuscript. The coordinating investigator and study coordinator will be part of interpretation of data and order of authors for each publication from the sub-committees. One author (principal investigator) from each participating site, pending data completeness and quality, is to be co-author on any publication reporting on the main findings of the RACC trial, that is, any report on oncological outcome and other key publications. If number of authors are limited by the respective scientific journal, contributing sites that have recruited most participants and closed follow up will be selected. All investigators must agree to the fact that upon completion of data collection and analysis of data by study statistician, if the investigators are not in agreement with the outcomes of the results, they may elect to not be part of the authorship of the manuscript; however, the data entered from their site will be maintained and analysed as agreed at the initiation of the study and confirmed as per of this agreement.

**14.2.1 Sub-analysis other than primary and secondary outcomes from the RACC trial**

Further sub-analysis (other than the stated primary and secondary outcomes of the RACC trial) or other research projects from the participating investigators using data from RACC trial is allowed and encouraged but permission must be granted from the Trial Steering Committee after written application. The application must include; primary and secondary objective, inclusion/exclusion criteria, name of individual who will write the manuscript (including first and last author), intended name of journal for submission, and approval from respective institutional review board. The ultimate decision on authorship will be approved by the Trial Steering Committee.
14.3 ADHERENCE TO PROTOCOL AND PROTOCOL AMENDMENT

The study protocol must be adhered to. Any deviation must be documented and the Trial steering committee must be informed. Changes or supplements to the study protocol can only be decided on and authorized by the coordination investigator, study coordinator, trial steering committee and statistician. Once approved by the appropriate Independent Ethics Committee or Institutional Review Board, the investigator shall implement such Protocol modifications. Protocol modifications for urgent safety matters shall however be directly implemented.

15 DATA MANAGEMENT AND QUALITY CONTROL

15.1 SOURCE DATA AND CASE REPORT FORM

Patient medical records will be source data and will be stored according to Good Clinical Practice (GCP) at, Karolinska Theme Cancer, Karolinska University Hospital. Data for this study will be recorded via an Electronic Data Capture (EDC) system, PheedIt, using an electronic Case Report Form (eCRF). It will be transcribed by the site from the paper source documents onto the eCRF. In no case is the eCRF to be considered as source data for this trial. Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the investigator’s records by the study monitor (source document verification).

The study database is situated in Sweden at the Center for Clinical Cancer studies, Theme Cancer at Karolinska University Hospital.

15.2 DATA RECORDING AND RECORD KEEPING

Data recording and data keeping will be managed by CTO, Center for Clinical Cancer studies, Theme Cancer, Karolinska University Hospital and stored for a minimum of 10 years after declaration of end of trial. All access to data via Principal Investigator or Investigators.

15.3 DATA PROTECTION

Recorded information is confidential and the database is privacy-protected; i.e., no data can be traced back to the patient in research reports and no unauthorized individuals may have access to the data about individuals in the database. The database will be maintained until further notice (at least 20 years after inclusion of the last patient) and be reported in
accordance with the GDPR. The authority responsible for the database is Karolinska University Hospital, Stockholm, Sweden.

15.4 PARTICIPANT CONFIDENTIALITY
The investigator must assure that patients’ anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Trial steering committee, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrolment log showing codes, names and addresses.

15.5 STORAGE OF STUDY DOCUMENTS
To comply with national and international guidelines patient’s identification list and patient records and other study related documents will be retained for at least 10 years after the closure of the trial. This data will only be available to investigator(s) and investigator appointed personnel involved in the clinical trial.

15.6 QUALITY CONTROL AND MONITORING
The quality control of this trial in Sweden will be performed by CTO, Center for Clinical Cancer studies, Theme Cancer, Karolinska University Hospital.

This trial will be monitored regularly according to GCP and local regulations. All information reported in the eCRFs will also be documented in the patient’s file unless otherwise specified. The investigator will allocate adequate time for visits performed by the monitor. The investigator will also ensure that the monitor is given access to source documents which support data entered into the eCRF’s. The investigator further assures direct access to source data for possible trial-regulated regulatory audits.
16 APPENDICES

16.1 FIGO

FIGO staging cervical cancer

Stage I:
The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)
- IA Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
  - IA1 Measured stromal invasion <3 mm in depth
  - IA2 Measured stromal invasion ≥3 mm and <5 mm in depth
- IB Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri
  - IB1 Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
  - IB2 Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
  - IB3 Invasive carcinoma ≥4 cm in greatest dimension

Stage II:
The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
- IIA Involvement limited to the upper two-thirds of the vagina without parametrial involvement
  - IIA1 Invasive carcinoma <4 cm in greatest dimension
  - IIA2 Invasive carcinoma ≥4 cm in greatest dimension
- IIB With parametrial involvement but not up to the pelvic wall

Stage III:
The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes
- IIIA Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
- IIIB Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
- IIIC Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)
  - IIIC1 Pelvic lymph node metastasis only
  - IIIC2 Paraaortic lymph node metastasis

Stage IV:
The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV
- IVA Spread of the growth to adjacent organs
- IVB Spread to distant organs

* Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages.
* The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.
* Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r and, if confirmed by pathological findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.
16.2 CLAVIEN

Postoperative complications within 30 days after surgery according to Clavien Dindo

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.</td>
</tr>
<tr>
<td>II</td>
<td>Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.</td>
</tr>
<tr>
<td>III</td>
<td>Requiring surgical, endoscopic or radiological intervention</td>
</tr>
<tr>
<td>IIIa</td>
<td>Intervention not under general anesthesia</td>
</tr>
<tr>
<td>IIIb</td>
<td>Intervention under general anesthesia</td>
</tr>
<tr>
<td>IVa</td>
<td>Life-threatening complication (including CNS complications) requiring ICU/ICU-management</td>
</tr>
<tr>
<td>IVb</td>
<td>Single organ dysfunction (including dialysis)</td>
</tr>
<tr>
<td>V</td>
<td>Death of a patient</td>
</tr>
<tr>
<td>'d'</td>
<td>If the patient suffers from a complication at the time of discharge (see examples in Appendix B, <a href="http://Links.Lww.com/SLA/A3">http://Links.Lww.com/SLA/A3</a>), the suffix &quot;d&quot; (for &quot;disability&quot;) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.</td>
</tr>
</tbody>
</table>

1. Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit

www.surgicalcomplication.info

16.3 CTCAE 3.0

Lymphatic side effects according to the Common Terminology Criteria (CTC) version 3.0

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower extremity lymphedema</td>
<td>5%-10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; pitting edema</td>
<td>10%-30% inter-limb discrepancy in volume or circumference at point of greatest visible difference</td>
<td>&gt;30% inter-limb discrepancy in volume; lymphoedema, interfering with activities of daily life</td>
<td>Progression to malignancy (i.e. lymphangiosarcoma), amputation indicated, disabling</td>
</tr>
<tr>
<td>Truncal/genital lymphedema</td>
<td>Swelling or obstruction of anatomic architecture on close inspection, pitting edema</td>
<td>Readily apparent obstruction of anatomic architecture; obliteration of skin folds</td>
<td>Lymphoedema; interfering with activities of daily life; gross deviation from normal anatomical contour</td>
<td>Progression to malignancy (i.e. lymphangiosarcoma); disabling</td>
</tr>
<tr>
<td>Lymphocele</td>
<td>Asymptomatic, clinical or radiographic findings only</td>
<td>Symptomatic; medical intervention indicated</td>
<td>Symptomatic and interventional radiology or operative intervention indicated</td>
<td>–</td>
</tr>
</tbody>
</table>
16.4 INTRAOPERATIVE ADVERSE EVENTS

According to Rosenthal et al.\(^8^4\).

![Table 2. Proposed Classification of Intraoperative Complications (CLASSIC)](image)

 grades.

![Table 1. Intraoperative Adverse Event Severity Classification Scheme](image)

![Table 2. Generic Examples of Intraoperative Adverse Events at Each Severity Class](image)

According to Kaafarani et al.\(^8^5\).
16.5 LABELLING OF LYMPH NODE SPECIMENS AND LOCATION OF SENTINEL LYMPH NODES

Labeling of lymph node specimens RACC trial  

<table>
<thead>
<tr>
<th>#</th>
<th>Lymph node basin/station</th>
<th># to pathologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LN External iliacs Right side</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>LN Obturator fossa Right side</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>LN Common iliac Right side</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>LN Presacral Right side</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>LN External iliacs Left side</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>LN Obturator fossae Left side</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>LN Common iliac Left side</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>LN Presacral Left side</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>LN Paraortic below the IMA</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>LN Paraortic above the IMA</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>SLN type 1</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>SLN type 1</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>SLN type 1</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>SLN type 1</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>SLN type 1</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>SLN type 1</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>SLN type 2</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>SLN type 2</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>SLN type 2</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>SLN macro</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>SLN macro</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>SLN sampling</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>SLN sampling</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>SLN sampling</td>
<td></td>
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<tr>
<td>25</td>
<td>SLN sampling</td>
<td></td>
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<tr>
<td>26</td>
<td>SLN sampling</td>
<td></td>
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<tr>
<td>27</td>
<td>SLN sampling</td>
<td></td>
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<tr>
<td>28</td>
<td>SLN sampling</td>
<td></td>
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<tr>
<td>29</td>
<td>SLN sampling</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>SLN sampling</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If a lymph node (LN) specimen from a station is missing the row is deleted but the number for each station remains. The position of the Sentinel Lymph Nodes (SLNs) are written by the surgeon during surgery and anatomic position of the SLN and type of SLN is also marked in the illustration. Each number have a corresponding sticker which is labelled on the jar for histopathological review. The stickers for SLNs are red. It is helpful to also write to location of SLN in the above chart by hand. Number 31-33 are for eventual circumstances and the sticker must be written and labelled by hand. *According to local guidelines if applicable.
Labeling of lymph node specimens RACC trial

<table>
<thead>
<tr>
<th>Display after 1st injection</th>
<th>Reinjection cervix: ☐ yes ☐ no</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPP</td>
<td>LPP</td>
</tr>
<tr>
<td>Right</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
</tr>
</tbody>
</table>

Instructions: Only one marking for each Sentinel lymph node with jar number and type of SLN, see below.

○ = **SLN type 1** (ICG positive sentinel node)

☐ = **SLN type 2** (ICG negative node with obvious afferent ICG positive lymphatic vessel adjacent to the uterus)

☒ = **SLN macro** (By the naked eye lymph node suspicious of metastasis with or without uptake of ICG)

∆ = **SLN-sampling** (non-display of ICG, mapping failure, see Figure 3 for exact anatomic locations to sample)
Positions of SLN in cervical cancer following cervical injection of ICG

- Left proximal obturator fossa (64%)
- Left medial external iliac (between external and internal iliac arteries) (78%)
- Left internal iliac/presacral (56%)
- Left lateral external iliac/distal common iliac (8%)
- Right proximal obturator fossa (62%)
- Right medial external iliac (between external and internal iliac arteries) (82%)
- Right internal iliac/presacral (64%)
- Right lateral external iliac/distal common iliac (16%)

*Figure 3*
## 16.6 ICG DILUTION, DOSE AND INJECTION

<table>
<thead>
<tr>
<th>Indocyanine Green solution (ICG)</th>
<th>2.5mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Pulsion medical system, Feldkirchen Germany</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>ICG will be provided by the manufacturer to each site.</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Is a sterile, lyophilized green powder containing 25 mg of Indocyanine green with no more than 5% sodium iodide.</td>
</tr>
<tr>
<td><strong>Preparation</strong></td>
<td>The ICG solution is prepared immediately before surgery and intended for single patient use. For preparation, 10mL of sterile water is injected directly into the lyophilized ICG in its glass vial. Invert the vial multiple times to ensure thorough mixing.</td>
</tr>
<tr>
<td></td>
<td>Draw up 0.25 mL in six 1 mL syringes from the vial with ICG solution (2.5mg/mL) for the cervical injection.</td>
</tr>
<tr>
<td></td>
<td>The content of four of the syringes are used for the initial injection and in case of non-display of any pathway one or two of the other are used for an ipsilateral re-injection.</td>
</tr>
<tr>
<td><strong>Injection site</strong></td>
<td>Half the ICG volume in each of four syringes is injected in the cervical sub-mucosa and half the volume 3 cm into the cervical stroma at 2-4-8-and 10 O’clock respectively to a total dose of 2.5mg ICG and a total volume of 1 mL.</td>
</tr>
<tr>
<td></td>
<td>The display of ICG in the respective pathways will be evaluated a minimum 10 minutes after the injection of ICG.</td>
</tr>
<tr>
<td></td>
<td>A second ipsilateral injection of 0.25mL ICG is performed in case of non-display of either of lymphatic pathways after a minimum of 10 minutes’ observation time after ICG injection. The injection is done at 3 and 9 O’clock respectively, half the volume in the cervical sub-mucosa and half the volume 3 cm into the cervix.</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>The ICG solution is stored at room temperature. The solution is active for 6 hours, and should be discarded after that period of time.</td>
</tr>
</tbody>
</table>
16.7 SITE IDENTIFICATION AND QUALITY ASSESSMENT FORM

RACC – Robotic approach to Cervical cancer
Robotic assisted surgery versus laparotomy in patients with early cervical cancer

Dear Investigator,

Thank you for being interested in participating in the RACC trial.

In order to evaluate the feasibility of your site for participation some information regarding surgical quality and resources needs to be disclosed.

Please read, complete and sign the following documents together with the required reports and send it by email to: sahar.salehi@sll.se

According to the study protocol the following criteria are to be fulfilled by centers considered for participation in the trial.

- Established robotic surgery unit for at least 3 years
- At least 10 radical hysterectomies for early stage cervical cancer per year in the unit
- Minimum of 20 radical upfront debulking surgeries per year for advanced ovarian cancer
- Intensive care unit available
- Ability to perform ultrastaging of lymph nodes
- Cooperation with a gynaecologic reference pathologist

The Trial Steering Committee requires following information from each institution before initiation, data is required for the last 24 months:

- 10 anonymous surgical reports of patients that have undergone radical hysterectomy for cervical
- 10 anonymous surgical reports of patients operated upfront with radical debulking surgery for advanced ovarian cancer
- For each patient, the surgical report is accompanied by corresponding anonymous pathological report.
- Attached to each surgical report, operation time in minutes, per-operative bleeding in mL and 30-day postoperative complications according to Clavien Dindo classification must be stated.
RACC – Robotic approach to Cervical cancer
Robotic assisted surgery versus laparotomy in patients with early cervical cancer

Information on study site

<table>
<thead>
<tr>
<th>Hospital name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Department</td>
<td></td>
</tr>
<tr>
<td>Street</td>
<td></td>
</tr>
<tr>
<td>Zip code/City/Country</td>
<td></td>
</tr>
<tr>
<td>Principal investigator</td>
<td></td>
</tr>
<tr>
<td>Participating surgeon’s</td>
<td></td>
</tr>
<tr>
<td>Research coordinators and study nurses/assistants</td>
<td></td>
</tr>
<tr>
<td>Telephone number</td>
<td></td>
</tr>
<tr>
<td>Investigator</td>
<td></td>
</tr>
<tr>
<td>Research Coordinator</td>
<td></td>
</tr>
<tr>
<td>Fax</td>
<td></td>
</tr>
<tr>
<td>Investigator</td>
<td></td>
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<tr>
<td>Research Coordinator</td>
<td></td>
</tr>
<tr>
<td>Email</td>
<td></td>
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<tr>
<td>Investigator</td>
<td></td>
</tr>
<tr>
<td>Research Coordinator</td>
<td></td>
</tr>
</tbody>
</table>
RACC – Robotic approach to Cervical cancer

Robotic assisted surgery versus laparotomy in patients with early cervical cancer

Facilities/Technique/Resources

<table>
<thead>
<tr>
<th>Facilities/Technique/Resources</th>
<th>□ yes</th>
<th>□ no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centralized care of cervical cancer patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive Care unit available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access to transfusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access to medical and radiation oncology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capacity to perform surgery within 4 weeks of enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modern anesthesiologic pain management established (e.g. epidural analgesia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Close documentation within 4 weeks after each planned visit according to protocol can be assured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specify available resources for documentation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of responsible person for documentation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measures established for follow up of overall survival, please describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agreement to use an e-CRF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agreement to register all patients with suspected invasive Cervical cancer stage IB1 and IIA1 into a screening log</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agreement to be visited and audited by RACC Trial Steering committee members during the recruitment period of the study (at least 1 surgical procedure).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RACC – Robotic approach to Cervical cancer
Robotic assisted surgery versus laparotomy in patients with early cervical cancer

Surgery and histopathology

Radical Hysterectomies with lymph node dissection

<table>
<thead>
<tr>
<th>Year</th>
<th>Pts Operated</th>
<th>Pts with Sentinel Node Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer patients with upfront surgery

<table>
<thead>
<tr>
<th>Year</th>
<th>Pts Operated</th>
<th>Pts with Sentinel Node Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Radical hysterectomy with lymph node dissection

Proportion of operations in robot = ______ %

Radical Upfront Debulking Surgery in FIGO Stage III-IV Ovarian or fallopian tube cancer patients

Proportion of complete tumor resection achieved ≈ ______ %

Ability to perform ultrastaging of lymph nodes and possibly many lymph nodes

Access to a gynaecologic reference pathologist

Ability to close documentation on pathology report within 6 weeks after surgery

Interest in participating in the sentinel node part of the RACC trial

Accepting on-site training from the sub-committee on sentinel lymph node biopsy

☐ yes  ☐ no
# RACC – Robotic approach to Cervical cancer

Robotic assisted surgery versus laparotomy in patients with early cervical cancer

## Adjuvant Treatment

Standard adjuvant treatment for patients fulfilling criteria after primary surgery for early stage Cervical cancer is Extern radiotherapy, standard dose 45 Gy with weekly Cisplatin 40 mg/m²

If no, please specify in a separate word document the standard adjuvant treatment.

Do you use Sedlis criteria to select patients for adjuvant treatment?

<table>
<thead>
<tr>
<th></th>
<th>yes</th>
<th>no</th>
</tr>
</thead>
</table>

If no, please specify in a separate word document how you select patients actual for adjuvant treatment and attach the document.

Please provide details on the proportion of operated patients with early stage cervical cancer subjected to adjuvant treatment during the last 24 months.

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
</table>
| %

The principal investigator of each centre is responsible that all the above criteria are met by the operating team and can assure that all required information is available and emailed after scanning to the study group at the following address:

sahar.salehi@sll.se

---

Date and Signature of Principal Investigator

Thank you very much for your interest in this study!
16.8 EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ______________________
Your birthdate (Day, Month, Year): ______________________
Today's date (Day, Month, Year): 31 ______________________

1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?  
   Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

2. Do you have any trouble taking a long walk?  
   Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

3. Do you have any trouble taking a short walk outside of the house?  
   Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

4. Do you need to stay in bed or a chair during the day?  
   Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

5. Do you need help with eating, dressing, washing yourself or using the toilet?  
   Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

During the past week:

6. Were you limited in doing either your work or other daily activities?  
   Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

7. Were you limited in pursuing your hobbies or other leisure time activities?  
   Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

8. Were you short of breath?  
   Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

9. Have you had pain?  
   Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

10. Did you need to rest?  
    Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

11. Have you had trouble sleeping?  
    Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

12. Have you felt weak?  
    Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

13. Have you lacked appetite?  
    Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

14. Have you felt nauseated?  
    Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

15. Have you vomited?  
    Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

16. Have you been constipated?  
    Not at All 1 A Little 2 Quite a Bit 3 Very Much 4

Please go on to the next page
During the past week:

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

   1  2  3  4  5  6  7

   Very poor                  Excellent

30. How would you rate your overall quality of life during the past week?

   1  2  3  4  5  6  7

   Very poor                  Excellent
16.9 QLQ-CX24

**EORTC QLQ – CX24**

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems, please answer by circling the number that best applies to you.

<table>
<thead>
<tr>
<th>During the past week:</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Have you had cramps in your abdomen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Have you had difficulty in controlling your bowels?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Have you had blood in your stools (motions)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. Did you pass water/urine frequently?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. Have you had pain or a burning feeling when passing water/urinating?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Have you had leaking of urine?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. Have you had difficulty emptying your bladder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. Have you had swelling in one or both legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Have you had pain in your lower back?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Have you had tingling or numbness in your hands or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Have you had irritation or soreness in your vagina or vulva?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42. Have you had discharge from your vagina?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. Have you had abnormal bleeding from your vagina?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44. Have you had hot flushes and/or sweats?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. Have you felt physically less attractive as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. Have you felt less feminine as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47. Have you felt dissatisfied with your body?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*Please go on to the next page*
### During the past 4 weeks:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>48. Have you worried that sex would be painful?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Have you been sexually active?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Answer these questions only if you have been sexually active during the past 4 weeks:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>50. Has your vagina felt dry during sexual activity?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>51. Has your vagina felt short?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>52. Has your vagina felt tight?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>53. Have you had pain during sexual intercourse or other sexual activity?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>54. Was sexual activity enjoyable for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
16.10  **LYMQOL**

---

### Lymphoedema Quality of Life Study (LYMQOL) **LEG**

If any of the items are not applicable to you, please write N/A in the relevant answer box(es).

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) your walking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) your ability to go up and down stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) your ability to bend, e.g. to tie shoes or cut toenails</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) your ability to reach</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) your ability to stand</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>f) your ability to get in/out of a car</td>
<td></td>
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<tr>
<td>g) your ability to get on/off public transport, e.g. train/buses</td>
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</tr>
<tr>
<td>h) your ability to get up from a chair</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>i) your ability to drive a car</td>
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<tr>
<td>j) your occupation</td>
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<td></td>
</tr>
<tr>
<td>k) your ability to do housework</td>
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</tr>
</tbody>
</table>

---

**2** Does the swelling affect your leisure activities/social life?

Please give example(s) of this:

---

**3** How much do you have to depend on other people?

---

**4** How much do you feel the swelling affects your appearance?

---

**5** How much difficulty do you have finding clothes to fit?

---

**6** How much difficulty do you have finding clothes you would like to wear?

---

**7** Do you have difficulty finding shoes to fit?

---

**8** Do you have difficulty finding socks/tights/stockings to fit?

---

**9** Does the swelling affect how you feel about yourself?

---

**10** Does it affect your relationship with your partner?

---

**11** Does it affect your relationships with other people?

---

**12** Does your lymphoedema cause you pain?

   If so, do you have pain in the:

   - leg/legs
   - hip(s)
   - back
   - elsewhere — if so, where?

---

**13** Do you have any numbness in your swollen leg(s)?

---

**14** Do you have any feelings of pins and needles or tingling in your swollen leg(s)?

---

**15** Does (do) your swollen leg(s) feel heavy?

---

**16** Does (do) your swollen leg(s) feel tight?

---

**17** Have you had any leakage of fluid from your leg(s)?

---

**18** In the past week:

   - Have you had trouble sleeping?
   - Have you had difficulty concentrating on things, e.g. reading?
   - Have you felt tense?
   - Have you felt worried?
   - Have you felt irritable?
   - Have you felt depressed?

---

**19** Overall, how would you rate your quality of life at present? Please mark your score on the following scale:

   - Poor: 0
   - 1
   - 2
   - 3
   - 4
   - 5
   - 6
   - 7
   - 8
   - 9
   - 10
   - Excellent

---

Thank you for completing this form.

If you have any comments or queries about this, please discuss these with [Dr V L Kossy Consultant](mailto:DrV.L.Kossy@coquitlamhospital.ca).

---

*Questions 19 to 25 have been reproduced with permission from the EORTC. These questions are only part of the QLQ C30 Questionnaire.*
16.11 EQ5D-3L

By placing a tick in one box in each group below, please indicate which statement describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities** *(e.g. work, study, housework, family or leisure activities)*
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain / Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety / Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
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