Laparoscopic Approach to Cervical Carcinoma

A Phase III Randomized Clinical Trial of Laparoscopic or Robotic Radical Hysterectomy versus Abdominal Radical Hysterectomy in Patients with Early Stage Cervical Cancer

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PROTOCOL SYNOPSIS

Protocol Title	LACC - Laparoscopic Approach to Cervical Cancer
Full Protocol Title	A Phase III Randomized Clinical Trial Comparing Laparoscopic or Robotic Radical Hysterectomy versus Abdominal Radical Hysterectomy in Patients with Early Stage Cervical Cancer
Indication	Cervical Cancer - FIGO Stage 1A, FIGO Stage 1B1 (as determined by the following examinations: Cervical biopsy/cone biopsy, PV/PR examination, EUA, xray)
Primary Objective	To compare disease-free survival amongst patients who undergo a total laparoscopic or robotic radical hysterectomy (TLRH) versus those who undergo a total abdominal radical hysterectomy (TARH) for early stage cervical cancer.
Secondary Objectives	1. Compare patterns of recurrence between arms. 2. Compare treatment-associated morbidity within 6 months from surgery. 3. Compare the cost effectiveness of TLRH or TRRH versus TARH 4. Compare the impact on Quality of Life (QoL) between arms. 5. Assess pelvic floor function 6. Compare overall survival between arms 7. Determine the feasibility of sentinel lymph node biopsy in this group of patients
Study Design	• International Multicenter • Randomized 1:1 • Phase III Two-Stage Clinical Trial • Stratification for Site and FIGO Stage.
Stage 1	The first stage will assess feasibility of recruitment and delivery of the intervention and collect quality of life on the first 100 patients
Stage 2	Should the trial be extended, the Trial Management Committee will select one of the following options: Option #1: The disease-free survival at 4.5 years of the TLRH group is compared against the control group disease-free survival rate Option #2**:** The trial is expanded to a larger randomized equivalence clinical trial (additional 640 patients) assessing disease-free survival at 4.5 years from treatment
Planned Sample Size	Phase 1: 100 participants randomized 1:1 (50 TLRH/TRRH: 50 TARH) Phase 2: Additional 640 participants randomized 1:1 (320 TLRH/TRRH: 320 TARH)

Inclusion Criteria	1 Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix; 2 Patients with FIGO stage IA1 (with lymph vascular space invasion), IA2, or IB1 disease; 3 Patients undergoing either a Type II or III radical hysterectomy (Piver Classification) 4 Patients with adequate bone marrow, renal and hepatic function using Standard International Units: 4.1 WBC > $3.0x10^9$ cells/L 4.2 Platelets >$100x10^9$ cells/L 4.3 Creatinine <180 µmmol/L (non-IDMS) 4.4 Bilirubin <1.5 x normal and AST/SGOT or ALT/SGPT <3 x normal 5 Performance status of ECOG 0-1; 6 Patient must be suitable candidates for surgery; 7 Patients who have signed an approved Informed Consent; 8 Patients with a prior malignancy allowed if > 5 years previous with no current evidence of disease; 9 Females, aged 18 years or older. 10 Negative serum pregnancy test ≤ 30 days of surgery in pre-menopausal women and women < 2 years after the onset of menopause
Exclusion Criteria	1 Any histological type other than adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix; 2 Tumor size greater than 4 cm; 3 FIGO stage II-IV; 4 Patients with a history of pelvic or abdominal radiotherapy; 5 Patients who are pregnant; 6 Patients with contraindications to surgery; 7 Patients with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2cm; or histologically positive lymph nodes 8 Unfit for Surgery: serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator); 9 Patients unable to withstand prolonged lithotomy and steep Trendelenburg position 10 Patient compliance and geographic proximity that do not allow adequate follow-up. 11 Patients who agree to intra-operative lymphatic mapping (IOLM) must not have: ▪ Known allergies to triphenylmethane compounds. ▪ History of retroperitoneal surgery. ▪ History of pelvic irradiation. ▪ Cold knife or LEEP cone biopsy within 4 wks of enrollment.
Standard Treatment	Total Abdominal Radical Hysterectomy (TARH) + / pelvic/ +/- aortic lymph

	node dissection.
Experimental Treatment	Total Laparoscopic (TLRH) or Robotic Radical Hysterectomy + laparoscopic pelvic and +/- para aortic lymph node dissection
Primary Outcome	Disease-Free Survival (DFS)
Secondary Outcomes	• Recurrence: Pattern/Site of recurrence • Morbidity: Intraoperative, perioperative, early postoperative (<4 weeks) and long-term morbidity (4 weeks to 6 months); transfusion requirements; postoperative pain and analgesic consumption • Treatment costs • Quality of Life • Pelvic Floor function • Overall Survival at 4.5 years follow-up. • Feasibility of sentinel lymph node biopsy in this group of patients

GLOSSARY OF ABBREVIATIONS

AAGL	American Association of Gynecologic Laparoscopists
ABS	American Brachytherapy Society
AE	Adverse event
AJCC	The American Joint Committee on Cancer
CDMU	Central Data Management Unit
CONSORT	Consolidated Standards of Reporting Trials
CORE	The Centre on Outcomes, Research and Education
CT	Computed tomography
CTCAE V3.0	Common terminology criteria for adverse events Version 3.0
CRF	Case Report Form
DFS	Disease free survival
DSMC	Data safety monitoring committee
EBRT	External beam radiotherapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form(s)
EQ-5D	EuroQoL-5d
FACT-CX	Functional assessment of cancer therapy – cervix
FIGO	Federation of Gynecologists and Obstetricians
FDA	Food and Drug Administration
GCP	Good clinical practices
GOG	the Gynecologic Oncology Group
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HREC	Human Research Ethics Committee
IB	Investigational brochure
ICH	International Conference on Harmonisation
IC-Green	Indocyanine Green for Injection
IDMS	Isotope-dilution mass spectrometry
IRB	Institutional Review Board

IOLM	Intra-operative Lymphatic Mapping
ITT	Intent to treat
LACC	Laparoscopic Approach to Cervical Carcinoma
LARVH	Laparoscopy-assisted radical vaginal hysterectomy
LDR	Low Dose Rate
LFT	Liver function test (s)
LVSI	Lymphovascular Space Invasion
MDASI	The MD Anderson Symptom Inventory
MRI	Magnetic resonance imaging
NHMRC	National Health and Medical Research Council
Non-IDMS	Non-Isotope Dilution Mass Spectrometry
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFDI	Pelvic Floor Distress Inventory
PFS	Progression-free survival
PAOLND	Para-aortic Lymph Node Dissection
PLND	Pelvic Lymph Node Dissection
PS	Performance status
QALYs	Quality-Adjusted Life Years
QCGC	Queensland Centre for Gynecological Cancer
QOL	Quality of life
RT	Radiotherapy
SAE	Serious adverse event
SCC	Squamous Cell Carcinoma
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedure
SSE	Significant safety event
SSL	Secure Socket Layer
SPECT	Single Photon Emission Computed Tomography

TAH	Total Abdominal Hysterectomy
TARH	Total Abdominal Radical Hysterectomy
TGA	Therapeutic Goods Administration
TMC	Trial Management Committee
TLH	Total Laparoscopic Hysterectomy
TLRH	Total Laparoscopic Radical Hysterectomy
TRRH	Total Robotic Radical Hysterectomy
TSC	Trial Safety Committee
ULN	Upper limit of normal
UQ	University of Queensland

1.0 STUDY OBJECTIVES

Primary Objective:

To compare disease-free survival amongst patients who undergo a total laparoscopic (TLRH) or robotic radical hysterectomy (TRRH) verses those who undergo a total abdominal radical hysterectomy (TARH) for early stage cervical cancer.

Secondary Objectives:

- Compare patterns of recurrence between arms.
- Compare treatment-associated morbidity within 6 months from surgery.
- Compare the cost effectiveness of TLRH/TRRH versus TARH
- Compare the impact on Quality of Life (QOL) between arms.
- Assess pelvic floor function
- Compare overall survival between arms
- Determine the feasibility of sentinel lymph node biopsy in this group of patients

2.0 BACKGROUND

2.1 DISEASE

Cervical cancer is the most common cause of death from gynecological cancer world-wide. In developed countries with an excellent public health infrastructure and a high compliance of women, early cytological detection of cervical cancer (PAP smear) has led to an impressive reduction of mortality while in other world regions including Central America, South East Africa and India, incidence and mortality rates are still very high. Today, more than 80 per cent of all cervical cancer deaths occur in developing countries. However, the number of cases estimated to be diagnosed with cervical cancer every year is an alarming 13,000 in the USA, 25,000 women in Europe and 1000 in Australia and New Zealand.

Risk factors for cervical cancer include early onset of sexual activity, multiple sexual partners, and a high-risk sexual partner (e.g. promiscuous sexual activity, sexual exposure to a partner with human papilloma virus infection, as well as smoking and immunosuppression). The most common symptoms at presentation are: abnormal vaginal bleeding (including postcoital bleeding) and vaginal discharge. A lesion may or may not be visible or palpable on physical examination.

The mean age at diagnosis for cervical cancer is 47 years. Diagnosis is initially established by biopsy. Approximately 80% to 90% of cervical cancers are squamous cell carcinomas, which are composed of cells that resemble squamous cells with the remaining 10% to 20% of cervical cancers being adenocarcinomas arising from the mucus-producing glandular component of the uterine cervix. Less commonly, cervical cancers have features of both squamous cell carcinomas and adenocarcinomas. These are called adenosquamous carcinomas or mixed carcinomas.

Cervical cancer is staged by the FIGO staging system, which is based on clinical examination, rather than surgical findings. It allows only the following diagnostic tests to be used in determining the stage: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton and cervical conization.

Cervical cancer is known to spread directly into adjacent tissues such as the vagina, parametria, uterine corpus, peritoneal cavity, bladder and rectum. In addition, cervical cancer tends to spread through lymphatic channels into lymph nodes. Typically, the pelvic nodes are affected first followed by aortic lymph nodes. According to the International Federation of Gynecologists and Obstetricians (FIGO) the risk of lymph node metastasis increases with increasing depth of invasion[1 2 3 4 5].

2.2 TREATMENT

There are currently several options for the treatment of early stage cervical cancer. These include[6];

- Radical hysterectomy plus pelvic and +/- paraaortic lymphadenectomy +/- adjuvant chemotherapy
- Definitive radiation therapy (RT)
- Radical trachelectomy (for Stage IA2 to IB1)
- Conization (only for stage IA1)

The optimal choice for treatment is dependent upon the patient's age and childbearing plans. Also disease stage, comorbidities, physician and patient preference as well as whether histopathological review of surgical specimens reveals characteristics associated with increased risk of recurrence.

2.2.1 SURGERY

Radical hysterectomy

In contrast to a standard hysterectomy, in a radical hysterectomy the uterus, the upper one to two cm of the vagina and the soft tissues around the cervix has to be excised. This makes a radical hysterectomy a far more complex procedure associated with a higher complication rate than a standard hysterectomy.

Lymphadenectomy

Cervical cancer not only spreads directly into adjacent organs but also through lymphatic channels into the pelvic and aortic lymph nodes. A comprehensive lymph node dissection is usually performed at the time of the radical hysterectomy. The necessity for, and extent of lymphadenectomy depends upon disease stage.

The risk of lymph node metastases with stage IA1 SCC is so small (1 percent or less) that lymphadenectomy is not performed unless there is lymphovascular space invasion, which is rare at this early stage[7].

For stage IA2 disease or small/microscopic IB1 disease, the risk of nodal metastasis is 2-8% and pelvic lymphadenectomy alone is generally sufficient as the risk for paraaortic nodal metastases is neglible[8 9 10 11]. However, if the pretreatment staging PET and/or CT scan is positive in the paraaortic region, or if suspicious pelvic lymph nodes are encountered at surgery and metastases are confirmed by frozen section, enlarged lymph nodes should be removed.

In patients with stage IB1 disease, the risk of pelvic node involvement is up to 18% but the risk of aortic node involvement is as small as 4%.

Intraoperative lymphatic mapping

Published studies on lymphatic mapping and sentinel lymph node biopsy show a high detection rate of sentinel nodes for patients with cervical cancer. Levenback et al.[12] utilized this combined technique in cervical cancer patients undergoing laparotomy with radical hysterectomy and retroperitoneal lymph node dissection and found the sentinel node

technique had a sensitivity of 87.5% for histologically node-positive patients and a negative predictive value for metastatic disease in non-sentinel lymph nodes of 97%. Using the same methods adapted for laparoscopic radical hysterectomy and lymph node dissection, Pijpers et al.[13] reported the sentinel node technique had a sensitivity of 92%. In a meta-analysis of 16 lymphatic mapping studies which included 649 patients who had either a laparotomy or laparoscopy, Frumovitz et al.[14] found an overall sensitivity of 91% and negative predictive value of 97%.

Fertility-preserving surgery

At present, no randomized clinical trials exist which directly compare outcomes of fertility preserving surgery versus radical hysterectomy for treatment of early stage cervical cancer. However, observational series support the view that women who strongly desire to retain fertility may be treated successfully without a hysterectomy.

Conization for stage IA1 disease

Conization is an acceptable therapeutic alternative to hysterectomy in young woman desirous of maintaining fertility. Instances where conization may be performed include when the depth of invasion is less than 3 mm, when there is no lymphovascular invasion, and if the margins and endocervical curettage are negative for dysplasia[15] [16].

If the endocervical conization margin or endocervical curettings are positive, repeat conization is recommended to exclude more deeply invasive residual disease.

Radical trachelectomy for stage IA2/IB1 disease

Radical trachelectomy is also a reasonable approach for highly selected young women with stage IA2 or small stage IB1 disease for whom fertility preservation is an issue[17,18]. With this procedure, the cervix and parametria are resected with placement of a cerclage so that the uterus can be preserved with a competent vaginal-uterine junction. A radical trachelectomy allows for the preservation of the uterus. Radical trachelectomy can be performed transvaginally or transabdominally and combined with a laparoscopic or open diagnostic/therapeutic lymphadenectomy.

2.2.2 INDICATIONS FOR ADJUVANT THERAPY

High Risk Disease

High risk disease patients have positive or close resection margins, positive lymph nodes or parametrial involvement.

Intermediate-risk disease

Patients with intermediate-risk disease are those that have been identified as having large tumor size, deep stromal invasion or LVSI. Evidence supports a reduction in both the risk of death and an improvement in PFS when these are managed with adjuvant RT alone. There are no randomized trials showing an improvement in outcomes with CRT. Smaller tumors appear to derive quantitatively less benefit from the addition of chemotherapy to RT.

In its most recent protocol, which incorporates adjuvant postoperative RT for women with invasive cervical cancer, the GOG recommends concomitant chemoradiotherapy for women with both intermediate-risk and high-risk disease[19].

2.2.3 DEFINITIVE RADIOTHERAPY (RT)

Definitive RT and radical surgery are the two accepted treatments for stage IA, IB, and IIA cervical cancer, since the oncologic outcomes are similar for both[20 21 22 23]. Concomitant chemoradiotherapy however, has been shown to be superior to RT alone, with a 31% reduction in the risk of death and a 34% improvement in PFS [24 25 26 27 28 29 30].

Radiotherapy Techniques

The two main methods of radiation delivery for cervical cancer are external beam radiotherapy (EBRT) and brachytherapy. EBRT delivers radiation through a four-field technique and usually 52 Gy will be delivered in daily fractions. Brachytherapy can either be delivered using an intracavitary approach with a variety of applicators, or via an interstitial approach using needles or afterloading catheters. Although intracavitary brachytherapy alone is adequate treatment for stage IA1 disease, external beam RT is generally added to brachytherapy to improve pelvic control with more advanced disease.

The incidence of major complications from RT is 3-5 % for women with stage I and IIA disease[31]. It has been shown that there is also an absolute risk of 0.4 % of a second malignancy developing following RT[32]. Woman who undergo pelvic RT are also known to develop premature ovarian failure.

2.2.4 SURGERY VERSUS RADIOTHERAPY

As discussed above, definitive RT and radical surgery are both accepted treatments of early stage cervical cancer. Therefore, the decision to proceed with one versus the other is based on other factors, such as childbearing plans, comorbidities, physician and patient preference, and quality of life (QOL) issues. Both hysterectomy and RT can lead to changes such as vaginal shortening and decreased vaginal lubrication, which adversely influence sexual function, overall QOL, and psychosocial well-being following treatment[33 34 35 36 37].

For women with stage IA and IB1 cervical carcinoma, surgery is generally preferred, particularly for premenopausal women, for the following reasons:

- A desire to preserve ovarian function in young women
- The greater possibility of a more functional vagina following surgery as compared to RT
- Staging lymphadenectomy enables individualization of the RT field if RT is indicated

If definitive RT is chosen over radical hysterectomy, concomitant cisplatin-based chemotherapy should also be administered.

2.3 PROGNOSIS

The major prognostic factors affecting survival among women with cervical carcinoma include stage, nodal status, tumor volume, depth of cervical stromal invasion, lymphovascular space invasion (LVSI), and, to a lesser extent, histologic type and grade. Disease stage is undoubtedly the most important prognostic factor, followed then by lymph node status. After radical hysterectomy and lymphadenectomy, women with stage IB or IIA disease who have negative pelvic lymph nodes have a five-year survival rate of 88 - 96 %, compared to 64 - 74 % for those with similar stage disease and pelvic nodal metastasis[38 39 40]. The overall outcome for women with involved paraaortic nodes has

been found to be poorer than for women with uninvolved nodes[41 42 43 44 45]. Among the patients who have undergone surgical staging or lymphadenectomy an increase in the number of involved lymph nodes is linked to a decrease in survival rate. At this stage however, the prognostic significance of pelvic lymph node micrometastases in women with early stage disease is unclear[46 47 48 49].

Overall, the five year survival rate is approximately 90% for the entire group of patients with Stage I cervical cancer (FIGO Ann. Report)

2.4 LAPAROSCOPY FOR SURGICAL TREATMENT

Laparoscopic radical hysterectomy was described initially by Canis et al.[50] and Nezhat et al.[51]. Since those initial reports, a number of other groups have published their experiences showing the feasibility and safety of this procedure[52 53 54 55 56 57]. These reports suggest performing the procedure laparoscopically in no way adversely affects the patient's overall prognosis and survival[58 59 60 61 62 63]. Nevertheless, few long-term data are available on the morbidity of laparoscopic radical hysterectomy and survival after this procedure.

To date, no randomized trials have been completed which directly compare laparoscopic and open radical hysterectomy. The largest series thus far on laparoscopic radical hysterectomy, by Spirtos et al[64], describes 78 consecutive patients, all with early cervical cancer. In that series, 94% of the procedures were completed laparoscopically. The average operative time was 205 min, and the average blood loss was 225 mL. One patient (1.3%) required a blood transfusion, 3 patients had unintended cystotomies, 2 patients required laparotomy to control bleeding, and 1 patient suffered an ureterovaginal fistula. Three patients had microscopically positive or close margins. The authors reported a recurrence rate of 5%.

Obermair et al.[65] reported upon the feasibility and safety of total laparoscopic radical hysterectomy (TLRH) in 55 patients with cervical (39), endometrial (8), vaginal (2), or recurrent colon cancer (1), or severe pelvic endometriosis (5) followed for 3 years. The median total operating time was 210 minutes, and median hospital stay was 5 days. Intraoperative complications included three vascular injuries and one obturator nerve palsy, all of which occurred in the first half of the series. Early postoperative morbidity included deep vein thrombosis, pulmonary embolism, bladder infection and dysfunction, and vaginal fistula. These events occurred less frequently in the second half of the series. Late

postoperative morbidity consisted of lymphedema, pelvic abscess and lymphocyst formation, pelvic cellulitis, hyperesthesia of the leg, and small bowel obstruction. It was concluded that TLRH carries acceptably low morbidity that can be reduced with experience with the technique.

Abu-Rustum et al.[66] reported a retrospective review of 19 patients with stage IA1-IB1 cervical cancer who underwent total laparoscopic radical hysterectomy with pelvic lymphadenectomy. The authors found that the mean blood loss and mean hospital stay were significantly less than in historical controls that underwent radical hysterectomy with a laparotomy approach. However, this was at the cost of longer operating times. In that series, 2 patients required conversion to laparotomy to control parametrial bleeding (1 patient) and repair a cystotomy (1 patient). The surgeons in that study also used ureteral catheters in 37% of patients. Intraoperative complications in that series comprised of cystotomy (5 patients), iliac vein injury (5 patients), and ureteral transection (1 patient). The mean length of hospitalization for patients in that study was 4.5 days.

In another series of 50 patients with cervical cancer who underwent total laparoscopic radical hysterectomy, Pomel et al.[67] noted that the median operative time was 258 minutes and the mean number of harvested lymph nodes was 13. The median postoperative hospital stay was 7.5 days. The authors reported that 10 patients had early (<2 months) complications and that 3 of those patients required reoperation. They also reported that 3 patients had late complications (>2 months) and that 2 of those patients required reoperation. Three patients experienced recurrence with a median follow-up time of 44 months. Of note, this series excluded all patients with a body mass index greater than 29.

Recently, Gil-Moreno et al. [68] reported a small series of patients with cervical cancer who underwent total laparoscopic radical hysterectomy with sentinel lymph node identification. The authors reported that the mean operating time was 271 minutes and the mean blood loss was 445 mL. The mean length of hospital stay was 5.25 days. No intraoperative complications were reported, and no recurrences were detected with a median follow-up of 20 months. In that study, patients with a body mass index greater than 35 were excluded.

In a study by Ramirez et al.[69], the authors did not need to convert the procedure to a laparotomy in any of the cases. None of the patients were excluded on the basis of weight or body mass index. The number of lymph nodes removed in that series compared favorably with other series in the literature.

The rate of intraoperative blood transfusions in that same series was lower than that reported in the literature for open abdominal radical hysterectomies (40-80%) [70] [71] [72] [73]. The post-operative complications noted in the series by Ramirez et al. was not exclusively related to the laparoscopic approach and these have also been reported with open radical hysterectomy. This series was the first to show a median length of stay of 1 day.

3 RATIONALE

3.1 RATIONALE FOR STUDY DESIGN

Total abdominal radical hysterectomy (TARH) and pelvic lymph node dissection (± aortic lymph node dissection ± postoperative [chemo-] radiotherapy) is the current standard treatment for early cervical cancer. While this is an accepted effective treatment, a laparotomy is highly invasive, visibly scarring and is associated with tissue trauma, blood loss and a significant risk of wound and infectious adverse events[74] [75]. Additionally, radical hysterectomy by laparotomy is associated with an average hospital stay of approximately 5 to 7 days and an average recovery period (from surgery) of 5 to 6 weeks.

Laparoscopic techniques have been demonstrated to be feasible and safe with previous retrospective studies on TLH showing encouraging results[76]. In a number of retrospective and prospective, non-controlled series the incidence of treatment-related morbidity was less in patients who had a laparoscopic hysterectomy compared to patients who underwent a TAH[77]. Retrospective data suggest that the recurrence rate and patterns of recurrence are similar in patients who had a laparoscopic or an open approach[78].

Treatment recommendations ideally are based on prospective, randomized trials comparing the current standard technique (TARH) with the proposed better technique (TLRH). However, there are currently no prospective studies available which directly compare TLRH against the standard treatment of TARH in regards to disease-free or overall survival.

The proposed clinical trial will be biphasic. The primary outcome variable in stage 1 will be feasibility of recruitment as determined by overall trial recruitment. Following completion of Stage 1, the data of this study will become the basis for assessing recurrence and disease-free survival in the Stage 2 design.

3.2 RATIONALE FOR THE QUALITY OF LIFE

Retrospective studies suggest equivalency between the laparoscopic and open approaches to radical hysterectomy in regards to surgical specimens obtained [79] and likely disease-free and overall survivals [80] [81] [82] [83] [84] [85] [86]. Thus, quality of life could be seen as one of the most significant factors in recommending one approach over the other and therefore an extremely important endpoint for this protocol. In the GOG LAP-2 protocol[87], a trial evaluating a comparison between hysterectomy by laparotomy or laparoscopy, the investigators found equivalency adequacy of the two surgical approaches however a significant difference in short term quality of life favoring laparoscopy. As expected, patients who underwent laparoscopy had a faster return to baseline functioning compared with those patients who had undergone laparotomy which translated into improved short-term quality of life. By 6 months, however, patients in both cohorts were reporting equivalent quality of life parameters. Quality of life surveys employed with this Phase III clinical trial will encompass important endpoints such as postoperative pain and related symptoms using the MD Anderson Symptom Assessment Index (MDSAI), as well as cancer specific Functional Assessment of Cancer Therapy (FACT-Cx) and the general 12-Item Short-Form Health Survey (SF-12).

3.3 RATIONALE FOR LYMPHATIC MAPPING

Published experience with the techniques for lymphatic mapping and sentinel lymph node detection in women with cervical cancer has been very limited. To date, no single study has enrolled more than 100 patients undergoing lymphatic mapping as part of their surgical treatment for cervical cancer. In fact, the majority of studies report on less than 50 patients. In addition, this procedure has not yet been shown to be viable in a multi-institutional setting. The limitations of previously published reports are important as these techniques are associated with a significantly high learning curve with early procedures less successful than later ones. This study will provide us the opportunity to enroll large numbers of patients for validation of intraoperative lymphatic mapping in women with cervical cancer in an international, multi-institutional setting.

3.3.1 DRUG INFORMATION:

Isosulfan Blue (Lymphazurin®)

- Formulation: Sterile aqueous solution in 5 ml vials.
- Preparation: None.
- Storage: Room temperature, avoid excess heat.

- Supplier: Hirsch Industries, Richmond, VA 23230.
- Adverse Effects: All adverse effects are allergic in nature and occur in <1% of patients. These include localized swelling and pruritus of the hands, feet, abdomen and neck. Severe reactions including edema of the face and glottis, respiratory distress, and shock have been occasionally reported with other similar compounds. In rare instances, isosulfan blue can cause a transient drop in oxygen saturation as measured by pulse oximetry. Isosulfan blue will turn the urine blue-green for up to 24 hours following injection.
- Contraindications: Known hypersensitivity to phenylethane compounds.

Methylene Blue

- Formulation: Sterile solution of 1% methylene blue in water for injection in 1 ml and 10 ml vials.
- Preparation: None.
- Storage: Room Temperature (15-25 ^{o}C).
- Supplier: Taylor Pharmaceuticals, Decatur, IL 62522.
- Dose: Up to 4 ml subcutaneous. Not for IV use for this protocol.
- Metabolism: Methylene blue is reduced in tissues to leucomethylene blue.
- Adverse Effects: Subcutaneous necrosis has been reported at injection sites. In this study the injection site is resected with the primary tumor. This complication has not been described in lymphatic mapping studies. Allergic reactions such as rash, hives, or hypersensitivity reactions have been described. They appear to occur in approximately 1% of patients.
- Contraindications: No contraindications for subcutaneous use other than a history of allergic reaction to this compound.
- Drug-lab interactions: Pulse Oximetry: inaccurate and artificially low.

Indocyanine Green (IC-Green™)

- Formulation: 25mg Sterile Indocyanine Green Single-dose Vials and Sterile Aqueous Solvent Ampoules
- Preparation: None
- Storage: 20°- 25°C (68°- 77°F)
- Supplier: AKORN, Lake Forest, IL 60045
- Dose: Up to 10ml subcutaneous. Not for IV use in this protocol

- Adverse Effects: IC-Green™ is non-irritating when administered subcutaneously. In this study the injection site is resected with the primary tumor. Anaphylactic or urticarial reactions have been reported in patients with or without history of allergy to iodides. Treatment with appropriate agents, e.g. epinephrine, antihistamines and corticosteroids should be administered.
- Contraindications: IC-Green™ contains sodium iodide and should be used with caution with those with a history of allergies to iodides.
- Drug-lab interactions: Heparin preparations containing sodium bisulfite reduce the absorption peak of IC-Green™ in blood and therefore should not be used as an anticoagulant for the collection of samples for analyses. Radioactive iodine uptake studies should not be performed for at least a week following the uses of IC-Green™.

4.0 PATIENT ELIGIBILITY AND EXCLUSIONS

4.1 INCLUSION CRITERIA

1. Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix;
2. Patients with Histologically confirmed stage IA1 (with lymph vascular invasion), stage IA2, or stage IB1 disease
3. Patients undergoing either a Type II or III radical hysterectomy (Piver Classification)
4. Patients with adequate bone marrow, renal & hepatic function using Standard International Units:
   - 4.1 WBC > $3.0x10^9$ cells/L
   - 4.2 Platelets >$100x10^9$ cells/L
   - 4.3 Creatinine <180 µmmol/L (non-IDMS)
   - 4.4 Bilirubin <1.5 x normal and AST/SGOT or ALT/SGPT <3 x normal
5. ECOG Performance Status of 0 or 1.
6. Patients must be suitable candidates for surgery.
7. Patients who have signed an approved Informed Consent
8. Patients with a prior malignancy allowed if > 5 years ago with no current evidence of disease
9. Females, aged 18 years or older
10. Negative serum pregnancy test ≤ 30 days of surgery in pre-menopausal women and women < 2 years after the onset of menopause

4.2 EXCLUSION CRITERIA

1. Any histology other than adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix;
2. Tumor size greater than 4 cm;
3. FIGO stage II-IV;
4. Patients with a history of pelvic or abdominal radiotherapy;
5. Patients who are pregnant;
6. Patients with contraindications to surgery;
7. Patients with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2cm; or histologically positive lymph nodes
8. Unfit for Surgery: serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator);
9. Patients unable to withstand prolonged lithotomy and steep Trendelenburg position
10. Patient compliance and geographic proximity that do not allow adequate follow-up

12 Patients who agree to IOLM must not have:

- Known allergies to triphenylmethane compounds.
- A history of retroperitoneal surgery.
- A history of pelvic irradiation.
- A cold knife or LEEP cone biopsy within 4 wks of enrollment.

5.0 STUDY DESIGN

This Phase III international, multi-centre, open-label, randomized clinical trial design is an equivalence study with the hypothesis that TARH is equivalent TLRH in terms of disease free survival (DFS). The study will be conducted in two stages.

5.1 STAGE 1

The first stage will assess feasibility of recruitment and delivery of the intervention and collect quality of life on the first 100 patients.

5.2 STAGE 2

The Trial Management Committee (refer to Section 19.2) will decide whether the trial will progress along Option 1 or Option 2 based on clinical and economical feasibility and the level of interest amongst the clinical community.

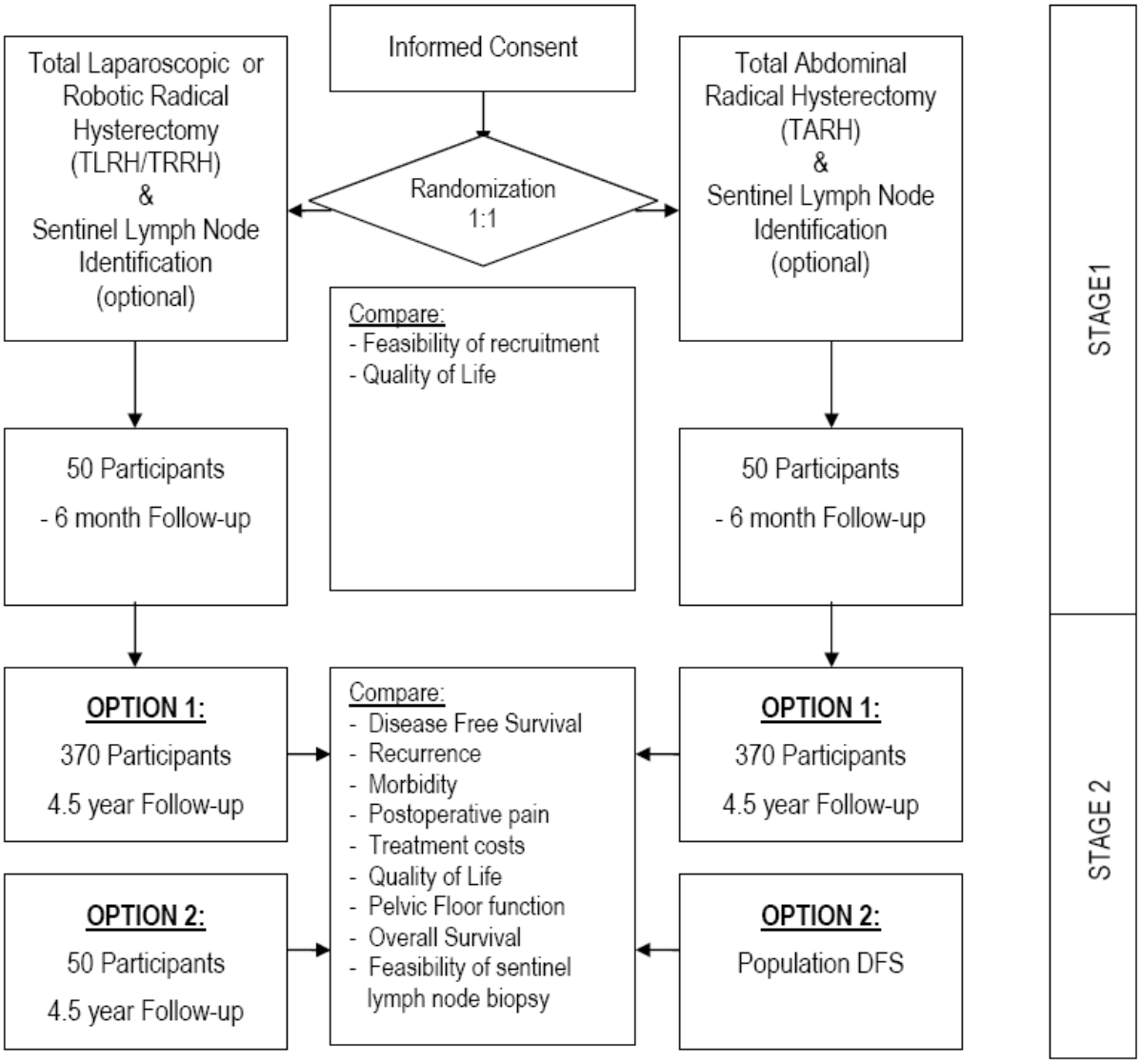
Option 1

A randomized equivalence trial with disease-free survival as the endpoint is the definitive means of determining whether TLRH is at least equivalent to TARH. As such, it is planned to extend the trial to a larger randomized equivalence clinical trial (additional 640 patients) assessing disease free survival at 4.5 years from surgery.

Option 2

The study will follow-up the cohort of patients who had received a total laparoscopic or robotic radical hysterectomy for a minimum of 4.5 years post-surgery to determine whether the estimate of disease-free survival for patients who undergo laparoscopic or robotic surgery is consistent with the (control group) four-year disease-free survival rate of 90%.

5.3 SCHEMA


Informed Consent
Randomization 1:1
Total Laparoscopic or Robotic Radical Hysterectomy (TLRH/TRRH) & Sentinel Lymph Node Identification (optional)
Total Abdominal Radical Hysterectomy (TARH) & Sentinel Lymph Node Identification (optional)
Compare:
- Feasibility of recruitment
- Quality of Life
50 Participants
- 6 month Follow-up
50 Participants
- 6 month Follow-up
OPTION 1:
370 Participants
4.5 year Follow-up
OPTION 2:
50 Participants
4.5 year Follow-up
Compare:
- Disease Free Survival
- Recurrence
- Morbidity
- Postoperative pain
- Treatment costs
- Quality of Life
- Pelvic Floor function
- Overall Survival
- Feasibility of sentinel lymph node biopsy
OPTION 1:
370 Participants
4.5 year Follow-up
OPTION 2:
Population DFS
STAGE1
STAGE 2

6.0 STUDY TREATMENT

Given the extensive range of possible instrumentation for this procedure, the choice of instrumentation for the laparoscopic or robotic approach will be left to the discretion of the surgeon.

At the commencement of surgery, a thorough inspection of all peritoneal surfaces should be performed including direct inspection of the diaphragm. The location of any metastatic disease should be documented in the operative report and a biopsy should be performed to confirm the diagnosis. If intraperitoneal cancer is detected, the aim of treatment should shift to palliation and the radical hysterectomy should be abandoned.

The pelvic lymphadenectomy may be performed before or after the radical hysterectomy and the sequence choice will be left to the discretion of the physician. Decision planning regarding continuing the radical hysterectomy based on intraoperative status of lymph nodes will be left to the discretion of the physician. In patients undergoing sentinel node identification and lymphatic mapping, the choice of that technique is left to the discretion of the individual surgeon.

Patients who undergo sentinel node identification will undergo a complete pelvic lymphadenectomy. This includes common iliac lymph nodes. The time allocated to sentinel node identification should be noted separately in the operative report.

In patients with macroscopic evidence of metastatic disease to the pelvic lymph nodes based on intraoperative assessment, a complete pelvic lymphadenectomy is not required and the radical hysterectomy may even be abandoned. Such patients should have a para-aortic lymph node sampling to determine extent of disease, with this being at the discretion of the individual surgeon.

During the operative procedure, the surgeon should document the specific surgical instruments used in patients randomized to the laparoscopic/robotic approach. The surgeon should also note in the operative report the following information:

- Operative time from start of radical hysterectomy, as documented by skin incision, until all trocar sites have been closed or abdominal incision is closed.

- Blood loss
- Intraoperative complications
- Reasons for conversions to laparotomy in patients randomized to the laparoscopic or robotic approach
- For patients who undergo a robotic radical hysterectomy, the time that was taken to set up and dock the robot should be noted in the operative note and subtracted from the total procedure time.
- For patients who undergo a para-aortic lymph node dissection, the time taken to do this procedure should be noted in the operative note.

6.1 STANDARD TREATMENT: TARH + PELVIC/AORTIC LYMPH NODE DISSECTION

- Preoperative antibiotic is given at least 15 minutes before skin incision;
- Apply sequential compression device (SCD)
- Positioning in the supine or lithotomy position;
- Given the extensive range of possible instrumentation for this procedure, the choice of instrumentation for the laparoscopic approach will be left to the discretion of the surgeon.
- Vertical midline or lower transverse incision;
- A thorough inspection of all peritoneal surfaces should be performed including direct inspection of the diaphragm. The location of any metastatic disease should be documented in the operative report and a biopsy should be performed to confirm the diagnosis.
- The lateral pelvic spaces are opened and bulky, suspicious lymph nodes are removed if feasible and submitted for frozen section examination. If those lymph nodes are positive, aortic lymph nodes are sampled but the radical hysterectomy procedure will be abandoned and the patient is referred to definitive chemoradiotherapy.
- If the pelvic nodes are not suspicious, a radical hysterectomy (Piver type 2 or 3) with or without bilateral salpingo-oophorectomy is performed;
- Ovaries may be removed or preserved and/or transposed.
- A pelvic lymph node dissection includes removal of the lymph nodes along the external iliac artery, the internal iliac artery and the common iliac artery as well as in the obturator fossa;
- An aortic lymph node dissection for staging purposes would include removal of the lymphoid tissue up to the level of the inferior mesenteric artery;

- Intra-abdominal drains are not mandatory;
- Mass closure of sheath, skin closure.
- Indwelling catheter (days documented) according to local protocol.

6.2 INTERVENTION: TLRH or TRRH + LAPAROSCOPIC PELVIC / AORTIC LYMPH NODE DISSECTION

- Preoperative antibiotic is given at least 15 minutes before skin incision;
- Apply sequential compression device (SCD)
- Positioning in the lower lithotomy position with the arms parallel to the patient or the arms resting on the patient's chest;
- Given the extensive range of possible instrumentation for this procedure, the choice of instrumentation for the laparoscopic approach will be left to the discretion of the surgeon.
- The laparoscopic entry technique and the number of ports used to perform the procedure are up to the surgeon's discretion.
- A thorough inspection of all peritoneal surfaces should be performed including direct inspection of the diaphragm. The location of any metastatic disease should be documented in the operative report and a biopsy should be performed to confirm the diagnosis.
- Transection of the round ligament in order to enter the retroperitoneum. The lateral pelvic spaces are opened and bulky, suspicious lymph nodes are removed if feasible and submitted for frozen section examination. If those lymph nodes are positive, aortic lymph nodes are sampled but the radical hysterectomy procedure will be abandoned and the patient is referred to definitive chemoradiotherapy.
- If the pelvic nodes are not suspicious, a radical hysterectomy (Piver type 2 or 3) with or without bilateral salpingo-oophorectomy is performed;
- Ovaries may be removed or preserved and/or transposed.
- A pelvic lymph node dissection includes removal of the lymph nodes along the external iliac artery, the internal iliac artery and the common iliac artery as well as in the obturator fossa;
- A tube or a similar device for uterine mobilization is inserted transvaginally, the bladder peritoneum is reflected and the bladder pillars are lateralized over the edge of the tube;
- The uterine artery is identified, secured and divided at the level of the origin of the internal iliac artery;

- The parametria and the uterosacral ligaments are dissected. A sufficient surgical margin is aimed for. The vagina is circumcised over the vaginal tube and the specimen is removed through the vaginal tube;
- A systematic pelvic lymph node dissection is performed, which includes removal of external iliac nodes, obturator nodes, and common iliac nodes ± removal of the aortic nodes up to the level of the inferior mesenteric artery;
- The tube is used as a conduit to remove the lymph nodes from the abdominal cavity or the lymph nodes may be removed through an endo-catch bag;
- Closure technique for the vaginal vault is left to the discretion of the surgeon;

6.3 INTERVENTION: INTRAOPERATIVE SENTINEL LYMPH NODE (SLN) IDENFICATION WITH ISOSULFAN BLUE AND HAND HELD GAMMA COUNTER OR WITH INDOCYANINE GREEN (IC-Green™.

- Injection of radionuclide
  a. Inject 0.5 mCi to 1.0 mCi of radiolabeled Tc-99 sulfur microcolloid (volume 1.0-4.0 ml) in four divided doses around the tumor or into the 12, 3, 6, and 9 o'clock positions if the tumor involves the endocervix. The volume for injection is small; therefore, take care to preserve enough radionuclide to inject in all 4 quadrants.
  b. The radionuclide may be injected in the nuclear medicine suite up to 6 hours prior to the sentinel lymph node procedure or in the operating room after induction of anesthesia prior to prepping and draping of the patient. The radionuclide should not be injected at the same time as the blue dye since the blue dye will reach the sentinel node more quickly than the radionuclide.
  c. Other radionuclide's may be substituted if Tc 99 labeled sulfur microcolloid is not available.

- Injection of Blue Dye
  a. The patient must be positioned, prepped and draped so that a speculum examination can be performed
  b. The injection of blue dye is performed after the abdomen is explored by palpation (laparotomy) or visually (laparoscopy or robotic).

c. Clamps should not be placed on the uterus that might interfere in any way with distribution of the dye. The uterus should be manipulated by hand until blue dye is seen in the retro peritoneum.
d. With a speculum in the vagina, inject 1 ml of isosulfan blue into four locations in the cervix. Use the same injection sites as with the radionuclide. A total of 4 ml of dye should be used. Allow approximately 5 minutes for the blue dye to reach the sentinel nodes.
e. A tenaculum may be used to manipulate the cervix while injecting blue dye.
f. Avoid spillage of blue dye into the vagina by using a narrow gauge needle (21- 25 gauge) under low pressure. A needle extender, spinal needle, or control grip syringe may be used if needed.
g. Methylene blue, isosulfan blue, patent blue, or other blue dye compounds, depending on local availability, may be used for this procedure.

- <u>Identification of sentinel nodes</u>
  a. Cover the hand-held gamma counter with a sterile sleeve. While waiting for distribution of blue dye, the hand held gamma counter can be used to identify “hot” nodes. The gamma probe should be fitted with a collimator if available.
  b. Incise the peritoneum lateral to the infundibular pelvic ligament and bluntly explore the retroperitoneum with care so that the afferent lymphatic channels are not transected. The afferent lymphatic channel is commonly seen adjacent to the uterine artery near the site where it passes over the ureter.
  c. All blue nodes are to be considered sentinel. If a blue channel leads directly to a lymph node but the lymph node itself is not blue, it should still be considered sentinel.
  d. Special attention to the detection of parametrial SLNs should be made. Parametrial SLNs are found medial to the superior vesical artery.
  e. Grossly involved lymph nodes that are not hot or blue should be considered SLNs and labeled “not hot, not blue SLN”.
  f. The probe counts for a lymph node in-situ must be at least twice the background count in the pelvis to be considered a sentinel node.
  g. The background counts in the pelvis are determined by holding the gamma counter over the sacrum pointed away from the cervix.

h. Following removal of the sentinel node, it should be separated from extraneous material or other non-sentinel nodes and moved off the surgical field. The gamma counter is used to determine if the node is “hot”. The probe count of the lymph node should be 10 times higher than the background count of the room to be considered sentinel.

i. If two sentinel nodes are adjacent to each other they should be separated and labeled as separate specimens.

j. Following completion of the lymphadenectomy as described in section 4.1 the operative field is inspected with the gamma probe to see if there are any remaining “hot” nodes.

k. The half-life of the radionucleotide is much longer than the blue dye and therefore is more likely to be transported to second echelon lymph nodes. For this reason there may be more “hot” nodes than “blue” nodes. The sentinel node usually retains higher counts than second echelon nodes; however this may be difficult to distinguish intraoperatively. Therefore, all “hot” nodes should be submitted as sentinel (label as described in Appendix 3).

l. A laparoscopic gamma probe must be used to identify hot sentinel nodes in-vivo in patients undergoing laparoscopic or robotic procedures.

- <u>Injection of Indocyanine Green (IC-Green™)</u>

  a. The patient must be positioned, prepped and draped so that a speculum examination can be performed

  b. The injection of IC-Green™ is performed after the abdomen is explored by palpation (laparotomy) or visually (laparoscopy or robotics).

  c. Clamps should not be placed on the uterus that might interfere in any way with distribution of the dye. The uterus should be manipulated by hand until IC-Green™ is seen in the retro peritoneum.

  d. With a speculum in the vagina, the concentration used should be 1.25 mg/mL. For each patient, a 25 mg vial with IC-Green™ powder is diluted in 20 cc of aqueous sterile water. Four cc of this IC-Green™ solution is injected into the cervix alone divided into the 3- and 9-o'clock positions, with 1 cc deep into the stroma and 1 cc submucosally on the right and the left of the cervix, usually prior to initiating laparoscopic or robotic entry. Allow approximately 5 minutes for the IC-Green™ to reach the sentinel nodes. Please note that when using IC-Green™, blue dye or radionuclide is not necessary.

e. A tenaculum may be used to manipulate the cervix while injecting IC-Green™.

f. Avoid spillage of IC-Green™ into the vagina by using a narrow gauge needle (21- 25 gauge) under low pressure. A needle extender, spinal needle, or control grip syringe may be used if needed.

- Identification of sentinel nodes

a. Incise the peritoneum lateral to the infundibular pelvic ligament and bluntly explore the retroperitoneum with care so that the afferent lymphatic channels are not transected. The afferent lymphatic channel is commonly seen adjacent to the uterine artery near the site where it passes over the ureter.

b. All green nodes are to be considered sentinel. If a green channel leads directly to a Lymph node but the lymph node itself is not green, it should still be considered sentinel.

c. Special attention to the detection of parametrial SLNs should be made. Parametrial SLNs are found medial to the superior vesical artery.

d. Grossly involved lymph nodes that are not green should be considered SLNs and labeled “not hot, not green SLN”.

e. Following removal of the sentinel node, it should be separated from extraneous material or other non-sentinel nodes and moved off the surgical field.

f. If two sentinel nodes are adjacent to each other they should be separated and labeled as separate specimen

- Labeling Specimens

a. Careful description of sentinel nodes in the operating room is vital part of this study. To facilitate this process, standardized labels will be printed for use in the operating room. These labels provide information on the location, type (blue/green, hot, or both), and amount of radioactivity. Pathologists should be requested to enter all these data into the trial pathology report. The amount of radioactivity should be entered in terms of counts per second. This will allow determination of the most radioactive nodes in an individual and will not be used for comparison between patients.

b. A sentinel node that is blue/green but not hot should be labeled “blue or green sentinel node”.

c. A sentinel node that is hot but not blue/green should be labeled “hot sentinel node”.
d. A sentinel node that is both blue/green and hot should be labeled “blue or green/hot sentinel node”.
e. Sentinel nodes should be labeled by location using the following categories and definitions:
    - Para-aortic: Sentinel nodes between the origin of the inferior mesenteric artery and bifurcation of the aorta. In addition, these nodes should be labeled right, left, or inter-aortic (between the inferior vena cava and aorta). Retroaortic or retrocaval locations are also acceptable for labeling the nodes resected from behind these vessels.
    - Common iliac: Sentinel nodes between the bifurcation of the aorta and bifurcation of the common iliac artery. Sentinel nodes should be labeled “right” or “left”. Retroiliac nodes can be specified if appropriate.
    - External iliac: Any sentinel node in contact with the external iliac vein or artery. Sentinel nodes should be labeled “right” or “left”.
    - Obturator: Any sentinel node that is apparent after the obturator space is opened and is in close proximity to the obturator nerve. Sentinel nodes should be labeled “right” or “left”.
    - Parametrial: Sentinel nodes that are in the lateral parametrium are usually adjacent to the uterine artery and are clearly not in the other groups described above. These sentinel nodes should also be labeled “right” or “left”. Medial parametrial nodes are usually not visible and may be quite small. In addition, the gamma probe cannot separate medial parametrial nodes from the high radioactivity originating from the cervix. Parametrial sentinel nodes have been described infrequently in other series.
    - Presacral: Sentinel nodes that are in the posterior lymphatic trunks of the cervix traverse the pararectal space to presacral nodes. These have been described infrequently in previous studies. When present, they are usually medial to the common iliacs and directly over the sacrum.

6.4 PELVIC / AORTIC LYMPH NODE DISSECTION

Surgeons will be required to perform pelvic ± para-aortic lymph node dissection as part of the treatment in both arms.

6.5 PREOPERATIVE SENTINEL NODE MAPPING WITH SPECT (Single Photon Emission Computed Tomography)

All consecutive patients who met the stage inclusion criteria stated in LACC protocol underwent pre-operative lymphoscintigraphy followed by surgery at San Gerardo Hospital, Monza, Italy. The cervical injection was carried out by a gynecologist oncologist with the assistance of a member from the Nuclear Medicine Department the day of surgery or the day before (within 24 hours before the planned surgical intervention).

Pre-operative LSG was obtained following four injections of 0.5-1.0 mCi radiolabeled filtered ^{99m}Tc albumin nanocolloid in 1-4 ml volume, using 22 gauge spinal needles (0.7 x 90 mm) as suggested in LACC Trial protocol (6.3 page 28). Under direct visualization four submucosal injections of the radiotracer were performed slowly in each of the four quadrants of the uterine cervix. Following the injection, a 10 minutes planar anterior dynamic LSG (10 frames, 1 minute per frame) was carried out, followed by planar anterior static images, performed immediately after the dynamic acquisition. The SPECT/CT study was performed 3 hours after the radiotracer injection, with a hybrid system composed of a dual-head gamma camera with a low dose x-ray tube installed in its gantry (Infinia Hawkeye 4, GE Medical Systems). SPECT acquisitions of the lower abdomen and the pelvis were performed with the following parameters: matrix size 128 x 128, rotation 360°, 6° view angle steps 25 seconds time frame; the CT acquisition parameters were as follows: slice thickness 5.0 mm, axial acquisition with 5.0 mm interval, full per slice, velocity 2.6 RPM. Reconstruction parameters were as follows: matrix 512 x 512, pixel 1.10 mm, filters standard and extended FOV. Cross-sectional attenuation images in which each pixel represented the attenuation of the imaged tissues were generated. The overall acquisition time of a SPECT/CT study was about 20 minutes. Images were analyzed on a Xeleris Workstation (GE Medical Systems).

Blue-dye injection

Under general anesthesia and just before surgery all patients were injected with Methylene blue dye (Methylene Blue 1%, Bioindustria L.I.M, Novi Ligure, Italy). A total of 2 to 4 mL of blue dye (1-2 mL per

injection) were injected into the cervix through a 20-gauge spinal needle at 3 and 9 o'clock position. The 12 o'clock injection was avoided to reduce the blue staining in the vesico-cervico-vaginal space, which makes the bladder dissection more difficult as recently suggested by Abu-Rustum et al (NR Abu-Rustum, F Khoury-Collado, ML Gemignani. Techniques of sentinel lymph node identification for early-stage cervical and uterine cancer. (Gynecol Oncol 2008; 111: S44–S50).

6.6 HISTOPATHOLOGIC EVALUATION OF THE SENTINEL NODES

Sentinel nodes will be classified according to a modification of the AJCC staging for axillary nodes from breast cancer as follows:

1) metastases present – tumor greater than 2.0 mm in diameter;
2) micrometastases present – tumor cell aggregates between 0.2 and 2.0 mm in diameter;
3) isolated tumor cells – individual tumor cells or aggregates that are less than 0.2 mm in diameter, usually detected by immunohistochemistry; or
4) tumor absent – no tumor cells identified in H&E (or immunohistochemically, if applicable) stained sections.

Non-sentinel lymph nodes will simply be reported as positive or negative for metastases based upon routine sectioning and examination of a single H&E stained section.

Grossing:

- All SLNs will be serially sectioned perpendicular to the long axis at 2.0 mm intervals. Lymph nodes 0.5 cm and smaller may be bisected.
- If the lymph node is submitted for frozen section (permitted but discouraged under most protocols), the lymph node should be submitted for frozen section as if it were being grossed routinely.
- Blocks are then submitted for routine processing.

Histologic examination, ultrastaging, and reporting:

- If a SLN has a metastasis *in the initial H& E section*, no further work up is necessary on that lymph node. In a comment, state the size of the metastasis.
- If a SLN is negative *on the initial section*, perform the ultrastaging protocol:
  - Five wide H&E levels at 200µm intervals. With each level, 2 unstained slides are cut (total of 10 unstained slides).
  - If the wide H&E intervals are negative, choose an unstained slide (usually the first

unstained with the first level) for immunostaining with pankeratin

- It is acceptable to release the ultrastaging results as an addendum report.

- Important note: In a case with multiple SLN parts (e.g. A-D) and one of the parts (e.g. part A) has a positive SLN but the other parts (e.g. B-D) are negative, the ultrastaging protocol is still performed on the negative parts (B-D); within a single part, if one SLN is positive (e.g. 1/7 lymph nodes positive), the ultrastaging protocol DOES NOT need to be performed on the remaining six negative SLNs in that part.

6.7 ADJUVANT RADIOTHERAPY/CHEMORADIOTHERAPY

Findings at surgery are used to determine the need for adjuvant post-operative treatment. For this study, the Sedlis criteria will be reviewed in making recommendation for adjuvant radiotherapy (refer to Appendix 2).

The delivery and management of radiation therapy will be carried out according to local institutional clinical practice guidelines. Preliminary and final dosimetry information as well as concurrent administration of chemotherapy will be recorded. This data will later be analyzed by the study statistician according to the intention to treat principle.

6.8 ACCREDITATION OF PARTICIPATING SURGEONS

Participating surgeons are required to be qualified gynecological oncologists with a proven track record in clinical research and hospital privileges to perform abdominal, laparoscopic, or robotic radical hysterectomy and pelvic lymphadenectomy (for cervical or endometrial cancer), radical trachelectomy or radical parametectomy to qualify as a surgeon for this clinical trial.

In order to minimize surgical complications during a surgeon's initial learning phase, participating gynecologic oncologists must provide evidence to the Trial Management Committee (TMC) of a minimal number of 10 documented cases performed as the main surgeon. Cases will be de-identified to protect the patient confidentiality. The details of the information required should include:

a. age

b. BMI

c. stage

d. OR time

e. EBL

f. Length of stay

g. Intraoperative complications

h. Postoperative complications (<30 days)

i. Red blood cell transfusion requirements (intraoperative and postoperative)

In addition, the prospective Principal Investigator of each site should submit at least 1 unedited video/DVD for approval before submitting to their respective IRB. Each video/DVD will be evaluated and judged by the Trial Management Committee based on the criteria below:

• surgeon technique and tissue handling
• competency in identification and dissection of proper anatomical structures and pelvic spaces
• surgical technique with respect to blood loss and prevention of intraoperative injury
• appropriate decision making based on intraoperative findings
• appropriate use of instrumentation for all parts of the procedure

However, if the institution/investigator has published results and outcomes in peer reviewed literature that demonstrates their skill and technique within this area, then they *may* be exempt from providing the above evidence of their skill.
Once the Principal Investigator is accredited at a site, he/she can then judge the competency of local collaborating surgeons in their institution who wish to enroll patients ensuring the above requirement criteria is met.

Surgeons are not required to have prior experience with lymphatic mapping in order to enroll patients on this study, however skill verification is required. Surgeon skill will be confirmed during the first three cases from each institution. These patients will be excluded from the statistical analyses.

Surgeons who plan to enroll patients and perform the study procedure should be present for the mapping portion of at least one of the first three cases and their presence documented in the operative report. If a surgeon who was not present during one of the first 3 cases wants to enroll a patient and perform the procedure then one of the "verified" surgeons must be scrubbed for the mapping portion of the case. The operative note must include the presence of the verified surgeon during the study procedure.

This process ensures that the surgeon's skill is verified by either 1) scrubbing for one of the first 3 cases or 2) ensuring that a previously verified surgeon is scrubbed for the mapping portion of a case when the patient enrolled after the verification period.

6.9 PATHOLOGY

Every patient will need to have histologically confirmed, adenocarcinoma, squamous cell carcinoma, or adenosqaumous carcinoma of the uterine cervix. If biopsy from an apparent cervical cancer demonstrates the presence of sheets of squamous cells without unequivocal stromal invasion, the patient will still be eligible for treatment in the trial if the lesion clinically represents invasive cervical cancer.

7.0 OUTCOMES

7.1 PRIMARY OUTCOME MEASURES

Treatment equivalence as evaluated by: Disease-free survival at 4.5 years post-surgery, as measured by the time interval between date of surgery and date of first recurrence. Histological confirmation of recurrent disease will prove the presence of recurrent disease.

7.2 SECONDARY OUTCOME MEASURES

- Patterns of recurrence: date and localization of 1st recurrence as confirmed histologically – pelvic versus distal.

- Treatment related morbidity, as evaluated by:
    - Intraoperative complications – injury to bladder, ureter, bowel; vascular injury and bleeding, nerve injury;
    - Perioperative (time to discharge from hospital): urinary tract infection, urinary retention, ileus, cardiac (myocardial infarction, atrial fibrillation), pulmonary (edema, atelectasis, pneumonia), renal and cerebrovascular morbidity. Wound and vault complications (infection, breakdown, and dehiscence). Septicaemia and thromboembolic complications (DVT, PE). Lymphocyst or abscess formation;
    - Early postoperative (< 4 weeks): Wound and vault complications (infection, dehiscence). Lymphocyst, Abscess formation, Lymphoedema or Fistula formation;
    - Long-term morbidity (4 weeks to 6 months): Lymphoedema, incisional hernia formation, vaginal eviseration.
    - Estimated blood loss: As defined by the total volume of suctioned fluids minus the volumes of irrigation fluids used at the completion of surgery. In addition, blood loss will be reviewed in hemoglobin change from baseline. A Full Blood Count (hemoglobin) will be taken before and the morning after the operation;
    - Postoperative pain and analgesic consumption using pain scores and analgesic consumption measurements;
- Costs: measured as the incremental cost per unit of improvement in functional outcome, measured in terms of the primary outcome plus using quality-adjusted life years (QALYs) to undertake a cost-utility analysis;
- Quality of life: Change in Quality of Life using Functional Assessment of Cancer Therapy Cervical (FACT-Cx), the MD Anderson Symptom Inventory (MDASI, Short Form-12 (SF-12) and EuroQoL-5D (EQ-5D) between Baseline (pre-surgery) and 6 months after surgery.
- Pelvic Floor Distress Inventory: measures symptom severity and quality of life changes in women with pelvic floor disorders. The Pelvic Floor Distress Inventory (PFDI) provides a standardized, reproducible assessment of the patient's symptoms and their effect on daily life[88].
- Overall survival at 4.5 years follow-up
- Feasibility of sentinel lymph node biopsy in this group of patients.

8.0 RANDOMISATION

All eligible patients will be required to provide informed signed consent before being randomized. Prior to randomization, each patient will be screened for eligibility according to the inclusion and exclusion criteria. A web-based computer randomization procedure will be coordinated centrally from Australia.

Randomization will be performed using the method of minimization with an equal allocation between the two treatment groups. Randomizations will be stratified according to treating centre, and disease stage as determined clinically according to the current FIGO guidelines and patient's age (≤ 70 and > 70 years).

9.0 SAMPLE SIZE

The primary objective of this study is to determine whether Total Laparoscopic (TLRH) or Robotic Radical Hysterectomy (TRRH) is equivalent to Total Abdominal Radical Hysterectomy (TARH) with respect to 4.5 year disease free survival. If the disease free survival does not differ by more than 7% then the two procedures will be considered to be equivalent.

The 4.5 year disease free survival rate for patients undergoing TARH is estimated to be 90%. The following table, based on exponential survival times, gives the sample sizes required for levels of differences in disease free survival rates at 4.5 years. These differences will be regarded as being equivalent based on different accrual and follow-up times. The sample sizes assume a power of 80%, 95% confidence and two-tailed comparisons.

Based on these numbers, for a 4.5-year accrual and 4.5-year follow-up, a total of 740 patients (370 per arm) would be sufficient to declare equivalence with an equivalence margin of 7.2% or less at 4.5 years. If accrual is sufficiently rapid (ie less than 4.5 years), consideration will be given to increasing the sample size to reduce the amount of follow-up required but maintain the equivalence margin. This sample size will have 87% power to detect a non-inferiority margin of the same magnitude.

Table for Option 1 Randomised Design

4yr Disease Free Survival difference to be regarded as equivalent		Years		Total Sample Size
TLRH/TRRH	TARH	Accrual	Follow-up	
85	90	3	3	1660
		3	4	1380
		3	5	1190
		4	4	1280
		4	5	1114
84	90	3	3	750
		3	4	760
		3	5	654
		4.5	4.5	740
		4	5	614
		5	4	656
85	92	3	3	794
		3	4	660
		3	5	568
		4	4	612
		4	5	532

10.0 STATISTICAL ANALYSES

Primary endpoints will be analyzed according to the intention-to-treat principle. However, as this is a non-inferiority design, there is a view by some biostatisticians that, if there are patients who do not receive the allocated treatment (and in fact 'cross-over' to the alternate arm) an analysis by intention to treat will bias the analysis in favour of the alternate hypothesis that the two groups are not inferior. To overcome this issue, a 'per protocol' analysis i.e. only include those patients who were treated according to the protocol would be used. Therefore being a "modified" version of intent to treat analysis as conveyed to the Trial Safety Committee on 1st October 2014.

10.1 ANALYSIS OF STAGE 1 (FEASIBILITY PILOT)

After the accrual of 100 patients, data will be analyzed to allow determination of several key components of the study which are not the primary endpoints specified in the protocol. These will include:

- Rate of accrual
- Compliance with randomized treatment allocation

Consideration to stopping the study after 100 patients have been accrued will be given if:

1. Annual patient accrual is less than 30;
2. Less than 75% of patients are available for follow-up
3. There is an unacceptable rate of the incidence of complications (>8%) in the TLRH/TRRH group

If these components are satisfied, the Trial Management Committee will make a decision to proceed to the second stage of the complement of 740 patients.

10.2 ANALYSIS OF STAGE II (PHASE III STUDY)

Disease-free survival and overall survival curves will be estimated using the Kaplan-Meier method. The primary comparison of survival distributions will be with the logrank test. Secondary analyses will adjust for prognostic factors using appropriate regression models (e.g. Cox proportional hazards model). All measures of efficacy will be compared by an intention-to-treat analysis including all randomized patients. Toxicity will be analyzed by treatment received. Ninety-five percent confidence intervals will be reported for the differences between the treatment arms.

Descriptive statistics for treatment-related adverse events as well as Quality of life (FACT-Cx, SF-12, MDASI, EQ-5D) and subscales (physical well-being, social well-being, emotional well-being, functional well-being, cervical cancer specific well-being and body image scale), will be calculated for each randomization group at each assessment.

Similarly, descriptive statistics will also be calculated for other outcomes, such as pain scores, anxiety and depression scores and analgesic consumption, etc.

Continuous variables will be assessed for normality and equality of variances between groups. Discrete variables (eg. presence/absence of post-operative infection) will be summarized by frequencies/proportions.

For continuous variables, analysis of variance and/or regression will be used, where appropriate. If assumptions for these tests are violated, alternative non-parametric tests will be used. Difference between groups with respect to discrete variables will be evaluated by using chi-squared tests.

Exploratory analyses adjusting for prognostic factors including age, tumor size, stage, grade of differentiation, depth of myometrial invasion, lymph node involvement, type of treatment, and ECOG status will be performed using proportional hazards regression methods. The impact of baseline QoL on survival will also be investigated.

Provided sufficient patient numbers, outcomes in regards to treatment costs will be analyzed country-specific by the individual investigator of that country.

10.3 ANALYSIS OF IOLM COMPONENT

The ability to successfully identify at least one sentinel lymph node in each patient undergoing radical hysterectomy and IOLM will be calculated. In addition, location, number, and laterality of identified sentinel node(s) will be reported. In patients where at least one sentinel node is identified, sensitivity, specificity, positive and negative predictive values of the procedure will be calculated.

10.4 INTERIM ANALYSES AND EARLY STUDY TERMINATION

There is some concern as to whether there may be an increased rate of severe adverse events in the TLRH/TRRH group. The rate of complications will be monitored and formally assessed after 50, 100, 150, 200 and 300 patients randomized into the TLRH group have completed surgery. Early termination will be considered if there are surgery related deaths. The following table gives the upper bound of the number of deaths caused by surgery.

Number of subjects in TLRH/TRRH group	Consider stopping the study if the number of deaths caused by surgery is ≥
50	2
100	3
150	4
200	5
300	6

All toxicity data will be reviewed by a Trial Safety Committee (TSC) (please refer to section 20.1) who will make recommendations to the Trial Management Committee in regards to changes to the protocol and/or stopping the trial. Additional revised power calculations will be undertaken at these times based on both local and total recurrence which may indicate that larger (or smaller) relapse rates may be worth detecting.

Toxicities/complications which will also be considered by the independent Trial Safety Committee (TSC) include:

a) Conversion to laparotomy as a result of bleeding;
b) Injury to abdominal or pelvic viscera secondary to endoscopic instrument placement or manipulation. This includes injury to the bowel, bladder, vessels, ureter or kidney;
c) Development of symptomatic lymphocysts requiring percutaneous drainage or hospitalization;
d) Nerve injury requiring physical therapy or restricting function;
e) Unplanned ICU admission.

11.0 ANALYSIS OF COST EFFECTIVENESS

Participation in the economic analysis component is optional for study sites and analyses will be country specific.

11.1 ECONOMIC ANALYSIS

We will assess the cost-effectiveness of the intervention (TLRH ± Laparoscopic Pelvic/Aortic Lymph Node Dissection) relative to standard treatment alone (TARH ± Pelvic/Aortic Lymph Node Dissection), calculated as the incremental cost per unit of improvement in functional outcome, and measured in terms of the primary outcome.

The outcomes of this part of the economic analysis will be in terms of costs per disease and treatment specific difference in quality of life at six months. More specifically, costs per fewer days' treatment-related morbidity, shorter hospital stays, less days with post-operative pain, and less analgesic consumption. By assessing the difference in cost between the standard treatment and the proposed intervention, it can be ascertained which of the two treatments represents the most sound investment in terms of the improvement in quality of life.

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. Several viewpoints will be considered for the economic analyses, including those of health system purchasers, households and society in general.

This part of the economic analysis allows us to express outcomes in costs per QALY. The aim of this generic outcome measure is to assess whether the study intervention represents value for money as compared to alternative interventions (including for other conditions), and as compared to the various threshold values below which an intervention is considered good value for money (in Australia $40,000 per QALY is often used).

In terms of measuring costs, a number of components will be considered, including: the intervention costs; the provision of information booklets to patients; GP and specialist consultations; radiology and imaging; prescriptions, over-the-counter medications; community health and social services; days off work; and informal care by family and friends. Direct costs will be obtained for samples of patients, stratified by hospital, operation and outcome, using a bottom-up approach by recording the volume of resource use in both arms of the trial, and then applying a unit cost to each component. Data on all patients' use of healthcare services will be collected using a combination of retrospective

questionnaires and clinical files. All questionnaires have to be amended to the protocol and approved by the IRB prior to giving to patients. Where possible, local cost tariffs will be used and national sources will be used as comparators.

12.0 STUDY VISITS

12.1 PRE-OPERATIVE (VISIT 1)

A cervical biopsy that confirms one of the following cancer types:

Adenocarcinoma
Squamous Cell Carcinoma
Adenosquamous Carcinoma

The following procedures will be performed within six weeks before surgery:

- Chest X-ray (not required in patients with other imaging of the chest);
- CT scan and/or MRI Scan and/or PET Scan and/or Ultrasound of the abdomen and the pelvis, if clinically indicated
- 12-lead Electrocardiogram (if indicated);

The following procedures will be performed < 30 days before surgery:

- Sign IRB/HREC-approved written informed consent;
- Collect demographic data, medical history and baseline toxicity data (documented and graded according to CTC Version 3);
- Record all concomitant medications (including prescription, over the counter remedies, vaccination, vitamin, or herbal preparations) used presently and within the past 12 weeks;
- Administer Quality of Life instruments (FACT-Cx, SF12, EQ-5D, MDASI);
- Administer Pelvic Floor Distress Inventory;
- Complete physical and pelvic examination;
- ECOG performance score;
- Weight (kg) and height (cm);
- Standard preoperative laboratory workup as determined by each institution
- Complete Randomization form that verifies the inclusion criteria have been met;
- Complete on-line randomization procedures to randomize the patient and document the result.
- Serum pregnancy test (if clinically indicated)
- E/LFT – must include creatinine, bilirubin, albumin, alkaline phosphatase (ALP), aspartate, aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT)
- Full blood count

12.2 SURGERY (VISIT 2)

The following procedures will be performed at this visit;

- Perform surgery as per Randomization result: Standard or Intervention;
- Record intra-operative and post operative information (including operation details, histological findings, intra-operative complications, transfusion details and any other special conditions around the operation).

12.3 POST-OPERATIVE (VISITS 3 -VISIT 6)

The following procedures will be performed at visits scheduled at 1 week, 6 weeks, 3 months, and 6 months post surgery:

Day 1 – after surgery:

- Record post operative Hemoglobin level to Surgery eCRF if done (Day 1 after surgery)
- Record laboratory results (if clinically indicated)

Visit 3 – Post Op Visit 1 = Week 1 (must be collected within 3 days either side of due date and may be obtained via medical visit, telephone contact or postal correspondence):

- Provide patient with Quality of Life instruments (FACT-Cx, SF-12, EQ-5D, MDASI);
- Provide patient with Health Services Questionnaire;
- Review ECOG performance score;
- Weight if available
- Assess patients for their individual pain level using linear analogue scale
- Record Full blood count and ELFT's if available
- Physical examination – not a requirement at this time point, however record done/not done
- Adverse events assessment (CTCAE v3.0);
- Update concomitant medications
- Update concomitant illnesses

Visit 4 – Post Op Visit 2 = Week 6 (must be collected within 1 week either side of due date and may be obtained via medical visit, telephone contact or postal correspondence)

Visit 5 – Post Op Visit 3 = Month 3 (must be collected within 2 weeks either side of due date and may be obtained via medical visit, telephone contact or postal correspondence)

Visit 6 – Post Op Visit 4 = Month 6 (must be collected within 1 month either side of due date and may be obtained via medical visit, telephone contact or postal correspondence)

The following procedures will be performed at Visit 3-5 (aka Post Op Visits 1-4)

- Provide patient with Quality of Life instruments (FACT-Cx, SF-12, EQ-5D, MDASI)
- Provide patient with Pelvic Floor Distress Inventory (every 6 months postoperatively)
- Provide patient with Health Services Questionnaire;
- Review ECOG performance score;
- Assess patients for their individual pain level using linear analogue scale
- Record Weight (kg);
- Adverse events assessment (CTCAE v3.0);
- Update concomitant medications
- Update concomitant illnesses
- Record laboratory results (if clinically indicated)

12.4 FOLLOW-UP VISITS

Follow-up visits begin at 9 months following surgery and continue every 3 months thereafter for the first 2 years and every 6 months until year 4.5.

Follow Up eCRF Visits (not including QoL questionnaires) can be collected using the following time frames:

Time point	Patient Disease Status Data can be gathered (not including QoL)
Visit 1 PO	3 days either side of due date of Week 1
Visit 2 PO	1 week either side of due date of Week 6
Visit 3 PO	2 weeks either side of due date of Month 3
Visit 4 PO	1 month either side of due date of Month 6
FU 1	Anytime between date of Month 6 visit and 2 weeks after due date of 9 Months post op
FU 2	Anytime between date of Month 9 visit and 2 weeks after due date of 12 Months post op
FU 3	Anytime between date of Month 12 visit and 2 weeks after due date of 15 Months post op
FU 4	Anytime between date of Month 15 visit and 2 weeks after due date of 18 Months post op
FU 5	Anytime between date of Month 18 visit and 2 weeks after due date of 21 Months post op
FU 6	Anytime between date of Month 21 visit and 2 weeks after due date of 24 Months post op
FU 7	Anytime between date of Month 24 visit and 2 weeks after due date of 30 Months post op
FU 8	Anytime between date of Month 30 visit and 2 weeks after due date of 36 Months post op
FU 9	Anytime between date of Month 36 visit and 2 weeks after due date of 42 Months post op
FU 10	Anytime between date of Month 42 visit and 2 weeks after due date of 48 Months post op
FU 11	As close to Month 54 as possible (can be a month either side) to accurately assess disease free survival following 4.5 years post op.

The following procedures will be performed at follow-up visits if data available (if no data available for a FU visit, this is not considered a deviation of Protocol unless it is continual):

- A Clinical assessment including an internal examination will be performed from visit 5 (3 months postoperatively)
- Histological and/or Radiological confirmation of recurrent disease will be obtained to prove the presence of recurrent disease. The date of recurrence, its localization and its subsequent treatment will be recorded.
- The date of death will be recorded and every effort will be made to obtain a cause of death (possibly disease-related, possibly treatment-related).
- Provide patient with the Pelvic Floor Distress Inventory and FACT-CX at Follow-Up 4, 7, 9 and 11 – these must all be done within 1 month of due date (if not received by patient, this is not considered a deviation from the Protocol).

13.0 PATIENT WITHDRAWAL

Patients will be advised that they may voluntarily withdraw from the study at anytime, for any reason and it will not affect their medical care. However, in such cases, appropriate effort will be made by the Investigator to determine the reason for voluntary withdrawal from the study and to document reason for withdrawal in the medical record, if known.

The last known status of these patients will be reported with the study results and all attempts to locate patients lost to follow up will also be documented.

Patients will be informed that, should they withdraw from the study, they should remain under the care of an appropriately experienced physician until the physician deems further follow-up unnecessary.

The following are circumstances for which a patient would be identified as not continuing her participation in the study:

- Study Completed / Terminated
- Death
- Voluntary Withdrawal
- Unable to Return

- Unwilling to Return
- Intercurrent Illness
- Move to another area
- Lost to follow-up
- Other

If a patient relocates to another geographic area, which requires a change of physician, reasonable attempts will be made to locate and request cooperation from that physician in order to complete follow-up.

In many instances patient withdrawal from the study constitutes a cessation of treatment and/or cessation of completing associated forms such as quality of life. In these cases, permission should be obtained from patients by study staff to continue monitoring their disease state (relapse, survival, toxicity etc) via patient records as this is a crucial component of the study for which consent was originally obtained.

14.0 QUALITY OF LIFE INSTRUMENTS

The measures selected to comprise the Quality of Life Questionnaire will address postoperative symptoms (such as pain) as well as disease-specific and general health related quality of life. These surveys are designed for self-administration and should take less than 20 minutes to complete.

14.1 FACT-CX

The Functional Assessment of Cancer Therapy[89] has been widely used in oncology because it is a multidimensional instrument that is easy to administer. The series of FACT questionnaires are also well-regarded particularly because they contain several disease-specific subscales, including the cervical cancer subscale FACT-Cx. This subscale was developed to incorporate several disease-specific issues, both physical and emotional, including sexual function and fertility. The entire survey is 42 items and should take the patient less than 10 minutes to self-administer. The Fact-Cx has been successfully used in many studies of women with cervical cancer[90 91]. The FACT Cx will be provided to the patients for completion at Pre and Post Op Visits 1, 3, 4, 5 and 6 as well as Follow-Up Visits 4, 7, 9 and 11.

14.2 MDASI

The MD Anderson Symptom Inventory (MDASI) is a 19-item questionnaire. The first 13 items assess patient symptoms during the prior 24 hours should take less than 3 minutes to complete. Symptoms assessed include pain, fatigue, nausea/vomiting, anorexia, sleep symptoms, and distress. The last six items assess how those symptoms have interfered with the patient's general well-being including their general activity, mood, ability to walking and perform normal work, as well as their relationships with others and enjoyment of life. The validity and reliability of the MDASI have been well-established in previous studies[92]. The MDASI will be provided to the patients for completion at Pre and Post Op Visits 1, 3, 4, 5 and 6.

14.3 SF-12

The Short Form-12 Health Survey measures generic health concepts relevant across age, disease, and treatment groups. It provides a comprehensive, psychometrically sound, and efficient way to measure health from the patient's point of view by scoring standardized responses to standard questions. The SF-12 is designed for self-administration, reducing the burden of data collection for health care providers. Most patients can complete the SF-12 in less than 3 minutes without assistance.

The SF-12 was designed to measure general health status from the patient's point of view. It includes 8 concepts commonly represented in health surveys: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional, and mental health[93]. Results are expressed in terms of two meta-scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). SF-12 will be provided to patients for completion at Pre and Post Op Visits 1, 3, 4, 5 and 6.

15.0 OTHER QUESTIONNAIRES

15.1 HEALTH SERVICES QUESTIONNAIRE (HSQ)

Seven items assessing health care utilization during the past 6 months were adapted from Health Care Utilization items developed by the Stanford Patient Education Research Centre (http://patienteducation.stanford.edu/research/utilization.html). The original items were reported to have to excellent test-retest reliability ranging from 0.76-0.97 and to validly report use of such services[94]. The HSQ will be provided to patients for completion at Post Op Visits 3, 4, 5 and 6.

15.2 EuroQoL-5D (EQ-5D)

EQ-5D is a standardized instrument for use as a measure of health outcome. It provides a descriptive profile and a single index value for health status. EQ-5D was originally designed to complement SF-36. EQ-5D will measure changes in health status and quality of life to calculate the quality-adjusted life years (QALYs) gained with the intervention. EQ-5D will be provided to patients for completion at Pre and Post Op Visits 1, 3, 4, 5 and 6.

15.3 PELVIC FLOOR DISTRESS INVENTORY

Measuring symptom severity and quality of life changes in women with pelvic floor disorders is an important part of the evaluation and treatment of women. The Pelvic Floor Distress Inventory (PFDI) provides a standardized, reproducible assessment of the patient's symptoms and their effect on daily life[95]. Use of this psychometrically robust self-administered questionnaire is the most valid way of measuring the presence, severity, and impact of a symptom or condition on a patient's activities and well-being. The PFDI will be provided to patients for completion at Pre and Post Op Visits 1 and 6 and Follow-Up Visits 4, 7, 9 and 11.

16.0 CONCOMITANT MEDICATION AND TREATMENT

All **Concomitant Medication(s)** must be reported in the electronic case report form. In addition, any diagnostic, therapeutic or surgical procedure performed during the study period, should be recorded including the date, indication, description of the procedure(s) and any clinical findings. Patients should receive full supportive care including transfusions of blood and blood products, antibiotics, anti-emetics etc., where applicable. The reason(s) for treatment and treatment dates should be recorded in the **Concomitant Illness(s)** electronic case report form.

Concomitant radiotherapy treatment and/or chemotherapy treatment is permitted and may be offered to patients at the treating Investigator's discretion according to each center's practice. Adherence to local institutional clinical practice guidelines for the use of adjuvant treatment is recommended. Treatment information has to be recorded in the electronic case report form.

17.0 ADVERSE EVENTS (AEs)

17.1 DEFINITIONS

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to treatment or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study treatment.

A treatment-emergent AE is defined as any event not present prior to surgery or any event already present that worsens in either intensity or frequency following surgery.

All AEs that occur after surgery during the study must be reported in detail in the patient's source/chart and the relevant electronic case report forms and followed to a satisfactory resolution or until the local Investigator deems the event to be chronic or the patient to be stable. The description of the AE will include the onset date, duration, date of resolution, severity, seriousness, etiology, and the likelihood of relationship of the AE to study treatment.

Severity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTC-AE v3.0),

If an adverse event occurs which is not contained in the CTC-AE v3.0, the five-point scale below will be used:

1. Mild: discomfort noticed but no disruption of normal daily activity.
2. Moderate: discomfort sufficient to reduce or affect daily activity.
3. Severe: inability to work or perform normal daily activity
4. Life Threatening: represents an immediate threat to life
5. Death

17.2 COMMON ADVERSE EVENTS

The most common postoperative adverse events from study treatment include:

- Intraoperative injury (bowel, bladder, ureter, nerves or blood vessels)
- Wound complication (vault or pelvic hematoma or collection)

- Infectious complications (bladder, chest, septicaemia)
- Postoperative hemorrhage/ bleeding, thromboembolic events (DVT, pulmonary embolus)
- Prolonged Ileus > 7 days, fistula formation (any) or hernia formation
- Cardiac, pulmonary renal or cerebrovascular complications
- Returned to theatre in same admission (re-operation)
- Bladder dysfunction
- Lymphoedema

17.3 LABORATORY TEST ABNORMALITIES

Laboratory test value abnormalities will not be reported as AEs, unless there is an associated clinical condition for which the patient is given treatment, concomitant treatment is altered or the event is considered a serious adverse event.

17.4 SERIOUS ADVERSE EVENTS (SAE)

An SAE is defined as any event that:

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Reporting requirements:

Any Adverse Event considered Serious by the local Investigator or which meets the previous criteria must be reported to the Trial Safety Committee. The following must occur within one business day from the time that the site personnel first become aware of the serious adverse event:

- The site personnel **must** complete the SAE case report form and submit this to the Lead Site/Central Data Management Unit (CDMU):

  Vanessa Behan (Clinical Trial Manager)
  Queensland Centre for Gynecological Cancer (QCGC),
  Level 6, Ned Hanlon Building
  Herston QLD AUSTRALIA 4029
  Fax Number: +61 7 3646 1721
  Email: Vanessa.Behan@health.qld.gov.au

As well as providing the SAE form to CDMU the site is also required to email a brief notification of SAE data transmission. All SAE's will be reported by the CDMU to a central IRB/HREC and the Trial Safety Committee. However, all sites are required to submit these locally occurring SAEs to their relevant IRB/HREC within 24 hours of first notification of SAE occurrence or according to local IRB/HREC policy. QCGC will provide CRF for SAE reporting, however sites should use their governing bodies requested documentation when making local submissions.. If English is not the primary language used at the reporting site, the site must provide a copy of the original IRB/HREC report of SAE and a copy which has been translated into English.
If the patient is hospitalized because of or during the course of an SAE, then preferably a copy of the hospital discharge summary and any other reports/results (and a translated version if applicable) should be faxed/emailed to the Queensland Centre for Gynecological Cancer, Australia as soon as it becomes available.

All therapeutic measures will be at the discretion of the Investigator. All reported SAEs (related or not to the surgery) will be followed until satisfactory resolution or until the Investigator deems the event to be chronic or the patient to be stable. SAEs will be reported till 30 days from completion of primary therapy and up to 6 months if directly related to primary therapy.

17.5 ADVERSE EVENT REPORTING (AE)

Information regarding AEs will be collected from the time the patient signs the informed consent form up to 6 months post treatment.

All AEs reported or observed during the study will be recorded as an AE in the patient's source/chart/eCRF and CRF. Information to be collected includes:

- Drug treatment
- Type of event
- Time of onset
- Dosage
- Investigator-specified assessment of severity and relationship to treatment
- Time of resolution of the event
- Grade
- Any required treatment or evaluations
- Outcome.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be recorded. All AEs will be followed to adequate resolution. Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study it should be recorded as an AE.

17.6 OBTAINING ADVERSE EVENT INFORMATION

At every study visit, patients will be asked a standard non-leading question to obtain any medically related changes in their well being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription, over-the-counter medications, and herbal supplements). In addition to patient or Investigator observations, AEs will be documented from any data collected (eg, laboratory values, physical examination findings), or other documents that are relevant to patient safety.

17.7 ASSESSMENT OF CAUSALITY

The Investigator's assessment of an AE's relationship to treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

- **Unrelated:** This relationship suggests that there is no association between the surgery and the reported event.
- **Possible:** This relationship suggests that treatment caused or contributed to the AE, i.e. the event follows a reasonable temporal sequence from the time of surgery and/or follows a known response pattern to the surgery, but could also have been produced by other factors.
- **Probable:** This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and the likely association of the event with the surgery. This will be based upon the known or previously reported complications to the surgery, or judgment based on the Investigator's clinical experience.
- **Definite:** This relationship suggests that a definite causal relationship exists between the surgery and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

17.8 ASSESSMENT OF SEVERITY

Adverse Event severity will be rated by the Investigator as mild, moderate, or severe using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (Appendix 7).

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

18.0 CRITERIA FOR PREMATURE WITHDRAWAL

Patients have the right to withdraw from trial treatment or the study at any time for any reason. The investigator also has the right to withdraw patients from trial treatment or the study in the event of intercurrent illness, adverse events, protocol violations, administrative reasons or other reasons.

An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. The investigator should document the reason for the withdrawal, if known.

If a patient withdraws from the study, a complete final evaluation at the time of the patient's withdrawal should be made.

If the reason for removal of a patient from the trial treatment or the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded.

19.0 STUDY COMMITTEES

19.1 TRIAL SAFETY COMMITTEE (TSC)

An independent Trial Safety Committee (TSC) will be assembled to review the safety and efficacy data collected during the study. They will be composed of individuals who are independent of the study and are not involved (either directly or indirectly) in the management of this study. The membership includes the following:

- 3 gynecological oncologists who are otherwise not related to the trial;
- 2 Statisticians who are otherwise not related to the trial;
- 1 Public Member

The TSC will be responsible for monitoring, on an ongoing basis, any of the following events:

- General Toxicity (NCI-CTC AE, v3): grade 3 and grade 4 adverse events, serious adverse events
- A patient death (grade 5)

The first safety analysis will be performed after 20 patients have completed treatment. All further TSC reviews should take place twice per year and the committee will review all safety data collected during the study.

Following each meeting, the committee will recommend that the study continues according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases the committee may recommend stopping the study due to safety reasons.

19.2 TRIAL MANGEMENT COMMITTEE (TMC)

A Trials Management Committee (TMC) will be assembled to review and manage the trial's progress. The TMC will consist of the study chair, the co-chairs, two study coordinators, and the study statistician, in Australia and USA. The TMC will meet/confer every four months.

Following each meeting, the committee will recommend that the study continues according to the protocol or may suggest changes to the protocol based on the outcome of the data review.

20.0 DATA HANDLING AND QUALITY ASSURANCE

20.1 ELECTRONIC CASE REPORT FORMS

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate source documentation as part of the patient's case history.

QCGC plans to supply the CRF. The CRF will be a web-based eCRF allowing geographically dispersed sites to randomize participants, receive and transmit data to the central database located in Queensland Centre for Gynecological Cancer within the University of QLD, Australia in real time. The e-CRF application is in accordance with the U.S. Department of Health and Human Services Food and Drug Administration's (FDA) document: Guidance for Industry – Computerized Systems Used in Clinical Trials.

All requested information should be promptly entered into the eCRF optimally within 7 working days of a patient visit. Detailed instructions for completing the CRF will be available online. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed. Corrections to the CRF and the reason for the change are tracked in an audit trial with the user's log-in name and date and time the entry or correction is made.

At the completion of the trial a copy of the CRF (PDF file on CDROM) will be placed in the Investigator's files.

20.2 DATA SECURITY

The administrative burden and security issues at sites will be greatly reduced as a result of reduced data storage requirements at local sites. Data integrity is guaranteed through the use of transaction processing monitors, which allows for multiple users to enter data while simultaneously guaranteeing the completeness of the data.

Access to this data base will be by username and password and will be restricted to trial personnel. An audit trail will be in place for generating, retaining, importing or exporting the electronic data. By implementing a good design and 128-bit Secure Socket Layer (SSL) encryption software, the most widely implemented encryption system for the Web at present (as used by government agencies and internet banking); the CRF data entry will be extremely secure.

20.3 ELECTRONIC SIGNATURES

The electronic CRF will be compliant with all provisions of Food and Drug Administration's (FDA) part 11 of Title 21 of Regulations; Electronic Records; Electronic signatures that applies to records in electronic modified, maintained, archived, retrieved, or transmitted under any FDA regulations.

20.4 MONITORING OF THE STUDY

The central data management unit (CDMU) located at the Queensland Centre for Gynaecological Cancer; Australia will closely follow the study by way of a Monitor. The Monitor will maintain a working knowledge of the study by way of observation, review of study records and source documentation and/or Translation Forms, and report conduct of the study to the Investigator/s and staff. The Monitor is responsible for ensuring adherence to the Protocol and completion of the required eCRF's. In order to ensure accuracy of data, access to the source documents by the representatives of CDMU or its appointee and regulatory authorities is mandatory. CDMU or its appointee will carefully monitor all aspects of the study for compliance with applicable government regulation with respect to current good clinical practice and current standard operating procedures.

20.5 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial-related monitoring, audits, Institutional Review Board (IRB) or Human Research Ethics Committee (HREC) review, and regulatory inspection(s) by providing direct access to source data/documents.

The Investigator should promptly notify CDMU or its representative of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to CDMU.

20.6 DATA QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the applicable Standard Operating Procedures (SOPs) and project specific procedures. Safety reporting will be done according to CDMU SOPs. Data management will be performed by the CDMU in collaboration with The University of Texas M.D. Anderson Cancer Center. Accurate and reliable data collection will be assured by verification and cross–check of the electronic CRFs against the investigator's records by CDMU or its representative (source document verification). The data collected will be either entered directly onto the online database or entered into the study database from the CRF. A comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the investigator.

20.7 STUDY RECORD RETENTION

Essential Documents should be retained at least 10 years after the study is completed. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with CDMU. It is the responsibility of the Principal Investigator at each site to make provisions for study record retention. It is the responsibility of CDMU to inform the Principal Investigator and/or Co-Investigators as to when these documents no longer need to be retained.

21.0 ADMINISTRATIVE CONSIDERATIONS

The following administrative items are intended to guide the local Investigator's in the conduct of the trial but may be subject to change based on industry and government Standard Operating Procedures or Guidelines. Changes will be reported to the IRB/HREC but will not result in protocol amendments.

21.1 CONFIDENTIALITY

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient or

the patient's guardian, except as necessary for monitoring by CDMU or its representative, regulatory authorities, or the IRB/HREC.

The Investigator and all employees and co-workers involved with this study shall not disclose or use for any purpose, other than performance of the study, any data, records or other unpublished, confidential information disclosed to those individuals for the purpose of the study.

Prior written agreement from the study Sponsor the University of Texas MD Anderson Cancer Center and the Lead Site University of Queensland – Queensland Centre for Gynaecological Cancer must be obtained for the disclosure of any said confidential information to other parties. In the US, the patient must give approval, in addition to the study sponsor.

21.2 ETHICS APPROVAL

Federal, state, and local regulations and ICH guidelines require that approval be obtained from an IRB/HREC prior to participation of human patients in research studies. Prior to the study onset, the IRB/HREC must approve the protocol, informed consent, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's legal guardian. The site will maintain this and provide copies of the initial approval and ongoing approval to the Lead Site/CDMU and make available for review by the Sponsor or its representative, documentation of all IRB/HREC approvals and of the IRB/HREC compliance with Federal, state, and local regulations and ICH guidelines.

The Investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/HREC. The Investigator must supply Lead Site/CDMU with written documentation of continued review of the clinical research. All IRB/HREC approvals should be signed by the IRB/HREC Chairman and must identify the IRB/HREC name and address, the clinical protocol by title and/or protocol number and the date approval was granted.

21.3 MODIFICATION OF THE PROTOCOL

The TMC must review and approve any changes in this research activity. Amendments to the protocol must be submitted in writing to the Investigator's IRB/HREC for approval prior to patients being enrolled into an amended protocol.

21.4 INFORMED CONSENT

A written informed consent shall be obtained from each patient prior to the patient's entrance into the study. CDMU will provide an informed consent template to the investigative sites. If the site makes any institution-specific modifications, CDMU may review the consent prior to IRB/HREC submission. The Investigator will submit the approved, revised consent to the appropriate IRB/HREC for review and approval prior to the start of the study. If any safety information is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrolment, each prospective patient will be given a full explanation of the study and be allowed to read the approved informed consent form. The Investigator will inform the patient of the purpose of the study, randomization of study groups and the follow-up schedule. The Investigator will discuss foreseeable risks involved, as well as potential benefits that result from the use of the new surgical technique. The Investigator will inform the patient that her medical records will be subject to review by government authorities, members of TSC and by the IRB/HREC.

The patients will be informed by the Investigator that they are free to refuse participation in this study and, if they choose to participate, that they may withdraw from the study at any time without compromising further medical care.

Once the Investigator is assured that the individual understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the informed consent form. The Investigator shall provide a copy of the signed informed consent to the patient. According to institutional policy, the original form shall either be maintained in the patient's medical records at the site or a copy of which will be filed in the patient chart and the original stored in the site folder.

21.5 PROTOCOL VIOLATIONS AND DEVIATIONS

The Investigator or designee should document and explain any deviation from the approved protocol. The Investigator may deviate from the protocol to eliminate an immediate hazard to trial patients without prior IRB/HREC approval. As soon as possible after such an occurrence, the Investigator

should submit the implemented deviation or change, the reasons for it to the site IRB/HREC, to CDMU, and to regulatory authorities, if required.

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/HREC and agreed to by the Investigator. Deviations usually impact individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria. A protocol violation occurs when there is non-adherence to the protocol that results in a significant added risk to the patient, when the patient or Investigator has failed to adhere to major protocol requirements, or when there is non-adherence to regulatory authorities' regulations and/or ICH Good Clinical Practice (GCP) guidelines.

CDMU or its representative will document protocol violations and deviations during the monitoring visit and will notify the Investigator of violations and deviations verbally or in writing. The Investigator should notify the IRB/HREC of protocol violations and deviations in accordance with the IRB/HREC requirements.

21.7 FINANCIAL DISCLOSURE AND OBLIGATIONS

Investigators are required to provide financial disclosure information and a commitment to promptly update this information if any relevant changes occur.

21.8 INVESTIGATOR DOCUMENTATION

Prior to beginning the study, the Investigator will be asked to provide the following essential documents:

- A IRB/HREC approved Informed Consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardians;
- IRB/HREC approval;
- Accurate and current curriculum vitae (CV) for the Principal Investigator and each Co-Investigator;
- Laboratory certifications and normal ranges for any laboratories used by the site;
- Local institutional guidelines regarding the use of post-hysterectomy radiotherapy and/or chemotherapy;

- Signed study agreement.

TMC approval will be made in relation to the above documentation prior to the site commencing enrolment.

22.0 STUDY CONDUCT

The Investigator agrees that the study will be conducted according to the principles of the ICH E6 Guideline on GCP and the principles of the World Medical Association Declaration of Helsinki. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

In Australia, the study will also comply with Australian requirements as set out in the NHMRC National Statement on Ethical Conduct in Research involving Humans[96].

23.0 PUBLICATIONS

Data will be published in peer-reviewed journals and presented at relevant national and international conferences. Authorship depends on the intellectual input into the research question and / or the number of patients enrolled.

APPENDIX 1: Schedule of Assessments

Evaluation / Examination	Pre-Op[a]/ Baseline	Surgery	Post-op				Follow-up[h]
			1 week	6 weeks	3 months[e]	6 months[e]	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Informed Consent	X[a]						
Inclusion/Exclusion Criteria	X[b]						
Medical History	X[a]						
Randomisation	X[b]						
Physical Examination	X[a]		X[g]	X	X	X	X[i]
Height, Weight	X[a]		X[g]	X	X	X	
ECOG PS	X[a]		X	X	X	X	
Serum pregnancy test	X[b,c]						
Concomitant illnesses	X		X	X	X	X	
Concomitant medications	X		X	X	X	X	
FBC	X[b]		X[g]	X[c]	X[c]	X[c]	
E/LFT	X[b]		X[g]	X[c]	X[c]	X[c]	
COAG Profile	X[b,c]						
ECG	X[a,c]						
Chest X-Ray (not required in pts with Chest CT)	X[a]						
CT/MRI/PET/USS Abdo & Pelvis	X[a]						
Cervical biopsy/cone biopsy	X[a]						
Clinical staging (EUA)	X[a]						
FACT-Cx	X[b]		X	X	X	X	F/U 4, 7, 9, & 11
SF-12	X[b]		X	X	X	X	
EURO-QoL	X[b]		X	X	X	X	
MDASI	X[b]		X	X	X	X	
PFDI	X[b]					X	F/U 4, 7, 9, & 11
Health Services Questionnaire			X	X	X	X	
Demographics of Patients with Cervical Cancer	X[b]						
Surgical Treatment (TLRH/TRRH/ r TARH)		X					
Sentinel lymph node biopsy		X					
Operative Details		X					
Pain Scale (linear analogue scale)			X	X	X	X	
Treatment-related Morbidity			X	X	X	X	
Patient's Disease Status							

a = Within 6 weeks before surgery b = Within 30 days of surgery c = If clinically indicated d = Histologically confirmed cervical cancer e = 3 and 6 months from surgery f = Telephone contact acceptable
g = If done, record h = Follow-up visits begin at 9 months post-op & continue every 3 months for 2 years & every 6 months until year 4.5 I = Clinical assessment including an internal exam (see Section 12.4)

Please note:

* OR time for sentinel node biopsy should be noted as a separate procedure in operation report (Specific recording requirements for the sentinel node biopsy and intraoperative lymphatic mapping are located in Section 6.0).

** TLRH.TRRH/TARH: OR time should include the start of the procedure until all trocar sites/abdominal incisions are closed

*** For patients randomized to laparoscopy (not robotic), the surgeon should document specific surgical instruments used for the procedure

APPENDIX 2: Sedlis Criteria for Post Operative Radiotherapy in Cervical Cancer

CLS[a]	Stromal invasion	Tumor size
Positive	Deep 1/3	Any
Positive	Middle 1/3	≥ 2 cm
Positive	Superficial 1/3	≥ 5 cm
Negative	Deep or middle 1/3	≥ 4 cm

- [a] Capillary lymphatic space tumor involvement

APPENDIX 3: ECOG Performance Status

Description	Scale
Normal activity	0
Symptomatic but ambulatory self-care	1
Ambulatory more than 50% of the time	2
Ambulatory 50% or less of time, nursing care needed	3
Bedridden, may need hospitalisation	4

APPENDIX 4 Lymphatic Mapping and Sentinel Node Identification in Patients with Stage IB1 Cervical Carcinoma

Attending Physician:

Lymphatic Mapping (Day 1)

Time of injection: Given by:

Time of dye injection: Given by:

Time SN visualized: Location:

Neoprobe setting:

Blue/Green node (s) identified: Y N

Hot node (s) identified: Y N

Comments:

	Time	Count	Blue/Green		Hot		Location
			Yes			No	

Signature:

APPENDIX 5 Dictation Guidelines: CERVICAL INTRAOPERATIVE LYMPHATIC MAPPING

Include in operative dictation:

- Description of the location of the sentinel node(s) including whether they were identified as blue/green and/or hot sentinel nodes. Grossly involved lymph nodes that are neither hot nor blue/green should be considered SLNs and labeled "not hot, not blue/green SLN".

- Description of all other nodes removed. Special attention to the detection of parametrial SLNs should be made. Parametrial SLNs are found medial to the superior vesical artery.

Time first SN visualized: _____ Location: _____

#	Time	Count	Hot		Blue/Green		Node		Location	Sentinel	
			Yes	No	Yes	No	R	L		Yes	No

Signature:

APPENDIX 6: Questionnaires

LACC	Patient Initials: ☐☐☐	FACT - Cx
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Questionnaire
To Cervical Carcinoma		

Visit ☐ 1 = Pre-Op; 2 = Surgery; 3 = Wk 1; 4 = Wk 6; 5 = 3 mnths; 6 = 6 mnths; 7 = 18 mnths; 8 = 30 mnths; 9 = 42 mnths; 10 = 52 mnths

Date of visit: ☐☐ ☐☐ ☐☐☐☐

Below is a list of statements that other people with your illness have said are important. **By ticking one (1) box per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	☐	☐	☐	☐	☐
GP2	I have nausea	☐	☐	☐	☐	☐
GP3	Because of my physical condition, I have trouble meeting the needs of my family	☐	☐	☐	☐	☐
GP4	I have pain	☐	☐	☐	☐	☐
GP5	I am bothered by side effects of treatment	☐	☐	☐	☐	☐
GP6	I feel ill	☐	☐	☐	☐	☐
GP7	I am forced to spend time in bed	☐	☐	☐	☐	☐

	SOCIAL / FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	☐	☐	☐	☐	☐
GS2	I get emotional support from my family	☐	☐	☐	☐	☐
GS3	I get support from my friends	☐	☐	☐	☐	☐
GS4	My family has accepted my illness	☐	☐	☐	☐	☐
GS5	I am satisfied with family communication about my illness	☐	☐	☐	☐	☐
GS6	I feel close to my partner (or the person who is my main support)	☐	☐	☐	☐	☐
Q1	***Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section.***					
GS7	I am satisfied with my sex life	☐	☐	☐	☐	☐

LACC	Patient Initials: ☐☐☐	FACT - Cx
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Questionnaire
To Cervical Carcinoma		

By ticking one (1) box per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	☐	☐	☐	☐	☐
GE2	I am satisfied with how I am coping with my illness	☐	☐	☐	☐	☐
GE3	I am losing hope in the fight against my illness	☐	☐	☐	☐	☐
GE4	I feel nervous	☐	☐	☐	☐	☐
GE5	I worry about dying	☐	☐	☐	☐	☐
GE6	I worry that my condition will get worse	☐	☐	☐	☐	☐

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	☐	☐	☐	☐	☐
GF2	My work (include work at home) is fulfilling	☐	☐	☐	☐	☐
GF3	I am able to enjoy life	☐	☐	☐	☐	☐
GF4	I have accepted my illness	☐	☐	☐	☐	☐
GF5	I am sleeping well	☐	☐	☐	☐	☐
GF6	I am enjoying the things I usually do for fun	☐	☐	☐	☐	☐
GF7	I am content with the quality of my life right now	☐	☐	☐	☐	☐

LACC	Patient Initials: ☐☐☐	FACT - Cx
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Questionnaire
To Cervical Carcinoma		

By ticking one (1) box per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
Cx1	I am bothered by discharge or bleeding from my vagina	☐	☐	☐	☐	☐
Cx2	I am bothered by odour coming from my vagina	☐	☐	☐	☐	☐
Cx3	I am afraid to have sex	☐	☐	☐	☐	☐
B4	I feel sexually attractive	☐	☐	☐	☐	☐
Cx4	My vagina feels too narrow or short	☐	☐	☐	☐	☐
BMT7	I have concerns about my ability to have children	☐	☐	☐	☐	☐
Cx5	I am afraid the treatment may harm my body	☐	☐	☐	☐	☐
BL4	I am interested in sex	☐	☐	☐	☐	☐
C7	I like the appearance of my body	☐	☐	☐	☐	☐
Cx6	I am bothered by constipation	☐	☐	☐	☐	☐
C6	I have a good appetite	☐	☐	☐	☐	☐
BL1	I have trouble controlling my urine	☐	☐	☐	☐	☐
BL3	It burns when I urinate	☐	☐	☐	☐	☐
Cx7	I have discomfort when I urinate	☐	☐	☐	☐	☐
HN1	I am able to eat the foods that I like	☐	☐	☐	☐	☐

LACC	Patient Initials: ☐☐☐	MDASI
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Questionnaire
To Cervical Carcinoma		

Visit ☐ 1 = Pre-Op; 2 = Surgery; 3 = Wk 1; 4 = Wk 6; 5 = 3 mnths; 6 = 6 mnths;

Date of visit: ☐☐ ☐☐ ☐☐☐☐

M.D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been **in the last 24 hours**. Please fill in the circle below from 0 (symptom that has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad as you can Imagine
	0	1	2	3	4	5	6	7	8	9	10
1. Your **pain** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Your **fatigue (tiredness)** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Your **nausea** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. Your **disturbed sleep** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. Your feelings of being **distressed (upset)** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. Your **shortness of breath** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. Your problem with **remembering things** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. Your problem with **lack of appetite** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. Your feeling **drowsy (sleepy)** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. Your having a **dry mouth** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. Your feeling **sad** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
12. Your **vomiting** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
13. Your **numbness or tingling** at its WORST?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

LACC	Patient Initials: ☐☐☐	MDASI
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Questionnaire
To Cervical Carcinoma		

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere Completely										Interfered
	0	1	2	3	4	5	6	7	8	9	10
14. **General activity?**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
15. **Mood?**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
16. **Work** (including work around the house)?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
17. **Relations** with other people?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
18. **Walking**?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
19. **Enjoyment** of life?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

LACC	Patient Initials: ☐☐☐	SF-12
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Questionnaire
To Cervical Carcinoma		

Visit ☐ 1 = Pre-Op; 2 = Surgery; 3 = Wk 1; 4 = Wk 6; 5 = 3 mnths; 6 = 6 mnths;

Date of visit: ☐☐ ☐☐ ☐☐☐☐

This next set of questions asks for your views about your health, how you feel and how well you are able to do your usual activities.

1.	In general, would you say your health is excellent, very good, good, fair or poor?	☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor
2.	The following items are about activities you might do during a typical day. Does you health limit you in these activities? If so, how much? First, moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf. Does you health now limit you a lot, limit you a little, or not limit you at all?	☐ Limited a lot ☐ Limited a little ☐ Not limited at all
3.	Climbing several flights of stairs. Does your health now limit you a lot, limit you a little, or not limit you at all?	☐ Limited a lot ☐ Limited a little ☐ Not limited at all
4.	During the past four weeks, have you accomplished less than you would like as a result of your physical health?	☐ No ☐ Yes
5.	During the past four weeks, were you limited in the kind of work or other regular activities you do as a result of your physical health?	☐ No ☐ Yes
6.	During the past four weeks, have you accomplished less than you would like as a result of any emotional problems, such as feeling depressed or anxious?	☐ No ☐ Yes
7.	During the past four weeks, did you not do work or other regular activities as carefully as usual as a results of any emotional problems such as feeling depressed or anxious?	☐ No ☐ Yes
8.	During the past four weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere not at all, slightly, moderately, quite a bit, or extremely?	☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

LACC	Patient Initials: ☐☐☐	SF-12
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Questionnaire
To Cervical Carcinoma		

9.	These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much time during the past 4 weeks have you felt calm and peaceful? All of the time, most of the time, a good bit of the time, some of the time, a little of the time, or none of the time?	☐ All of the time ☐ Most of the time ☐ A good bit of the time ☐ Some of the time ☐ A little of the time ☐ None of the time
10.	How much of the time during the past 4 weeks did you have a lot of energy? All of the time, most of the time, a good bit of the time, some of the time, a little of the time, or none of the time?	☐ All of the time ☐ Most of the time ☐ A good bit of the time ☐ Some of the time ☐ A little of the time ☐ None of the time
11.	How much of the time during the past 4 weeks have you felt down? All of the time, most of the time, a good bit of the time, some of the time, a little of the time, or none of the time?	☐ All of the time ☐ Most of the time ☐ A good bit of the time ☐ Some of the time ☐ A little of the time ☐ None of the time
12.	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities like visiting with friends, relatives etc? All of the time, most of the time, some of the time, a little of the time, or none of the time?	☐ All of the time ☐ Most of the time ☐ A good bit of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

LACC	Patient Initials: ☐☐☐	**Health**
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	**Services**
To Cervical Carcinoma		**Questionnaire**

Week 1 ☐ Week 4 ☐ Month 3 ☐ Month 6 ☐

Date of visit: ☐☐ ☐☐ ☐☐☐☐

Below is a set of questions to see how often you needed to visit a doctor or health care professional other than those directly involved in your care for your gynaecological cancer surgery at this hospital.
Please indicate how many visits or days next to each question.

Questions	**Number of Visits/Stays**
a. How many times have you visited a doctor other than the doctor caring for you from Gynaecology Oncology at this hospital since your last visit?.....	_____
b. How many times have you visited a psychiatrist, psychologist or other mental health counsellor since your last visit?.....	_____
c. How many times have you visited the emergency room since your last visit?.....	_____
d. How many times have you visited a nurse practitioner, home health nurse, physical/occupational or respiratory therapist since your last visit?.....	_____
e. How many times have you stayed in hospital overnight or longer since your last visit?.....	_____
f. How many total nights have you stayed in hospital overnight since your last visit?.....	_____
g. How many times since your surgery have you had outpatient surgery (did not stay in hospital overnight) since your last visit?.....	_____

LACC	Patient Initials: ☐☐☐	PFDI
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Questionnaire
To Cervical Carcinoma		

Visit ☐ 1 = Pre-Op; 2 = 6 mnths; 3 = 18 mnths; 4 = 30 mnths; 5 = 42 mnths; 6 = 52 mnths

Date of visit: ☐☐ ☐☐ ☐☐☐☐

Please answer these questions by putting a **X** in the appropriate box. If you are unsure about how to answer a question, give the best answer you can. While answering these questions, please consider your symptoms over the **last 3 months.** Thank you for your help.

1.	Do you usually experience *pressure* in the lower abdomen?	☐ **Yes** → ☐ No	**If yes, how much does this bother you?** ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a bit
2.	Do you usually experience *heaviness or dullness* in the pelvic area?	☐ **Yes** → ☐ No	**If yes, how much does this bother you?** ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a bit
3.	Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?	☐ **Yes** → ☐ No	**If yes, how much does this bother you?** ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a bit
4.	Do you usually have to push on the vagina or around the rectum to have or complete a bowel movement?	☐ **Yes** → ☐ No	**If yes, how much does this bother you?** ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a bit
5.	Do you usually experience a feeling of incomplete bladder emptying?	☐ **Yes** → ☐ No	**If yes, how much does this bother you?** ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a bit
6.	Do you ever have to push up on a bulge in the vaginal area with your fingers to start or complete urination?	☐ **Yes** → ☐ No	**If yes, how much does this bother you?** ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a bit
7.	Do you feel you need to strain too hard to have a bowel movement?	☐ **Yes** → ☐ No	**If other than never, how much does this bother you?** ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a bit
8.	Do you feel you have not completely emptied your bowels at the end of a bowel movement?	☐ **Yes** → ☐ No	**If other than never, how much does this bother you?** ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a bit
9.	Do you usually lose stool beyond your control if your stool is well formed?	☐ **Yes** → ☐ No	**If yes, how much does this bother you?** ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a bit

LACC	Patient Initials: ☐☐☐	PFDI
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Questionnaire
To Cervical Carcinoma		

10.	Do you usually lose stool beyond your control if your stool is loose or liquid?	☐ Yes →	**If yes, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	
11.	Do you usually lose gas from the rectum beyond your control?	☐ Yes →	**If yes, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	
12.	Do you usually have pain when you pass your stool?	☐ Yes →	**yes, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	
13.	Do you experience a strong sense of urgency and have to rush to the bathroom to have a bowel movement?	☐ Yes →	**If other than never, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	
14.	Does a part of your bowel ever pass through the rectum and bulge outside during or after a bowel movement?	☐ Yes →	**If yes, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	
15.	Do you usually experience frequent urination?	☐ Yes →	**If yes, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	
16.	Do you usually experience urine leakage associated with a feeling of urgency, that is a strong sensation of needing to go to the bathroom?	☐ Yes →	**If yes, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	
17.	Do you usually experience urine leakage related to coughing, sneezing, or laughing?	☐ Yes →	**If yes, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	
18.	Do you usually experience small amounts of urine leakage (that is, drops)?	☐ Yes →	**If yes, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	
19.	Do you usually experience difficulty emptying your bladder?	☐ Yes →	**If yes, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	
20.	Do you usually experience *pain* or *discomfort* in the lower abdomen or genital region?	☐ Yes →	**If yes, how much does this bother you?**				
		☐ No	☐ Not at All	☐ Somewhat	☐ Moderately	☐ Quite a bit	

LACC	Patient Initials: ☐☐☐	EUROQOL
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Form
To Cervical Carcinoma		

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

Do not place more than one box in each group

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 activites ☐

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 ☐

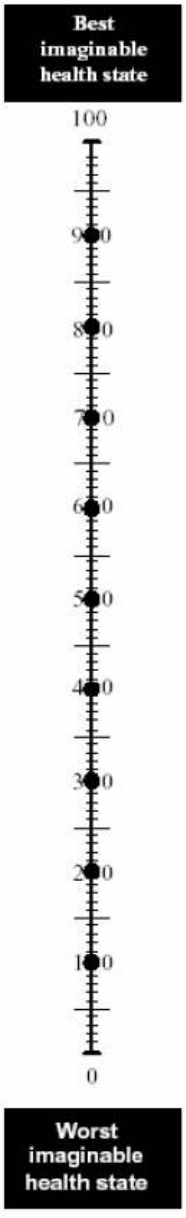
I am extremely anxious or depressed ☐

LACC	Patient Initials: ☐☐☐	EUROQOL
Laparoscopic Approach	Reg No: ☐☐☐☐☐☐	Form
To Cervical Carcinoma		

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 by 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.

Your own health state today



EuroQoL Group

APPENDIX 7: Patient Informed Consent

Insert Hospital Name

PATIENT INFORMATION STATEMENT

Laparoscopic Approach to Cervical Carcinoma
A Phase III Randomized Clinical Trial of Laparoscopic or Robotic Radical Hysterectomy versus Abdominal Radical Hysterectomy in Patients with Early Stage Cervical Cancer

PRINCIPAL INVESTIGATOR: **Insert Investigators Name**

Participant Selection and Purpose of Study

You are invited to participate in a study comparing two different surgical techniques for the treatment of cervical cancer. You were selected as a possible participant in this study because you were diagnosed with cervical cancer on a recent sampling of cervical cells. The work-up has revealed no spread of tumour and an "early" cancer is anticipated. The standard treatment of this condition is a surgical procedure called a hysterectomy. A hysterectomy is the removal of a women's uterus (womb) in an operation carried out under general anaesthetic.

Two surgical techniques are available:

Method 1 (Standard Technique): Most centres worldwide would open the abdomen (tummy) through an incision and remove the uterus, the upper one to two centimetres of the vagina and the soft tissues around the cervix. While you are still under anaesthetic (asleep) an assessment of the uterus is performed during the operation by a pathologist and the results of this assessment are reported to the surgeon in the operating theatre. Your surgeon will also remove some lymph nodes in the pelvis.

Method 2 (Experimental Technique): The other method is a new method and it is called laparoscopy ("keyhole surgery"). The surgery is carried out through small cuts in the abdomen, none of which is larger than 1 cm. The surgeon inserts a small tube carrying a tiny camera (laparoscope) through a small cut in the abdomen so that they can see the internal organs. The surgeon inserts other specialised tube like instruments through small cuts in the abdomen to remove the uterus, the upper one to two centimetres of the vagina and the soft tissues around the cervix. The extent of the operation is exactly the same as with the method above. While you are still under anaesthetic (asleep) an assessment of the uterus is performed during the operation by a pathologist and the results of this assessment are reported to the surgeon in the operating theatre. Your surgeon will also remove some lymph nodes in the pelvis.

We have performed laparoscopic surgery thousands of times and we are encouraged by the preliminary results. Our preliminary data have shown that laparoscopic treatment of early cervical cancer can be done, it is safe and it may have potential advantages for patients. Additional data have shown that no difference exists in the prognosis of patients with cervical cancer when they had laparoscopic or open surgery. However, no formal comparison has been made between laparoscopic and open surgery in this patients' group. This is an international study and in other counties laparoscopic surgery may be performed robotically. Robotic radical hysterectomies will not be performed at the Insert Hospital Name.

Therefore we want to compare both techniques to demonstrate that both techniques are equally effective in terms of prognosis but superior with respect to quality of life and treatment-related morbidity of surgery. Without such a formal comparison (clinical trial), final treatment recommendations cannot be made.

Description of Study

Should you agree to this important study, you will be asked to sign an informed consent. This means you are consenting to having surgery, receiving an anaesthetic and being involved in this research study. You will be randomly allocated to one of the two groups (laparoscopy or open surgery) with an equal chance being allocated to either group. Your surgeon and you will not know until the day before surgery which type of surgery you will have. This "randomisation" guarantees that a fair and balanced comparison can be made between the two different surgical groups. If randomisation would not be possible, the outcomes of the study would be flawed.

The preoperative work-up for both groups includes medical work-up, blood tests, X-rays, CT Scan or an MRI Scan and an ECG. The preoperative work-up is exactly the same for both groups and reflects our routine protocol. In addition to the routine protocol we ask you to complete a questionnaire taking approximately 20 minutes of your time about your quality of life before surgery and again one week, one month, three months and six months after surgery. You will also be asked to complete a questionnaire containing demographic information. We will then post you questionnaires which we will ask you to complete yearly for 4 ½ years following your surgery.

No difference would be made with respect to the recommendation of postoperative treatment (radiotherapy, chemotherapy) and your follow-up between the two treatment modalities.

Potential Risks

Every intervention (surgery) carries risks. Apart from medical and anaesthetic risks we also know of surgical risks. Uncommon events include injury to the bowel, the bladder, the ureter, nerves or large blood vessels. These injuries usually are corrected at the time of initial surgery but sometimes another operation is required. More commonly infections to the skin, the lungs or the bladder may occur. Therefore we administer antibiotics prior to surgery. We also give blood-thinning medication after surgery in order to prevent unwanted blood clots.

Preliminary data has shown that the risk of infections is lower in patients who had a laparoscopic procedure than in patients requiring open surgery. All other risks are similar, however there is a very small risk of of gas bubbles to the brain which could lead to brain damage from laparoscopic surgery There is a risk of 5% to 10% that the operation needs to be converted to an open procedure if a laparoscopy was aimed for. Usually, a procedure is converted because of unexpected difficulties at surgery may which include:

- Complications such as bleeding or adhesions
- Unacceptably long operating time
- Technical reasons such as equipment or instrument failure

Potential Benefits

The potential benefits are a shorter hospital stay for patients who will have a laparoscopic procedure. However, the main benefactors of this study will not be the women on this study but be the women in Australia requiring a hysterectomy for treatment of cervical cancer in the future. This study will be able to clarify which surgical technique is associated with the least treatment-related morbidity.

Confidentiality and Disclosure of Information

All aspects of the study, including results, will be strictly confidential and only your doctors and the staff involved in the study will have access to information on participants. A report of the

study may be submitted for publication, but individual participants will not be identifiable in such a report.

All or part of your medical records will be sent to a Safety Committee to be reviewed and analysed by clinicians and other study personnel, along with the records of all other people participating in this study from this and other institutions. Portions of your medical information may be transmitted electronically through the Internet, but this information will be encrypted (scrambled) to maintain confidentiality.

Your hospital records, doctor's office records, laboratory records, operating room and other records may be audited by representatives of the following organisations:

- Australian Therapeutic Goods Administration (TGA), or
- Royal Brisbane & Women's Hospital Human Ethics and Research Committee

These and the Trials Data Safety Committee may review the research to see that it being done safely and correctly. The representatives of these organisations all comply with privacy standards.

The Trial Safety Committee, an independent group of experts, will be reviewing the data from this research on an ongoing basis. If any important new information about the study develops that may affect your health, welfare, or willingness to stay on the study, your doctor will tell you. You may be asked to sign another consent form at that time.

Costs

Your participation in this study will not influence the amount of money (if any) you have to pay for your treatment at this institution. You will not be paid for taking part in the study. If any complications of the disease or treatment occur, the hospital will provide appropriate treatment for these problems.

Injury and Compensation

If you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect to be treated as a public patient at the public health service.

What are my rights as a participant?

Even after you agree to take part in this study, you may withdraw at any time. Before you withdraw, you should first talk to one of the researchers or nurses involved. This will allow them to inform you of any medical problems that could result when treatment stops. You can choose to withdraw one of two ways. You can stop your study treatment, but still allow the study doctor to follow your care. Alternatively, you can stop your study treatment and not have any further contact with the study staff. Either way, your decision will not affect your medical treatment, or your relationship with those treating you. You will still be offered all available care that suits your needs and medical condition.

Who can I call if I have questions or problems?

For questions about the study or a research-related injury, contact Insert Institution. You will be given a copy of this consent form to keep.

Principal Investigator: Insert Investigators Name - Insert Investigators Contact Details

Further Information

This study has been reviewed and approved by the Insert Ethics Committe/IRB Name. Should you wish to discuss the study with someone not directly involved, in particular in relation to matters concerning policies, information about the conduct of the study or your rights as a participant, or should you wish to make a independent complaint, you can contact the Coordinator or Chairperson, Insert Ethics Committee/IRB Name , Insert Committee/IRB Contact Details

HOSPITAL NAME

PATIENT CONSENT FORM

Laparoscopic Approach to Cervical Carcinoma

A Phase III Randomized Clinical Trial of Laparoscopic or Robotic Radical Hysterectomy versus Abdominal Radical Hysterectomy in Patients with Early Stage Cervical Cancer

PRINCIPAL INVESTIGATOR: **Insert Principle Investigators Name**

I, ... herewith declare that I fully understand the purpose and the implications of the study on the treatment of cervical carcinoma.
I understand that;

a) The aim of the study is to develop the best treatment for cervical carcinoma,
b) The study will not have any immediate benefits for myself,
c) Participation involves surgery,
d) The information obtained will be collected in a potentially identifiable, but de-identified fashion and will be used only in relation to Medical Research,
e) By signing this document I give permission for access to my medical records, for the purpose of this research,
f) I can withdraw from the study at any time.

I have read and understood the information sheet and I have had an opportunity to ask questions. I am satisfied with the answers given. I consent to participate in this research.

_____	_____
Signature of Research Participant	Signature of Witness
_____	_____
Name of Research Participant	Name of Witness
_____	_____
Date	Date

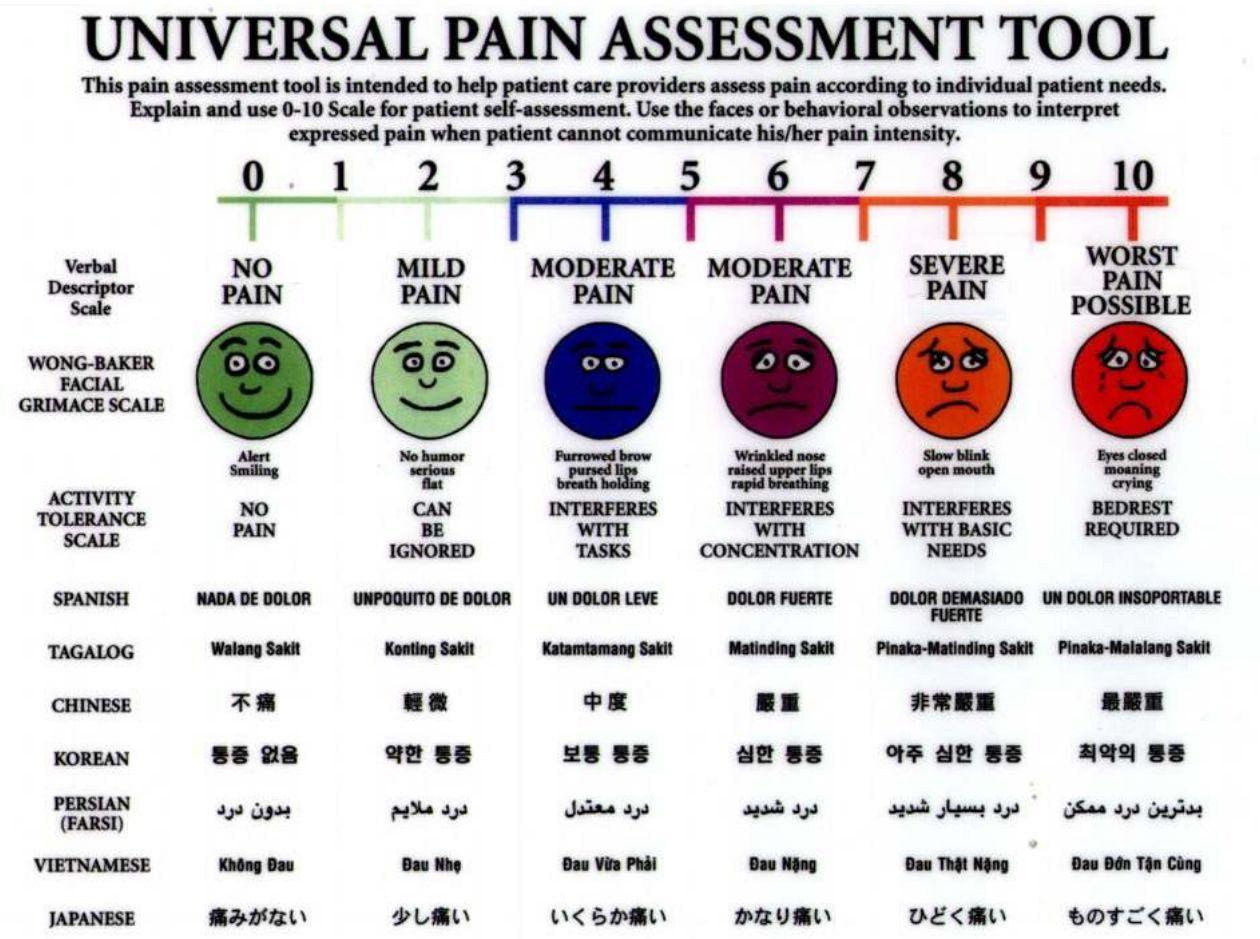
_____
Signature of Investigator

_____	_____
Name of Investigator	Date

APPENDIX 8: Clinical Staging – Carcinoma of the Cervix Uteri. FIGO Classification

FIGO stage	Extent of disease
Stage 0	Primary tumour cannot be assessed. No evidence of primary tumour. Carcinoma in situ.
Stage I	Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded) IA Invasive cancer identified only microscopically. All gross lesions, even with superficial staging, are stage IB cancers. Invasion is limited to measured stromal invasion with maximum depth of 5.0 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging. IA1 Measured invasion of stroma no greater than 3.0 mm in depth and no wider than 7.0 mm. IA2 Measured invasion of stroma greater than 3 mm and no greater than 5 mm and no wider than 7 mm. IB: Clinical lesions confined to the cervix or pre-clinical lesions greater than stage IA. IB1 Clinical lesions no greater than 4 cm in size. IB2 Clinical lesions greater than 4 cm in size.
Stage II	The carcinoma extends beyond the cervix but has not extended on to the pelvic wall. The carcinoma involves the vagina, but not the lower third. IIA No obvious parametrial involvement. IIB Obvious parametrial involvement.
Stage III	The carcinoma has extended onto the pelvic wall. On rectal examination, there is no cancer-free space between the tumour and the pelvic wall. The tumour involves the lower third of the vagina. All cases with hydro-nephrosis or non-functioning kidney should be included, unless they are known to be due to other causes. IIIA No extension on to the pelvic wall, but involvement of the lower third of the vagina. IIIB Extension on to the pelvic wall and/or hydro-nephrosis or non-functioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has clinically involved 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.

APPENDIX 9: Pain Scale



UNIVERSAL PAIN ASSESSMENT TOOL

This pain assessment tool is intended to help patient care providers assess pain according to individual patient needs. Explain and use 0-10 Scale for patient self-assessment. Use the faces or behavioral observations to interpret expressed pain when patient cannot communicate his/her pain intensity.

	0	1	2	3	4	5	6	7	8	9	10
Verbal Descriptor Scale	NO PAIN		MILD PAIN		MODERATE PAIN		MODERATE PAIN		SEVERE PAIN		WORST PAIN POSSIBLE
WONG-BAKER FACIAL GRIMACE SCALE											
	Alert Smiling		No humor serious flat		Furrowed brow pursed lips breath holding		Wrinkled nose raised upper lips rapid breathing		Slow blink open mouth		Eyes closed moaning crying
ACTIVITY TOLERANCE SCALE	NO PAIN		CAN BE IGNORED		INTERFERES WITH TASKS		INTERFERES WITH CONCENTRATION		INTERFERES WITH BASIC NEEDS		BEDREST REQUIRED
SPANISH	NADA DE DOLOR		UNPOQUITO DE DOLOR		UN DOLOR LEVE		DOLOR FUERTE		DOLOR DEMASIADO FUERTE		UN DOLOR INSOPORTABLE
TAGALOG	Walang Sakit		Konting Sakit		Katamtamang Sakit		Matinding Sakit		Pinaka-Matinding Sakit		Pinaka-Malalang Sakit
CHINESE	不痛		輕微		中度		嚴重		非常嚴重		最嚴重
KOREAN	통증 없음		약한 통증		보통 통증		심한 통증		아주 심한 통증		최악의 통증
PERSIAN (FARSI)	بدون درد		درد ملایم		درد معتدل		درد شدید		درد بسیار شدید		بدترین درد ممکن
VIETNAMESE	Không Đau		Đau Nhẹ		Đau Vừa Phải		Đau Nặng		Đau Thật Nặng		Đau Đớn Tận Cùng
JAPANESE	痛みがない		少し痛い		いくらか痛い		かなり痛い		ひどく痛い		ものすごく痛い

APPENDIX 10: Translation Forms for Source Data for Non-English Speaking Sites

Protocol Name: Laparoscopic Approach to Cervical Carcinoma LACC
Patient Initials and Number:

Baseline Translation Form

Please print and use a black pen

Initial Histopathology Details		
Adenocarcinoma	Yes ☐	No ☐
Squamous Cell Carcinoma	Yes ☐	No ☐
Adenosquamous Carcinoma	Yes ☐	No ☐
Other (*please specify*)	Yes ☐	No ☐
SOURCE ATTACHED	Yes ☐	No ☐

Staging		
1A1 (with lymph vascular invasion)	Yes ☐	No ☐
1A2	Yes ☐	No ☐
1B1	Yes ☐	No ☐
Other (*please specify*)	Yes ☐	No ☐
SOURCE ATTACHED	Yes ☐	No ☐

Baseline Information		
Is the patient premenopausal or < 2 years after the onset of menopause?	Yes ☐	No ☐
Did the patient have a pregnancy test within 30 days of surgery? Date of pregnancy test _____ *yyyy/ mm/dd*	Yes ☐	No ☐
SOURCE ATTACHED	Yes ☐	No ☐

LACC 1 Baseline Translation Form
Version 1

1

17 March 2014

Protocol Name: Laparoscopic Approach to Cervical Carcinoma
LACC

Patient Initials and Number:

Baseline Translation Form

Did the patient have baseline bloods done within 6 weeks of surgery? Date of surgery_____Date of baseline bloods_____ *yyyy/ mm/dd* *yyyy/ mm/dd* SOURCE ATTACHED	Yes ☐ Yes ☐	No ☐ No ☐
Did the patient have adequate bone marrow, renal and hepatic function as outlined in the Protocol?	Yes ☐	No ☐
Did the patient have Chest x-ray ? ☐ Yes ☐ No Date of Chest x-ray_____ Result: Normal ☐ Abnormal ☐ SOURCE ATTACHED	Yes ☐	No ☐
Did the patient have CT chest, abdomen, pelvic? ☐ Yes ☐ No Date of CT chest, abdomen, pelvic_____ Result: Normal ☐ Abnormal ☐ SOURCE ATTACHED	Yes ☐	No ☐
Did the patient have other imaging of chest (PET/MRI)? ☐ Yes ☐ No Date of Imaging _____ Result: Normal ☐ Abnormal ☐ SOURCE ATTACHED	Yes ☐	No ☐
Specify Abnormal Result:-		

Protocol Name: Laparoscopic Approach to Cervical Carcinoma LACC
Patient Initials and Number:

Baseline Translation Form

Source Documentation Attached		
Pre-Operative Histology	Yes ☐	No ☐
Documentation confirming Staging e.g. Pre Operative Clinic Note, Health Service Record	Yes ☐	No ☐
Serum pregnancy test result (*if relevant*)	Yes ☐	No ☐
Baseline bloods	Yes ☐	No ☐
All Imaging Reports	Yes ☐	No ☐

SIGNATURES

Translated by
Signature _____ **Date**_____
Investigator
Signature_____ **Date** _____

- **LABEL EACH SOURCE DOCUMENT WITH PATIENT NUMBER**
- **PLEASE DE-IDENTIFY PATIENT DETAILS**
- **PLEASE LABEL ALL SOURCE IN ENGLISH**

Protocol Name: Laparoscopic Approach to Cervical Carcinoma
LACC

Patient Initials and Number:

Post Operative Histopathology Translation Form

Please print and use a black pen

Post Operative Histopathology Details		
Adenocarcinoma	Yes ☐	No ☐
Squamous Cell Carcinoma	Yes ☐	No ☐
Adenosquamous Carcinoma	Yes ☐	No ☐
Other (*please specify*)	Yes ☐	No ☐
SOURCE ATTACHED	Yes ☐	No ☐

Pathology Details

Date of Histopathology Report _____
yyyy/mm/dd

Histological Grade:-

Well-differentiated (G1) ☐

Moderately differentiated (G2) ☐

Poorly differentiated (G3) ☐

Tumour Size	Length *mm*	Width *mm*
Depth of Cervical Invasion	Depth *mm*	

Please give a brief description of any **invasion** *e.g. lymphovascular, perineural, endometrial, vaginal, parametrial*

SOURCE ATTACHED Yes ☐ No ☐

LACC Histopathology Translation Form
Version 1

17 March 2014

Protocol Name: Laparoscopic Approach to Cervical Carcinoma
LACC

Patient Initials and Number:

Post Operative Histopathology Translation Form

Lymph Nodes

Total Number of Nodes Removed ☐☐

Total Number of Positive Nodes ☐☐

Location _____Number ☐

Location _____Number ☐

Location_____ Number ☐

Investigator Comment

Source Documentation Attached

Post Operative Histology Report	Yes ☐	No ☐
Documentation confirming Number of Nodes and Number of Positive Nodes *(if not already on Post Operative Histopathology Form)*	Yes ☐	No ☐

SIGNATURES

Translated by
Signature _____**Date**_____
Investigator
Signature_____**Date** _____

- **LABEL EACH SOURCE DOCUMENT WITH PATIENT NUMBER**
- **PLEASE DE-IDENTIFY PATIENT DETAILS**
- **PLEASE LABEL ALL SOURCE IN ENGLISH**

Protocol Name: Laparoscopic Approach to Cervical Carcinoma
LACC

Patient Initials and Number:

Surgery Translation Form

Please print and use a black pen

Surgical Details

Date of Surgery _____
yyyy/mm/dd

Date of Admission for Surgery _____
yyyy/mm/dd

Date of Discharge _____
yyyy/mm/dd

Type of Surgery: - Total Abdominal Radical Hysterectomy ☐

Total Laparoscopic/Robotic Radical Hysterectomy ☐

Robotic/Laparoscopy converted to Laparotomy ☐ Yes ☐ No
Robotic converted to Laparoscopy ☐ Yes ☐ No
Specify reasons:

If either surgery abandoned ☐ Yes ☐ No
Specify reasons:

Other Procedure_____

SOURCE ATTACHED Yes ☐ No ☐

Did the patient have Pelvic Lymph Node Dissection?	Yes ☐	No ☐
Did the patient have Para Aortic Lymph Node Dissection?	Yes ☐	No ☐

Protocol Name: Laparoscopic Approach to Cervical Carcinoma
LACC

Patient Initials and Number:

Surgery Translation Form

	Start Time *hh:mm*	Finish Time *hh:mm*
Duration of operation Estimated Blood loss (ml)_____ SOURCE ATTACHED	Yes ☐	No ☐
Did the Patient have a blood transfusion during surgery or post operatively up until date of discharge date? SOURCE ATTACHED	Yes ☐	No ☐
Date of Post Op Day 1 Haemoglobin (*if performed*)_____ *yyyy/mm/dd* SOURCE ATTACHED	Yes ☐	No ☐
Please add a brief description of the **surgical event** *e.g. type of surgery, observations.*		
Did the patient have any **Intra-Operative Complications**? Please Specify:	Yes ☐	No ☐

Protocol Name: Laparoscopic Approach to Cervical Carcinoma
LACC

Patient Initials and Number:

Surgery Translation Form

Length of Hospital Stay: ☐☐☐ Days		
Did the patient have any **Post Operative Complications**?	Yes ☐	No ☐
Please Specify:		
Please add a brief description of **discharge summary** *e.g. future treatments.*		
SOURCE ATTACHED	Yes ☐	No ☐

IOLM

Did patient undergo IOLM?	Yes ☐	No ☐
Specify Agent :- Technitium-99 ☐ Lymphazorin ☐ Indocyanine Green ☐ Other ☐		

IOLM

No.	Count	Blue/Green		Hot		Node		Location	Sentinel	
		Yes	No	Yes	No	R	L		Yes	No

Protocol Name: Laparoscopic Approach to Cervical Carcinoma LACC
Patient Initials and Number:

Surgery Translation Form

Investigator Comment

Source Documentation Attached		
Operation report	Yes ☐	No ☐
Duration of operation *(only if not on operation report)*	Yes ☐	No ☐
Estimated blood loss *(only if not on operation report)*	Yes ☐	No ☐
Details of blood transfusion (*if relevant*)	Yes ☐	No ☐
Post op Day 1 Haemoglobin (*if performed*)	Yes ☐	No ☐
IOLM (*if relevant*)	Yes ☐	No ☐
Discharge Summary	Yes ☐	No ☐

SIGNATURES

Translated by
Signature _____ **Date**_____
Investigator
Signature_____ **Date** _____

- **LABEL EACH SOURCE DOCUMENT WITH PATIENT NUMBER**
- **PLEASE DE-IDENTIFY PATIENT DETAILS**
- **PLEASE LABEL ALL SOURCE IN ENGLISH**

Protocol Name: Laparoscopic Approach to Cervical Carcinoma
LACC

Patient Initials and Number:

Relapse Translation Form

Please print and use a black pen

Relapse Details

Date of Relapse _____
yyyy/mm/dd

Site of Relapse/Other Cancer

Histology Diagnosis and/or Imaging Report		
SOURCE ATTACHED	Yes ☐	No ☐

Investigator Comment

Source Documentation Attached

Histopathology and/or Imaging Report	Yes ☐	No ☐

SIGNATURES

Translated by
Signature _____ **Date** _____
Investigator
Signature _____ **Date** _____

- **LABEL EACH SOURCE DOCUMENT WITH PATIENT NUMBER**
- **PLEASE DE-IDENTIFY PATIENT DETAILS**
- **PLEASE LABEL ALL SOURCE IN ENGLISH**

LACC Relapse Translation Form
Version 1

17 March 2014

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