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CANADIAN CANCER TRIALS GROUP (CCTG)

A RANDOMIZED PHASE III TRIAL COMPARING RADICAL HYSTERECTOMY AND PELVIC NODE DISSECTION VS SIMPLE HYSTERECTOMY AND PELVIC NODE DISSECTION IN PATIENTS WITH LOW-RISK EARLY-STAGE CERVICAL CANCER

A Gynecologic Cancer Intergroup (GCIG) Trial led by the CCTG

GCIG Trial Designation: The **SHAPE** Trial:
Simple **H**ysterectomy **A**nd **P**elvic node dissection in **E**arly cervix cancer

CCTG Protocol Number: **CX.5**
KGOG Protocol Number: **KGOG 1033**
AGO-AUSTRIA Protocol Number: **AGO 36 SHAPE**
UK NCRI Protocol Number: **SHAPE**
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BGOG Protocol Number: **BGOG-CX2**
DGOG Protocol Number: **SHAPE**
Fudan University Shanghai Cancer Center Protocol Number: **SHAPE**
GINECO Protocol Number: **CE104**

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This protocol contains information that is confidential and proprietary. The contents of this protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial may not be used for any other purpose and may not be disclosed to any other person or entity without the prior written permission of CCTG (and other applicable parties as designated by CCTG).

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(This form must be completed for all Canadian institutions prior to local activation).

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I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, in accordance with any modifications that may occur over the duration of the study, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission ofCCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to CCTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice toCCTG. The study may be terminated at any time by CCTG with or without cause.

Will your centre be performing sentinel node mapping for patients randomized to the CX.5 trial?
(*please indicate your answer by checking the appropriate box below*)

☐ **No,** our centre will not be performing sentinel node mapping for any patients randomized to the CX.5 trial.

☐ **Yes,** our centre will be performing a sentinel node mapping procedure for some or all patients randomized to the CX.5 trial.

I attest that all surgeons who will perform sentinel node mapping for CX.5 patients have previously performed the procedure for at least 10 prior endometrial or cervical cancer patients.

_____	_____	_____
Qualified Investigator Signature	Printed Name	Date

Protocol Number: CCTG CX.5

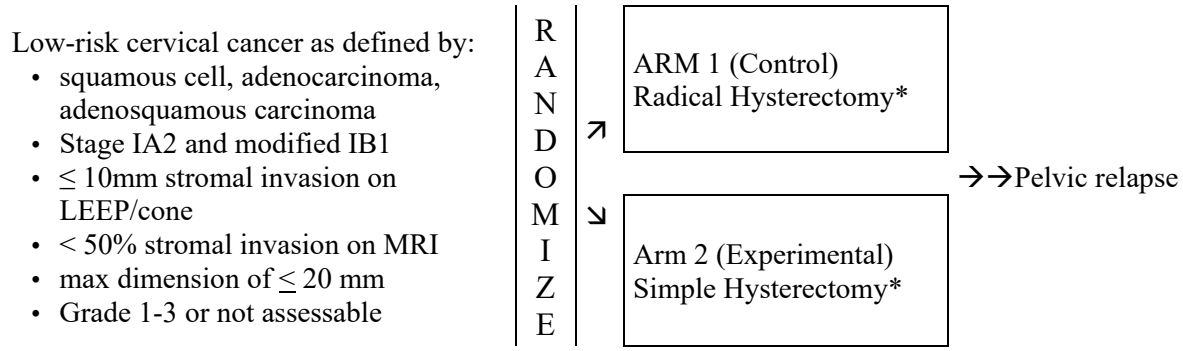
CENTRE: _____

TREATMENT SCHEMA

This is a multi-centre, international, prospective, randomized phase III trial of radical hysterectomy and pelvic node dissection versus simple hysterectomy and pelvic node dissection in patients with previously untreated, low-risk cervical cancer.

Stratification

1. Cooperative Group
2. Intended use of sentinel node mapping (yes vs. no)
3. Stage (IA2 vs. IB1)
4. Histological type (squamous vs. adenocarcinoma/adenosquamous)
5. Grade (1-2 vs. 3 vs. not assessable)



* Regardless of treatment assignment, surgery will include pelvic lymph node dissection with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

Planned sample size: 700 (non-inferiority at 0.05 level with 85% power)

Primary Endpoint

- Pelvicrecurrence rate at 3 years.

Secondary Endpoints

- To compare the two treatment arms with respect to:
  - Pelvic relapse-free survival
  - Extra pelvic relapse-free survival
  - Relapse-free survival (any site)
  - Overall survival
  - Treatment-related adverse events
  - Patient Reported Outcomes including global quality of life and measures of sexual health
  - Cost-effectiveness and cost-utility

- To observe rates of the following in this patient population:
  - Sentinel node detection
  - Parametrial involvement
  - Involvement of surgical margins
  - Pelvic node involvement

1.0 OBJECTIVES

1.1 Primary Objective

To evaluate whether treatment with simple hysterectomy and pelvic node dissection is non-inferior to treatment with radical hysterectomy and pelvic node dissection in terms of pelvic relapse-free survival at 3 years

1.2 Secondary Objectives

- To compare the two treatment arms with respect to:
  - Pelvic relapse-free survival
  - Extra pelvic relapse-free survival
  - Relapse-free survival (any site)
  - Overall survival
  - Treatment-related adverse events
  - Patient Reported Outcomes including global quality of life and measures of sexual health
  - Cost-effectiveness and cost-utility

- To observe rates of the following in this patient population:
  - Sentinel node detection
  - Parametrial involvement
  - Involvement of surgical margins
  - Pelvic node involvement

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Overview

Cancer of the cervix is the second leading worldwide cause of cancer death in women. Most recent global statistics indicate that in 2002, the estimated incidence was 493,243 new cases with 273,505 deaths *[Parkin 2006]*. The disease is much more prevalent in developing as opposed to developed nations. There is an almost two-fold increase in lifetime probability risk of developing cervical cancer (1.48% vs. 0.76%) and a more than three-fold increase in dying from it (0.84% vs. 0.25%) in underdeveloped countries *[Global Cancer Facts and Figures 2007]*. In Canada, the projected number of new cases in 2010 was 1300, with 370 deaths *[Canadian Cancer Statistics, 2010]*.

As a result of effective screening in developed countries, the overall incidence of cervical cancer has decreased over the past 20 years, while the proportion of younger women presenting with low-risk early-stage disease has increased. As surgical therapy is highly efficacious in providing durable disease control in women with low-risk disease, these patients are at risk of suffering "survivorship" issues related to long-term surgical effects, including compromised sexual, bowel and bladder function, as well as infertility. The CCTG CX.5 / GCIG SHAPE trial uses a non-inferiority design to test whether, in the long-term, less invasive surgical approaches can maintain high rates of disease control and improve quality of life through a reduction in late-effects associated with the surgical procedure.

Data from the recent 24th annual International Federation of Gynecology and Obstetrics (FIGO) report indicates that the 5-year stage-specific overall survivals of patients with stage IA2 squamous carcinoma were 99.1% (97.1% for adenocarcinoma) and for stage IB1 squamous carcinoma were 92.3% (91.8% for adenocarcinoma) *[FIGO Annual Report, 2009].* The FIGO report emphasizes that from an international perspective, extensive practice variation occurs in managing patients with micro-invasive disease. Overall, 75% of patients were treated with surgery alone. Among these patients, one-third underwent conization, one-third simple hysterectomy (with or without lymphadenectomy) and one-third radical hysterectomy (again with or without lymphadenectomy). The remaining 25% of patients received some form of adjuvant therapy. Overall, 20% of patients underwent lymph node removal, presumably when lymphovascular involvement was detected on the conization specimen *[FIGO Annual Report, 2009]*. The major reason for such discrepant practices is the lack of high-quality evidence upon which clinicians can base their decisions and advice to these women. There is a need to standardize treatments and potentially identify the patient and disease specifics associated with advantages with radical or more limited surgical approaches.

There are no studies comparing the efficacy and morbidity of simple hysterectomy to that of radical hysterectomy in patients with early-stage disease. However, as the purpose of removing the parametria at the time of the hysterectomy is to ensure safe and wide margins around the cervical tumour and/or to remove potential spread to the parametrial lymph nodes and, as will be described below, the occurrence of disease in these locations is essentially nonexistent in patients with low-risk disease, important advantages may be associated with a simple hysterectomy. This premise provides the foundation for this trial.

2.1.1 *Staging of Cervical Cancer*

According to FIGO classification, there are four stages of cervical cancer (see Appendix III), which include the two most common histologic forms, squamous (~70%) and adenocarcinoma (~30%). Determination of staging relies primarily on clinical evaluation. "Early-stage" cancer is referred to stages IA2-IB1, which are both amenable to surgical treatment. Stage IA2 is based on the microscopic evaluation of the cervical lesion, usually removed by conization, and includes stromal invasion measuring < 5mm in depth and ≤ 7mm in lateral extension. Stage IB1 refers to larger lesions that remain limited to the cervix and measure < 4 cm in maximum diameter. The 5-year survivals of patients with stage IA2 disease is 98% and for IB1is 92%.

Radical hysterectomy with complete pelvic lymph node dissection is the standard treatment for "early-stage" disease. As the primary mode of tumour dissemination is via lymphatics, either proximally to the parametrial tissue or directly to the pelvic lymph node, node status is one of the most important prognostic factors. The rate of lymph node metastasis is approximately 5% in IA2 disease and 15% in stage IB1 disease. The 5-year survival in node negative IB1 patients is in the range of 96%, whereas it reduces to 79% in node positive patients.

"Low-risk" disease refers to patients with early-stage disease who have stage IA2 or stage IB1 and lesions measuring less than 2 cm in size with less than 50% stromal invasion *[Schmeler, 2011]*. In these patients, the risk of lymph node metastasis is < 5% and parametrial extension is < 1%. In the CCTG CX.5 / GCIG SHAPE trial, we will evaluate patients with low-risk disease. We hypothesize that less radical surgery (simple hysterectomy) will be associated with similar efficacy and less surgical morbidity than more radical surgery. According to local practices, we will include lymph node assessment through the less morbid approach of sentinel node mapping.

2.2 Management of Patients with Low-risk Cervical Cancer

For over a century, radical hysterectomy with pelvic lymphadenectomy has been the standard surgical approach for patients with stage IA2- IB1 disease. Various rates of important acute morbidities have been reported following radical hysterectomy, with differences likely reflecting the rigor of assessment. Complications include urinary and rectal dysfunction, ureteral and vesical fistulas (2%), intraoperative bleeding, infections and lymphedema *[Sood 2002]*. Urinary dysfunction includes difficulty voiding, postoperative urinary retention and loss of urinary sensation. According to Ceballos, overall morbidity of radical hysterectomy reaches 10%, with a 2% risk of ureteric injury and a 7% risk of lymphedema *[Ceballos 2006]*. Matsuura reported that complete pelvic lymph node dissection is associated with up to a 20% risk of lymphocyst formation, 10-15% risk of lymphedema, and rare cases of neural or vascular damage *[Matsuura 2006]*. Others report severe perioperative complications in 10-15% of cases *[Averette 1993; Benedetti-Panici 2005]*. Urological and rectal dysfunction related to nerve injury has been reported in up to 20-30% of cases *[Averette 1993; Benedetti-Panici 2005]*. Sood evaluated the incidence of bowel symptoms, changes in anorectal physiology and quality of life after radical hysterectomy and concluded that bowel dysfunction is common and due to pudendal neuropathy, autonomic dysfunction or both *[Sood 2002; Sartori 1997]*.

Late complications are also important. Even though sensory and motor bladder dysfunction affect a majority of women in the immediate postoperative period, and may be a function of the extent of the operation, 1-2% will have long-term detrusor dysfunction or markedly decreased sensory function leading to inferior scores in assessments of quality of life *[Sood 2002]*. Late complications can also include hydronephrosis and lymphedema in up to 16% of cases *[Magrina 1995].*

Landoni prospectively assessed outcomes in patients randomized to undergo a type 2 or type 3 radical hysterectomy as treatment for stage IB disease. No differences in overall recurrence or survival were detected, but long-term urologic morbidity was seen with the more radical procedure *[Landoni 2001]*. Benedetti-Panici prospectively compared 63 patients who underwent a modified radical hysterectomy to 20 patients who underwent a radical hysterectomy and demonstrated a significant difference in morbidity, particularly long-term bladder dysfunction (11% vs. 70%); they also reported a significant reduction in operating time, blood transfusion and hospital stay *[Benedetti-Panici 2005]*. These data have led to the conclusion that bladder dysfunction is related to the extent of the parametrial dissection.

2.2.1 *Outcomes Justifying Testing of Less Radical Approaches in Stage IA2*

There is a growing body of literature suggesting that more conservative surgery can safely be performed in patients with stage IA2 disease, providing careful pathological evaluation is undertaken. A literature review performed by van Meurs identified 1063 patients with stage IA2 disease and reported an overall recurrence rate of 3.6% *[van Meurs 2009]*. No patients had parametrial infiltration and 4.8% (range 0 to 9.7%) were found to have lymph node metastasis, indicating the importance of accurate measurement of depth and lateral extension of microinvasive disease, particularly with adenocarcinomas. This principle is highlighted by the author's finding that following a thorough review of 47 cases that were previously identified in the Netherland registry as having IA2 disease, only 14 cases (30%) fulfilled criteria for stage IA2 *[van Meurs 2009]*. These authors also noted that the rate of lymph node metastasis was 12% in patients with lymphovascular space involvement (LVSI) compared with 1.3% in LVSI negative patients *[van Meurs 2009]*.

However, other investigators have not observed the same risks to be associated with LVSI. Rogers conducted an extensive literature review and compared the rate of lymph node metastasis and recurrence in a series that used strict FIGO-defined selection criteria for microinvasion with a series that did not comply with this definition *[Rogers 2009]*. In the former group, the rates of node metastasis and recurrence were 0.5% and 2.9%, whereas rates were 7.3% and 3.1% in the latter group. Careful pathological assessment is thus essential when considering conservative treatment.

These data are supported by findings of Bisseling, who reviewed more than 1565 patients with microinvasive adenocarcinomas, of which 52% (814) underwent lymph node dissection *[Bisseling 2007]*. Lymph node metastases were identified in only 1.5% of cases. The presence of LVSI did not seem to be associated with nodal metastasis. Parametria were removed in 713 cases (46%) and reported in 356 cases; none of these cases were found to have parametrial involvement. The authors emphasized the difficulty in distinguishing microinvasive adenocarcinoma from adenocarcinoma in situ and the importance of obtaining multiple serial sections for review by an experienced gynecologic pathologist. The authors conclude that: i) in cases with extensive LVSI positivity, lymph node dissection is advised; ii) given the low-risk of lymph node metastasis, lymph node dissection may not be necessary in the vast majority of stage IA2 cases, although sentinel node mapping may be of interest as a less morbid alternative; and, iii) the very low rate of parametrial infiltration does not justify its routine removal. Therefore, local treatment together with lymph node assessment, particularly in the presence of LVSI would be the favored approach for patients with stage IA2 adenocarcinomas *[Bisseling 2007]*. Of note, microinvasive adenocarcinomas do not appear to be associated with higher rates of lymph node metastasis as compared with stage-matched squamous carcinoma *[Rogers 2009]*.

In 92 patients with IA2 disease treated with radical hysterectomy, Jones found no cases with pathologic involvement of the parametrial or regional lymph nodes *[Jones 1993]*. On a subsequent pathologic analysis of 25 patients with microinvasive adenocarcinomas, again no cases with lymph node metastasis and no parametrial invasion were detected. Poynor concluded that conisation alone (if fertility preservation is desired) or simple hysterectomy should be considered adequate treatment for microinvasive adenocarcinomas *[Poynor 2006]*.

The Gynecologic Oncology Group (GOG) reported results of a prospective study of 51 patients with stage IA2 disease confirmed by conization and treated with radical hysterectomy *[Creasman 1998]*. No patients had residual disease detected with the pathologic hysterectomy specimen, including none with lymph node metastasis *[Creasman 1998]*. Recently, Suri confirmed that patients with IA2 disease and negative pathologic margins following a loop electrosurgical excision procedure (LEEP) or cone procedure have a very low-risk of disease detection on the radical hysterectomy pathology specimen *[Suri 2009]*. In their series of 42 patients, only one patient was found to have positive nodes (2.4%) and in this patient LVSI was present on her cone specimen. The authors concluded that in carefully selected women with IA2 disease and negative pathology margins with LEEP or cone procedures could be treated more conservatively, but patients with LVSI may require nodal assessment *[Suri 2009]*.

2.2.2 *Outcomes Justifying Testing of Less Radical Approaches in Stage IB1*

Fewer data are available regarding the safety of conservative treatment for the subset of patients with early-stage IB1 disease, defined as a tumour measuring less than 2 cm. In a retrospective study of 842 patients, Covens questioned the necessity of the parametrectomy based on observing a rate of parametrial extension of 0.6% and 2 and 5-year recurrence-free survivals of 98% and 96% in patients with low-risk features (tumour < 2cm, depth of stromal invasion < 10mm and negative pelvic nodes) *[Covens 2002]*. Wright conducted a retrospective review of 594 patients who underwent a radical hysterectomy; 0.4% of patients with lesions measuring < 2cm, negative nodes and no LVSI had parametrial spread and their recurrence rate was 0.7% *[Wright 2007]*. The authors concluded that simple hysterectomy in combination with pelvic lymphadenectomy may be adequate treatment for these patients. In a similar study plus literature review of 799 patients, only 0.63% of those with low-risk features had parametrial spread *[Stegeman 2007]*. Further supporting data include:

- In a retrospective analysis of 120 patients by Steed, no patients with negative nodes had parametrial infiltration. Parametrial infiltration was associated with tumour size (3 vs. 2 cm) and depth of stromal invasion *[Steed 2006]*.
- In a retrospective analysis of 83 patients by Kinney, no parametrial node metastases were seen in those with lesions measuring < 2cm in diameter and negative LVSI. Only 4 patients had pelvic node metastasis (4.8%), and the 5-year survival was 97.6% *[Kinney 1995]*.
- In a retrospective analysis of 136 patients by Frumovitz, no patients with tumours measuring < 2cm with negative LVSI had parametrial infiltration *[Frumovitz 2009]*. This group is now prospectively testing conservative surgery for patients with tumours < 2 cm who are LVSI negative.
- Coutant has reported that tumour size < 2cm and absence of LVSI are the most relevant preoperative factors that predict for parametrial infiltration *[Coutant 2009]*.

2.2.3 *Testing of Simple Hysterectomy*

There is only one published prospective study evaluating less radical surgery in early-stage cervical cancer *[Pluta 2009]*. Pluta reported the outcomes of 60 patients with lesions measuring < 2cm and < 50% stromal invasion who then underwent sentinel node mapping followed by complete pelvic lymphadenectomy and simple vaginal hysterectomy. All patients underwent preoperative MRI to evaluate for parametrial spread; the sensitivity of this modality is reported to be 89% *[Postema 2000]*. Among these patients, 5 were found to have lymph node metastasis (8.3%) and 3 had LVSI. With a median follow-up of 47 months, no recurrences have been observed in either the 55 node-negative patients or the 5 node-positive patients. These results form the basis and rationale for the current proposal.

Based on the above data, routine parametrectomy in patients with low-risk disease appears to be potentially unnecessary given the very low rate of parametrial extension seen with retrospective reviews and acknowledging the morbidity of the procedure. However, there are no randomized trials demonstrating the safety of simple hysterectomy in low-risk stage IB1 patients. This trial will provide a unique opportunity to compare the rate of lymph node metastasis, parametrial infiltration and outcome between the two procedures, and produce results that can drive a change in clinical practice.

2.3 The Feasibility of Sentinel Node (SN) Mapping

The risk of lymph node metastasis in low-risk patients is < 5% *[Kinney 1995]*. Even though it is not part of the FIGO staging, the presence of lymph node metastasis is one of the most important prognostic markers in cervical cancer *[Takeda 2002]*; FIGO reports that for patients with stage IB1 disease, 5-year survivals are 95.7% for patients with negative nodes and 78.8% in node-positive patients. In that report, the rate of lymph node metastasis in stage IA2 was 2.3% but increases to 15% for those with stage IB1 disease [*FIGO Annual Report, 2009]*. The data described in Section 2.1.1 confirm a low-risk of lymph node metastasis when lesions measure < 2cm. Similarly, data evaluating over 600 patients undergoing radical trachelectomy, where the vast majority of patients have lesions measuring < 2 cm, indicate a low-risk of pelvic node metastasis, a recurrence rate < 5%, a death rate 3%, and survival comparable to the radical hysterectomy cohort *[Plante 2008; Beiner 2008, Plante 2011]*. Thus, strategies to evaluate lymph node status may be particularly important, making many investigators uncomfortable with the concept of abandoning lymph node evaluation.

Traditional lymph node evaluation may be associated with significant morbidity, including intraoperative vessel damage, nerve injuries, and postoperative development of lymphocele and lymphedema in up to 15-20% of cases *[Matsuura 2006]*. The concept of SN mapping is to reduce morbidity associated with lymphadenectomy while providing accurate assessment of lymph node status. In vulvar cancer, SN mapping has reduced the rate of lymphedema of the legs from 25% following standard inguinofemoral lymphadenectomy to 1.9% after SN mapping *[Van der Zee 2008]*. This experience has also shown that accuracy of the SN mapping procedure is highly dependent on development of expertise, case load, adhering to strict guidelines, integration of a multidisciplinary team (nuclear medicine, pathologist) and availability of the technology *[Van der Zee 2008]*.

Mapping of SNs has been recently studied in cervical cancer. Pooled data from 20 studies that include 802 cases show a sensitivity of 93% and a false-negative rate of 6.8% *[Levenback 2008]*. Hauspy challenged these false negative results and determined that the true false negative rate is closer to 2%. Major causes of false negativity related to inadequate technique including limited or incomplete data on the laterality of the SN detection versus the side of the positive node, unilateral SN detection only and evaluation of only macroscopically involved nodes *[Hauspy 2007]*. The SN mapping technique has been shown to be more effective when lesions measure < 2 cm and Rob has reported a detection rate of 100% and false negative rate of 0% in patients with lesions measuring < 2cm using a combined technique that incorporates blue dye and technetium^{99} *[Rob 2005]*. The SN literature also demonstrates that in low-risk patients, the status of the SN is highly correlated with the risk of parametrial invasion *[Strnad 2008]*; Strnad reported no parametrial invasion in 53 patients with early cervical cancer and negative SN results *[Strnad 2008]*.

A recent publication suggests that SN mapping may be more accurate than standard lymphadenectomy because SNs submitted for pathological evaluation are identified through an ultrastaging procedure *[Gortzak-Uzan 2010]*. In a subgroup of 36 patients with cervical cancer with bilateral negative SNs, final pathology evaluating ultrastaging-negative nodes did not identify metastasis in those non-sentinel nodes (false positive rate 0) *[Popa 2006]*. Euscher has reported a 25% increase in the detection of lymph node metastasis in patients with cervical cancer who undergo an ultrastaging procedure *[Euscher 2008]*. Similarly, Marchiole identified micrometastasis in 5/26 patients (19%) following ultrastaging and serial pathologic sectioning and immunohistochemistry *[Marchiole 2005]*. The clinical significance of micrometastasis discovered by ultrastaging remains unsettled, but accumulating evidence suggests that micrometastasis may be associated with increases in recurrence rate and inferior disease-free and overall survivals *[Marchiole 2005; Horn 2008; Juretzka 2004; Darai 2008; Cibula 2012]*. Additional advantages of the SN mapping may be the detection of unusual or aberrant lymphatic drainage to the common iliac or low para-aortic regions, which are areas not routinely sampled with pelvic lymphadenectomy *[Rob 2005; Plante 2003; Roy 2011]*.

In patients with low-risk disease, SN mapping is an attractive alternative to reduce the morbidity of the complete lymph node dissection. This trial will provide the opportunity to determine the rate of SN detection in patients with lesions < 2cm, the proportion of micrometastasis.

2.4 The Roles of Adjuvant Therapy

Post-operative adjuvant radiation-based treatment is at the discretion of investigators as per local institutional policy.

2.5 Patient Reported Outcomes

2.5.1 *Global Quality of Life and Quality of Life Outcomes (QoL) Most Relevant to Pelvic Surgery*

Quality of life outcomes are relevant in cervix cancer patients in several domains, including global/functioning domains as well as domains specific to the pelvic consequences of surgery. In this study, therefore, we will assess QOL outcomes using both the EORTC QLQ-C30 core questionnaire and the QLQ-C24 module, as they have been shown to appraise QoL following treatment. In a study of 190 women with histologically confirmed FIGO Stages I through IV cervical cancer, administration of the EORTC Core QoL instrument and the QLQ-CX24 Cervical Cancer specific module found that most scales on the QLQ-CX24 correlated weakly with the QLQ-C30 scales (all correlations < 0.40) with a higher correlation between the Symptom Experience domain and the core module scales (r = 0.40-0.48) *[Greimel 2006]*. Items on the Symptom Experience scale included assessment of abdominal, bowel, and bladder pain and symptoms, as well as vaginal pain and discharge. Women receiving treatment reported significantly more symptoms than those who completed treatment on the Sexual/Vaginal functioning and the Symptom Experience scale. In a long-term study of treatment-related symptoms in 121 women with early-stage cervical cancer tested 7.3-9.7 years following diagnosis, women receiving surgery and radiation therapy reported significantly worse QoL outcomes on several scales compared to women receiving surgery only, or to those receiving surgery/chemotherapy *[Greimel 2008]*. On the QLQ-CX24 module, the three treatment groups significantly differed on items pertaining to frequent urination, leaking of urine, and feeling of a tight vagina in the surgery/radiation therapy group compared to the other two groups. Compared to reference data provided in the study taken from 1139 women without a history of cancer, women receiving surgery only had significantly higher three symptom scales and none of the functioning scales. No data were provided on the comparisons of these groups with the non-cancer reference group on the QLQ-CX24 domains. In both trials, all statistically significant effects were also considered to be clinically significant according to a >10 point mean difference.

In their pilot study comparison of simple vaginal hysterectomy plus laparoscopic lymphadenectomy versus radical hysterectomy for early-stage cervical cancer, Pluta and colleagues found it was feasible and safe to reduce the radicality of hysterectomy *[Pluta 2009]*. Radical resection of the parametria is associated with damage to the innervation of the rectum and bladder, leading to long-term bowel and bladder side effects which negatively impact on QoL. This pilot study did not report on the changes in these QoL domains. In a different pilot study which compared 12 premenopausal women treated with radical hysterectomy for cervical cancer with 12 premenopausal women treated with simple hysterectomy for benign reasons, the incidence of bowel and bladder dysfunction was highest in the radical hysterectomy group but the groups did not statistically differ from one another - perhaps attributable to the small sample sizes *[Maas 2004]*.

2.5.2 *Sexual Health*

Unlike hysterectomy for benign conditions, in which the type of hysterectomy does not appear to affect sexual function *[Roovers 2003; Thakar 2002]*, radical hysterectomy for early-stage cervical cancer is well documented to be associated with negative sexual side effects. In one of the earliest prospective trials, 61 women with stage IA, IB, or IIA disease who underwent radical hysterectomy with or without pelvic radiation took part in a 2-hour interview and completed questionnaires *[Schover 1989]*. Sexual desire, intercourse frequency, and range of activities decreased by one year post-surgery. Subjective excitement and vaginal lubrication decreased at one year and there were more frequent diagnoses of sexual arousal disorders. Psychological symptoms, however, improved over this period of time. In their long-term examination of QoL symptoms following early-stage cervical cancer using the Sexual Activity Questionnaire *[Thirlaway 1996]*, Greimel and colleagues found that 43.3% of the sample reported not being sexually active, with the leading reasons being absence of a partner and lack of sexual desire *[Greimel, 2008]*. Among the sexually active group, women receiving surgery/radiation therapy had the lowest rates of sexual frequency compared to the other two treatment groups. Women currently receiving treatment had significantly more Sexual Worry on the QLQ-CX24 compared to the group off-treatment *[Greimel 2006]*, but the groups did not differ on current sexual activity.

More recently, studies examining effects of radical hysterectomy have considered more specific indices of sexual functioning. Given that overall sexual frequency may not change and other factors may determine why women engage in sexual activity, frequency is not considered to be a good indicator of sexual response. A Swedish retrospective study comparing 256 women previously treated for cervical cancer (90% had undergone a radical hysterectomy) and 350 community non-cancer controls failed to detect differences between groups in the frequency of reduced sexual desire *[Bergmark 1999]*. However, among women treated for cervical cancer, there was a higher level of distress due to the reduced desire and more frequent reporting of reduced vaginal lubrication, which was significantly more distressing than that experienced in the control group. More women in the treatment group had reduced genital swelling, and reduced vaginal length, and these changes were more distressing for the cancer group than for non-cancer controls. The authors attributed these changes to reduced estrogen supply. These findings suggest that whereas sexual symptoms and overall sexual frequency may not be affected, women's perceptions of their sexuality may be and therefore result in significant sexual distress. This finding (of no change in sexual symptoms despite changes in sexual distress) is a common feature in the sexual dysfunction literature and provides the impetus for our focus on sexual distress as a study endpoint *[Hayes 2008]*.

In another study, conducted in Denmark, 173 women with early-stage cervical cancer who had been treated with radical hysterectomy and pelvic lymphadenectomy were compared with a control sample (n = 328) recruited from the general Danish population *[Jensen 2004]*. Questionnaires were completed at symmetric time intervals consistent with 5-weeks and 3, 6, 12, 18, and 24 months following surgery. Lack of sexual interest and lack of lubrication were common in the first 2 years among survivors, as were severe dyspareunia in the first 3 postoperative months and severe orgasm problems and reduced vaginal size interfering with intercourse ability for the first 6 postoperative months. There were psychological symptoms including anxiety over sexual activity and dissatisfaction with appearance after sex. After one year, one-third of survivors continued to report reduced sexual interest, vaginal lubrication, and vaginal dimensions as compared with the control group.

Nerve-sparing techniques as part of radical hysterectomy involve identification and preservation of the hypogastric nerve, the inferior hypogastric plexus within the parametrium and the most distal part of the inferior hypogastric plexus. A Dutch study compared nerve-sparing radical hysterectomy with conventional radical hysterectomy using endpoints of genital sexual arousal as measured by a vaginal photoplethysmograph *[Pieterse 2008]*. Women were recruited following surgery provided no chemotherapy or radiation therapy had been administered. The report included 13 women in the conventional radical hysterectomy group, 10 in the nerve-sparing hysterectomy group and a control sample of 14 women without sexual difficulties recruited from the community. Genital arousal (as assessed with a vaginal photoplethysmograph) was significantly lower in the conventional radical hysterectomy group as compared with each of the other groups. The authors attributed differences to fewer autonomic nerve fibres in the vascular smooth muscle of the vagina of women treated with conventional radical hysterectomy.

Maas and colleagues tested the hypothesis that damage to pelvic autonomic nerves during radical hysterectomy leads to interference with genital arousal response and can be detected using vaginal photoplethysmography during sexual stimulation *[Maas 2004]*; this research included 12 premenopausal women treated for cervical cancer with radical hysterectomy, 12 premenopausal women treated with simple hysterectomy for benign reasons (e.g. uterine fibroids), and 17 age-matched healthy controls. Women who had undergone radical hysterectomy had a significantly lower maximum genital arousal response; those treated by simple hysterectomy did not differ from the controls. No differences in strongest subjective sexual arousal were detected between any of the groups.

Some studies show fewer significant differences in sexual functioning between groups of women who have received radical versus simple hysterectomy. A prospective comparison of 20 women with stage IB cervical cancer treated with radical hysterectomy who did not receive radiotherapy or chemotherapy and 18 women treated for benign conditions with simple hysterectomy included evaluations performed preoperatively and 4 and 8 months postoperatively; women in the benign group showed steady improvements in all areas of sexual functioning, whereas women with cervical cancer showed a trend towards deteriorating sexual functioning. The authors attributed deterioration to reduced estrogen supply and to autonomic nerve damage *[Grumann 2001]*. Moreover, in both groups, all women resumed sexual intercourse by the end of the follow-up period, with no significant differences between the groups on this measure.

In another trial comparing women with early-stage cervical cancer treated with radiation therapy alone (n = 37), radical hysterectomy alone (n = 37), and a no-cancer control group (n = 40), failed to detect differences in 7-yr post-treatment scores of psychological functioning as assessed by the Brief Symptom Inventory and Global Severity Index *[Frumovitz 2005]*. No differences were observed between the surgery and control groups in menopausal symptoms; women receiving radiotherapy had significantly more menopausal symptoms. Women receiving radiotherapy had significantly worse scores for sexual arousal, lubrication, orgasmic ability, and level of satisfaction, with no group differences between the women receiving surgery only and the control group.

Taken together, this literature suggests that while hysterectomy for benign conditions is associated with few long-term adverse sexual outcomes, most studies of radical hysterectomy for cervical cancer demonstrate negative outcomes, particularly for genital arousal and sexual distress. Nerve-sparing techniques appear to attenuate some of these effects. To date, there has been no clear, prospective, systematic study comparing radical versus simple hysterectomy for early-stage cervical cancer that addresses sexual endpoints given that prior studies compared cancer versus no-cancer samples and these groups differ significantly in terms of diagnosis and treatment-related implications for sexual functioning, not the least of which is postoperative adjuvant treatment, symptoms of cancer before treatment, and the psychological impact of cancer and its treatment. Ours, therefore, represents the first study to directly compare women with cancer receiving standard versus less invasive surgery on sexual and quality of life outcomes.

2.5.3 *Summary of Quality of Life – Related Hypotheses*

Given that evidence of fewer side effects with a less radical procedure may drive women's decisions for treatment, examination of these symptom domains is considered to be of major importance in this trial. We will, therefore, explore three key hypotheses regarding these QoL/sexual health secondary endpoints:

Hypothesis 1: We hypothesize that both groups will experience an increase in bowel and bladder side effects, but that the impact of treatment will be of lesser magnitude, on average, in women managed with simple hysterectomy relative to the radical hysterectomy group. This hypothesis will be tested by using outcomes on the QLQ-CX24 QOL module of the EORTC QLQ-C30 instrument (see below).

Hypothesis 2: We hypothesize that both groups will have an increase in sexual distress, (as measured by the **Female Sexual Distress Scale-Revised, FSDS-R**), and that the radical hysterectomy group will show a greater increase relative to the simple hysterectomy group.

Hypothesis 3: We hypothesize that both groups will show a decrease in overall sexual function (as measured by the **Female Sexual Function Index, FSFI, Total Score)**, and that the radical hysterectomy group will show a greater decrease relative to the simple hysterectomy group.

Exploratory hypotheses: We hypothesize that most domains of the FSFI (e.g. desire, arousal, lubrication, orgasm, pain, satisfaction) will decrease in both surgery groups, and that the radical hysterectomy group will show a greater decrease relative to the simple hysterectomy group.

2.5.4 *Quality of Life Instruments*

The relative impact of surgery on pelvic symptoms will be evaluated with the 24-item Cervical Cancer Module (**EORTC QLQ-CX24**), which has three multi-item subscales: Symptom Experience, Body Image, and Sexual/Vaginal functioning, and five single items pertaining to menopausal symptoms, lymphedema, lower back pain, tingling and numbness, and sexual enjoyment. Higher scores correspond to worse symptoms except for items 49 and 54. Specifically, we will focus on the Symptom Experience subscale, which includes items pertaining to difficulty with bowel, bladder, and vaginal symptoms, and items can be analyzed separately. The QLQ-CX24 discriminates well between patient subgroups on the basis of treatment modality as well as stage of disease and is available in a variety of languages *[Greimel 2006]*. Cronbach's alpha ranges from 0.72-0.87 for the multi-item domains.

In addition to this module, the core questionnaire, the EORTC QLQ-C30, will be administered. This is a well validated 30-item questionnaire consisting of five function scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/emesis, and pain), six single-items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), along with a global QoL score *[Aaronson 1993]*. Higher scores on the functioning domains and the overall QoL domain correspond with better functioning whereas higher scores on the symptom domains correspond with poorer functioning. During validation studies, over 80% of women were able to complete the EORTC QLQ-C30 and QLQ-CX24 in less than 15 minutes. For estimation of effect sizes in this trial, we will use the data from the validation study of the QLQ-CX24 cited in Greimel [Greimel 2006]. Although a minimal important difference has not been established for this specific module, we will use 7 points (1/2 a standard deviation unit) as an indicator of meaningful clinical difference, as has been done in comparable studies *[Norman 2003; Sloan 2006]*.

Sexual distress is what motivates individuals to seek treatment for sexual difficulties. Given this, and given the finding that changes in genital sensations/arousal are considered to be the primary source of symptom-associated distress following surgical treatment of cervical cancer, sexual distress will be considered our primary outcome and overall sexual functioning as a secondary outcome within the sexual health analyses *[Bergmark 2002]*.

The FSFI *[Rosen 2000]* is a validated measure of sexual desire, orgasm, lubrication, pain, and satisfaction widely available in a variety of languages. It is a 19-item self-report measure of female sexual function that provides scores on six domains of sexual function as well as a total score. Domains include: Desire (2 items), Arousal (4 items), Lubrication (4 items), Orgasm (3 items), Satisfaction (3 items), and Pain (3 items). Items are scored on a 5-point Likert scale with higher scores corresponding with better sexual functioning. The FSFI has been shown to reliably discriminate women with Female Sexual Arousal Disorder from sexually-healthy controls on each of the six domains of sexual function as well as the Full Scale score *[Rosen 2000]*. The FSFI was found to be internally consistent (Cronbach's alpha ranged between 0.82 and 0.98;) and test-retest reliabilities using a 4-week interval ranged between r = 0.79 and 0.86 *[Rosen 2000]*.

The FSDS-R *[Derogatis 2002, Dergogatis, 2008]* is a 13-item measure of sexually-related distress available in English and French. Items are scored on a 5-point Likert scale. Scores range from 0 – 48, where higher scores represent higher levels of sexual distress. The FSDS-R has been shown to have good discriminant validity for differentiating between sexually dysfunctional and sexually functional women *[Derogatis 2002, Dergogatis, 2008]*. There is also satisfactory consistency, test-retest reliability, and moderate correlations with measures of nonsexual distress.

Table 1: Quality Of Life Instruments (in addition to the Global Quality of Life instrument EORTC QLQ-C30)

Instrument	Estimated mean baseline	Estimated change with simple hyst.	Estimated change with radical hyst.	Difference we wish to test for (delta) i.e. the differential between arms	Estimated pooled std deviation of the scores
EORTC CX.24 symptom subscale	3	+3 (mean score 6)	+10 (mean score 13)	7	13.5
FSDS-R total score	22*	+5	+10	5	10
FSFI Total Score	33.3*	-5	-10** (mean score 23)	5	21
* *Brotto, 2008* ** *Serati, 2009*					

2.6 Evaluation of Other Adverse Events

Evaluation of other adverse events will follow standard CCTG policies and will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V). Thus, adverse events that are patient-reported, detected by medical examination or are laboratory / imaging abnormalities will be included. The CTCAE v 4.0 entities that relate to surgical morbidities will be emphasized in the CX.5 analysis.

2.7 Health-Related Economic Evaluation

2.7.1 *Health Economics*

The topic of health economics is important to cancer patients, health care providers, policy makers, and society, as it evaluates the value of an intervention. Value is determined by examining the costs and benefits associated with an intervention and its management and can consider the benefits of prolongation of survival and/or QoL. Determining economic values is of relevance in CX.5, as they represent important secondary endpoints that may be policy drivers if non-inferiority of the primary and secondary endpoints related to efficacy is established. In comparison with radical hysterectomy, simple hysterectomy is hypothesized to be associated with less peri-operative morbidity, including hospital length-of-stay, transfusion requirements etc., and fewer and less severe long-term adverse effects, which may translate into improved survivorship. The economic analyses will compare the incremental costs and benefits associated with providing simple vs. radical hysterectomy both with respect to cost-effectiveness and cost-utility. Economic evaluations will be assessed from the public payer perspective and selective societal aspects will be measured as well.

2.7.2 *Costing and Cost-Effectiveness*

The health economic evaluation will be completed using standard CCTG economic-related case report forms and source documentation for each subject in Canada, the United Kingdom and other countries where assessment is feasible. Health care resource utilization related to the study intervention will be documented including supportive care medications, laboratory tests, imaging studies, radiotherapy, transfusions, hospitalization, and outpatient care, including physician, emergency room and home care visits will be documented. Resource utilization will be measured at baseline and at predetermined intervals on both arms of the study. Costs will be presented in Canadian currency in 2011 dollars. Unit costs will be applied to resource utilization to determine the cost per resource. Unit costs will be obtained from standard sources including provincial sources, literature and others. Effectiveness will be presented as pelvic relapse-free life expectancy in years and quality-adjusted life expectancy.

2.7.3 *Cost-Utility*

Health-related utility scores value preference for a health state on a scale with 0 and 1 representing death and perfect health respectively. Quality-adjusted life years (QALY) are derived by combining the utility score with the time period for the health state. The QALY is a common outcome measuring effectiveness in health economics since reimbursement decisions must consider how allocation of health resources affects the population as a whole. In particular, the cost-effectiveness of an intervention can be compared across different diseases and conditions with the QALY.

Utility scores can be obtained indirectly through generic multi-attribute QoL instruments such as the EQ-5D or Health Utilities Index. Preference weights are available for these instruments to convert the QoL variables into a utility score. Quality of life instruments may be disease specific or generic in nature. Generic instruments may be applied to all diseases, facilitating comparisons of quality of life across different populations. Instruments that focus on disease-specific aspects of quality of life may be able to detect smaller changes in aspects of QoL that are specific to the patient population evaluated. However, the QoL attributes measured may not be applicable for all diseases.

The EQ-5D is a validated generic QoL measure *[EurolQoL 1990]*. The descriptive system consisting of five health dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety depression. Patients are asked to choose one point that best describes their current health state for each dimension from a three-point Likert scale. The scale is commonly coded as 1, 2, or 3 where 1 represents no problems, 2 represents some problems, and 3 represents extreme problems. Patients are also asked to rate their current health state on a 20 cm vertical feeling thermometer or visual analogue scale (VAS) on the second page. The VAS is anchored by 0 (worst imaginable health state) and 100 (best imaginable health state).

An index or utility score can be derived from the descriptive system based on preference weights *[Dolan 1997; Shaw 2005]*. Health states, based on the 5 domains, are linked to a single utility score with 0 and 1 representing death and perfect health, respectively. Five health domains on a three-point scale results in a total of 243 possible health states. In extreme cases, a negative utility score representing a health state worse than death may be assigned.

2.7.4 *Summary of Health Economic – Related Hypotheses*

Given that simple hysterectomy may be associated with fewer short and long-term side effects, superior QoL and health-related utility scores may be associated with this procedure and may drive women's decisions for treatment. Furthermore, it is possible that simple hysterectomy will be associated with use of fewer health care resources in the immediate postoperative period, including reduced hospital length of stay and need for management of postoperative complications. The economic hypotheses tested will thus include:

Hypothesis 1: We hypothesize that, in comparison with radical hysterectomy, health care-related resource utilization will be less in the simple hysterectomy group, as there will be fewer immediate postoperative and long-term management requirements. If non-inferiority of the primary and secondary efficacy outcomes is established, benefits resulting from a reduction in health care resource utilization will be associated with a favourable incremental cost-effectiveness ratio (cost per life-year gained).

Hypothesis 2: Building upon hypothesis #1, we further hypothesize that simple hysterectomy will be associated with fewer long-term adverse events and improved survivorship, and will thus be associated with superior health-related utility scores, resulting in an acceptable incremental cost-utility ratio (cost per quality adjusted life year gained).

2.8 Processes for Surgical Quality Control

While this trial is designed to be pragmatic in nature and to test "real-world" practices, there is a need for assurances that the CX.5 results are robust and represent a true comparison of the two surgical approaches. Several processes are thus included in the CX.5 trial to facilitate this evaluation, including:

Description of Surgical Requirements: The surgical interventions, including the requirements that limit the extent of a simple hysterectomy and more extensive requirements of a radical hysterectomy, are detailed in Section 8.1 and the Surgery/Pathology Manual.

Systematic Pathologic Evaluation: Tissue removed at surgery is to undergo a standardized pathologic review process as described in the Surgery/Pathology Manual, with findings recorded in a standardized manner using a pathology checklist, as indicated in the Surgery/Pathology Manual. The data from the pathology checklist will be entered into the trial's database and evaluated using standardized processes.

Photographs of the Pathology Specimen: The gross pathology specimen will be photographed, as described in the Surgery/Pathology Manual. These photographs, along with the pathology checklist, will be reviewed by the CX.5 Study Chair to determine that the allocated surgical procedure was performed.

3.0 BACKGROUND THERAPEUTIC INFORMATION

The CX.5 trial compares radical and simple hysterectomy as therapy for patients with early stage cervical cancer. Details of the surgical procedures are described in Section 8.0 and in the Surgery Pathology Manual.

4.0 TRIAL DESIGN

This is a randomized, non-blinded, multicenter, international phase III Gynecologic Cancer Intergroup (GCIG) trial coordinated by the Canadian Cancer Trials Group.

4.1 Stratification

Patients will be stratified by:

1. Cooperative Group
2. Intended use of sentinel node mapping (yes vs. no)
3. Stage (IA2 vs. IB1)
4. Histological type (squamous vs. adenocarcinoma/adenosquamous)
5. Grade (1-2 vs. 3 vs. not assessable)

4.2 Randomization

Patients will be randomized (in a 1:1 ratio) to one of the following two arms:

Arm	**Treatment Strategy**
Arm 1	Radical hysterectomy with pelvic node dissection
Arm 2	Simple hysterectomy with pelvic node dissection

The planned sample size is 700.

All patients will be followed until death or trial completion.

4.3 Inclusion of Minorities

There are no exclusions based on race or ethnicity in this trial.

To date, there is no evidence of superiority of one form of treatment over another according to racial or ethnic group. The appropriate racial/ethnic mix will be recruited to this study based on the epidemiology of cervix cancer in the participating centres.

5.0 STUDY POPULATION

This study will recruit patients with previously untreated, histologically confirmed, low-risk early-stage invasive cervical cancer. Patients will be approached based on the following criteria:

1. Clinical examination of the cervix AND local pathology review of the loop electrosurgical excision procedure (LEEP), cone or biopsy specimen.
2. Staging assignment to IA2 or modified IB1 is according to the 2009 FIGO system (Appendix III).

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed prior to performing the randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfil all of the following criteria to be eligible for admission to the study:

5.1.1 Histologically confirmed adenocarcinoma, squamous, or adenosquamous cancer of the cervix. Diagnosis has been made by LEEP, cone or cervical biopsy and has been reviewed and confirmed by the local reference gynecological pathologist.

5.1.2 Patient has been classified as low-risk early-stage cervical cancer. These patients include:

- FIGO Stage IA2 *[FIGO Annual Report, 2009]*, defined as:
  - evidence of disease by microscopy;
    - *for patients who underwent a LEEP or cone:*
      - histologic evidence of depth of stromal invasion > 3.0 and ≤ 5.0 mm based on the local reference pathologist's measurement of the LEEP or cone specimen;
      - histologic evidence of lateral extension that is ≤ 7.0 mm based on the local reference pathologist's measurement of the LEEP or cone specimen; and
      - negative margins (patients with positive margins are considered IB1, see below)
    - *for patients who underwent a cervical biopsy only:*
      - radiologic evidence of less than 50% stromal invasion based on pelvic MRI

- FIGO Stage IB1 *[FIGO Annual Report, 2009]* with favourable (low risk) features, defined as:
  - measured stromal invasion and lateral extension that meet the criteria for IA2 (see above) but with positive margins;
  - evidence of disease by clinical exam; lesion must clinically measure ≤ 20 mm
  - evidence of disease by microscopy;
    - *for patients who underwent a LEEP or cone:*
      - histologic evidence of depth of stromal invasion between 5.1-10 mm and/or lateral extension between 7.1-20.0 mm based on the local reference pathologist's measurement of the LEEP or cone specimen *NB: the maximum depth of stromal invasion must be ≤ 10 mm.*

- *for patients who underwent a cervical biopsy only:*
  - radiologic evidence of less than 50% stromal invasion based on pelvic MRI
  - lateral extension ≤ 20 mm based on clinical exam or radiologic imaging

In addition to above criteria on maximal stromal invasion of ≤ 10 mm, **the lesion must be no larger than 20 mm in any dimension by any assessment method (MRI, clinical or histological exam)**. To ensure patients meet this criterion, investigators may need to sum the lesion measurements from biopsy and other methods that evaluate it in the same plane. For questions on eligibility with respect to this criterion please contact CCTG before randomization.

Patients are eligible irrespective of the presence or absence of lymph-vascular space involvement (LVSI).

5.1.3 Physical examination, recto-vaginal examination and visualization of the cervix by speculum or colposcopic examination have been done after the initial diagnostic procedure (LEEP, cone or biopsy) and prior to randomization. Staging criteria described in 5.1.2 must be satisfied based on these examinations.

5.1.4 Chest x-ray or CT scan of chest AND pelvic MRI* done after initial diagnostic procedure (LEEP, cone or biopsy) and prior to randomization. Staging criteria described in 5.1.2 must be satisfied based on these examinations.

The CT should be a 16 slice (or higher) helical scanner. Oral and intravenous contrasts are preferred (unless there is a contraindication to the use of contrast) with scan obtained in the portal phase at a slice thickness of 5mm or lower

Pelvic MRI should be performed on a 1.5 or 3 Tesla magnet with pelvic phased-array coils. The MR pulse sequences will consist of T1 gradient echo in the axial plane at 5 mm slice thickness and fast spin echo in the axial, sagittal, and coronal planes at 4 mm slice thickness. The short axis (perpendicular to the tumour's long axis) with a 3 mm slice thickness is required in the best plane to show the maximum thickness of stromal invasion. Use of an anti-peristaltic agent is mandatory while intravenous use of gadolinium or diffusion-weighted imaging (DWI) is optional.

* *Note: pelvic MRI is optional if the patient has stage IA2 disease and underwent a LEEP or cone.*

5.1.5 After consideration of a patient's medical history, physical examination and laboratory testing, patients must be suitable candidates for surgery as defined by the attending physician / investigator.

5.1.6 Patients must have no desire to preserve fertility.

5.1.7 Patients fluent in English or French must be willing to complete the Quality of Life Questionnaire. The baseline assessments must be completed within 6 weeks prior to randomization. Inability (illiteracy in English or French, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible. As additional GCIG groups join the study, more translations of some of the questionnaires may be added.

Patients fluent in English or French who reside in Canada and the United Kingdom must agree to participate in the economic evaluation component of this trial and complete the Health Economics Questionnaire. Similarly, patients fluent in English or French accrued from other GCIG groups who are participating in the economic evaluation must be willing to complete the Health Economics Questionnaires.

5.1.8 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrolment in the trial to document their willingness to participate.

5.1.9 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

5.1.10 Surgery is to be done within 20 weeks of initial diagnosis (NO EXCEPTIONS). The 20-week period includes time required for diagnosis, referral, diagnostic staging, randomization and scheduling of the surgical procedure.

5.1.11 Patients must be ≥ 18 years old.

5.2 Ineligibility Criteria

Patients who fulfil any of the following criteria are not eligible for admission to the study.

5.2.1 Patients with FIGO 1A1 disease *[FIGO Annual Report, 2009]*.

5.2.2 History of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours, Hodgkin's lymphoma or non-Hodgkin's lymphoma curatively treated with no evidence of disease for > 5 years.

5.2.3 Patients with evidence of lymph node metastasis on preoperative imaging or histology.

5.2.4 Patients who have had or will receive neoadjuvant chemotherapy.

5.2.5 Patients who are pregnant.

5.2.6 Patients for whom adjuvant radiation and/or chemotherapy is planned.

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations/Activity		Timing
Diagnostic Procedure	• LEEP, cone or biopsy[1]	Prior to randomization
History and Physical Exam including	• recto-vaginal examination with speculum or colposcopy[2] • medical, surgical and obstetrical history • co-morbidities • performance status • height and weight • tobacco smoking history	After diagnostic procedure and within 12 weeks of randomization
Other Investigations	• pregnancy test [3]	Prior to randomization
Adverse Events [4]	• baseline adverse events evaluation	Within 14 days prior to randomization
Radiology	• chest x-ray or chest CT scan • pelvic MRI [5] – see Section 5.1.5 for specific requirements of MRI	After diagnostic procedure and prior to randomization
Patient Reported Outcomes	• Quality of Life questionnaire (composed of the QLQ-C30, QLQ-CX24) • Sexual Health questionnaire (composed of the FSDS-R and the FSFI) [6] • Health Economics questionnaire (composed of the HUI3 and EQ-5D) [7]	Within 6 weeks prior to randomization.

1. The initial diagnostic specimen must be reviewed by the Local Reference Pathologist (LRP) per the criteria outlined in the Surgery/Pathology manual (see LEEP/cone/biopsy checklist).
2. A recto-vaginal examination is preferred but not mandatory. A bimanual exam is also acceptable.
3. A pregnancy test is only required for women of childbearing potential. This test can be a serum test or a urine test.
4. Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (Appendix V).
5. Pelvic MRI is not required for patients with stage IA2 disease who underwent a LEEP or cone.
6. For patients who consented to this optional study component.
7. Mandatory for English and French speaking patients from Canada, the UK and France.

7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All randomizations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering/randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the CX.5 trial specific web-site. If sites experience difficulties accessing the system and/or randomizing patients please contact the help desk (link in EDC) or the CX.5 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

The following information will be required at the time of study entry:

- trial code (CCTG CX.5)
- investigator CCTG user ID
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- stratification factors

7.2 Stratification

Subjects will be stratified by:

1. Cooperative Group
2. Intended use of sentinel node mapping (yes vs. no)
3. Stage (IA2 vs. IB1)
4. Histological type (squamous vs. adenocarcinoma/adenosquamous)
5. Grade (1-2, vs. 3 vs. not assessable)

7.3 Randomization

Randomization will be given by the CCTG website.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis.

All patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

All randomized patients are to be followed until death or trial closure. The follow-up requirements for ineligible patients are submission of the Form 1 eligibility checklist and initial evaluation form plus minimal follow-up using a Form 5M.

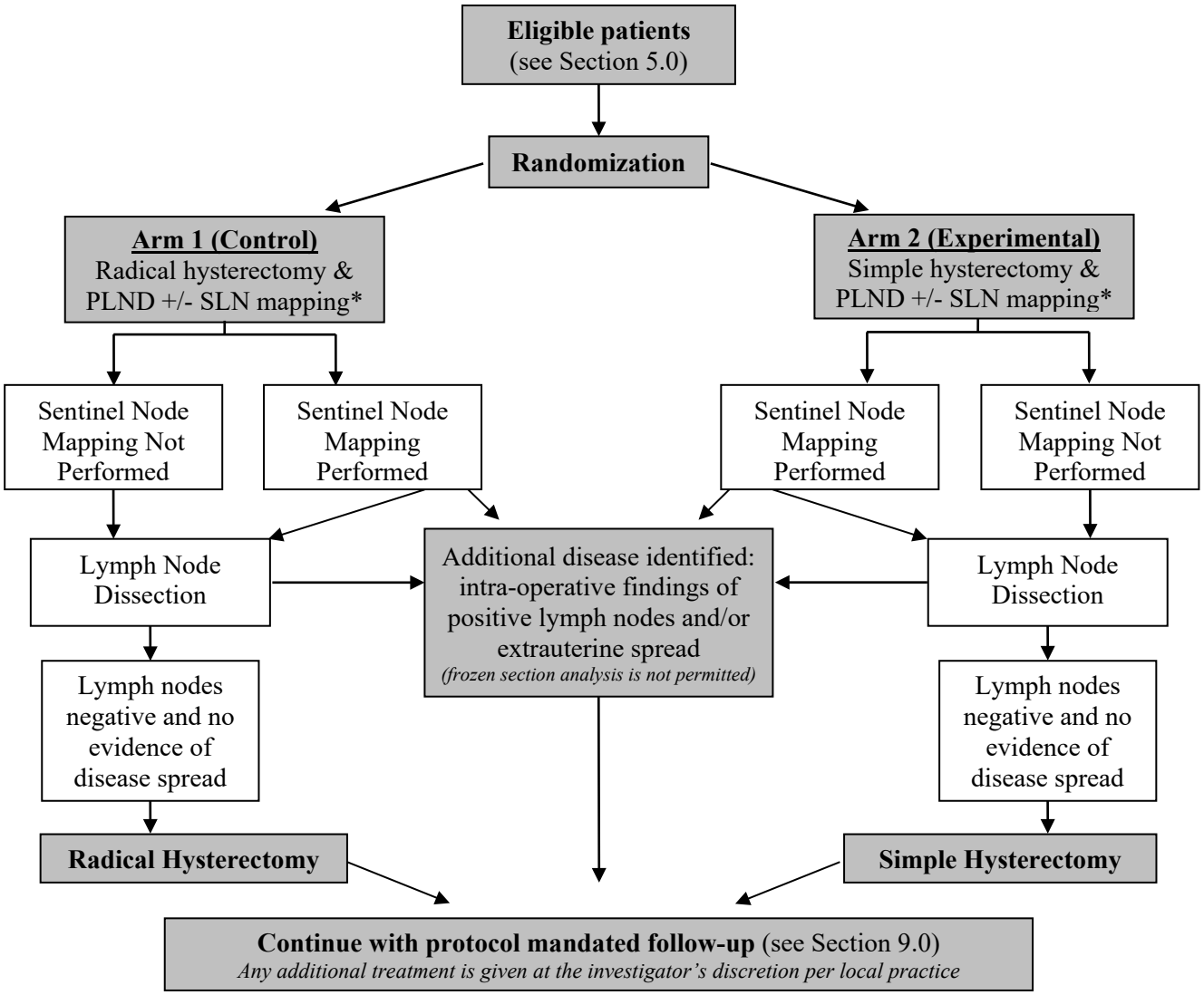
8.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator. Specific details related to trial conduct by each participating GCIG group are included in the Group-Specific Appendix provided by each Group.

After randomization, protocol-assigned surgery must take place within 8 weeks.

Regardless of when the patient is randomized, protocol surgery must be performed within 20 weeks of the date of the initial pathologic diagnosis (NO EXCEPTIONS). A schema of the treatment plan is shown below.

The decision regarding the use of SN lymph node mapping must be made at the time of randomization.



* Regardless of treatment assignment, surgery will include pelvic lymph node dissection with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

8.1 Hysterectomy Procedure

Patients meeting the entry criteria will be randomized prior to surgery to either undergo a radical hysterectomy and bilateral pelvic node dissection or simple hysterectomy and bilateral pelvic node dissection. It is understood that both types of hysterectomy are to be performed by a trained gynecologic oncologist.

All patients entered on this study are expected to undergo their assigned treatment as per the details below. In some cases, obvious evidence of lymph node involvement or extrauterine spread may be detected during surgery. If this occurs, then protocol-mandated surgery may be abandoned (see section 8.2.4 for further details).

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

Arm 1 - Radical Hysterectomy (Type 2)

This procedure may be performed abdominally, laparoscopically, robotically or vaginally. The uterus, cervix, medial 1/3 of parametria, 2 cm of the uterosacral ligaments and upper 1-2 cm of the vagina are to be removed *en bloc*. The uterine artery is ligated laterally to the ureters and the ureters are unroofed to the ureterovesical junction.

Arm 2 – Simple Hysterectomy (Extrafascial Hysterectomy)

This procedure may be performed abdominally, laparoscopically, robotically or vaginally. Extrafascial hysterectomy involves removal of the uterus with cervix without adjacent parametria. The uterine arteries are transected medial to the ureters at the level of the isthmus and the uterosacral ligaments are transected at the level of the cervix. Surgeons should pay special attention to make sure that the whole cervix is removed. As such, a maximum 0.5 cm of vaginal cuff can be removed to ensure the complete removal of the cervix.

8.2 Lymphadenectomy and Sentinel Node Mapping

Protocol therapy on both treatment arms will include pelvic lymph node dissection. Centres may choose to perform sentinel node mapping for some or all of their CX.5 patients if that is part of their usual practice. For centers not performing sentinel node mapping, a complete pelvic node dissection is considered protocol therapy. All the nodes are submitted for routine pathological analysis as per the Surgery/Pathology Manual. Frozen section analyses of sentinel nodes are not permitted for this trial unless the node is visually suggestive of metastatic spread.

8.2.1 *Pelvic Lymphadenectomy*

This procedure can be performed by open or laparoscopic technique. Bilateral skeletonization is to be performed with removal of all lymph node tissue from lower half of common iliac vessels, external iliac vessels, internal iliac vessels and the obturator fossa. The anatomic boundaries are to include the lower half of the common iliac artery proximally, the deep circumflex iliac vein distally, the mid portion of the psoas muscle laterally, to the ureters medially and above the obturator nerve in the obturator fossa inferiorly.

Following the complete bilateral pelvic node dissection, the nodes are submitted for routine pathological analysis as per the Surgery/Pathology Manual.

8.2.2 *Sentinel Node (SN) Mapping*

Only experienced surgeons are permitted to perform sentinel node biopsies as part of this trial. To be eligible for this procedure, individual surgeons will be required to have successfully performed at **least 10** previous SN procedures in cervix or endometrial cancer patients. Following the surgery, a quality assurance exercise will be conducted in the first 5 CX.5 patients treated by each surgeon. Please see section 13.3.2 for full details regarding this quality assurance exercise.

Investigators must identify whether sentinel node mapping will be performed **prior to** enrolling the patient in the trial. The SN mapping should be preferably done by **laparoscopy** and excised SNs are to be submitted for ultrastaging on final pathology (serial sectioning and immunohistochemistry) as per the Surgery/Pathology Manual. Additional details of the SN mapping technique are outlined in the Surgery/Pathology Manual.

8.2.3 *Management of Patients with Intra-operative Findings of More Advanced Stages of Cervical Cancer*

If lymph node metastasis and/or other extrauterine spread are identified during surgery, patients should be offered additional management according to local policy.

8.2.4 *Para-aortic Lymphadenectomy*

This procedure can be performed by an open or laparoscopic technique. The right sided para-aortic lymphadenectomy will involve removal of all lymph node tissue anterior to the inferior vena cava below the level of the inferior mesenteric artery proximally and to the upper half of the common iliac artery distally. The left sided para-aortic lymphadenectomy will involve removal of all lymph node tissue between the aorta and left ureters from the level of the inferior mesenteric artery proximally to the upper half the left common iliac artery.

8.3 Principles of Adjuvant Treatment

The decision as to whether participants will require radiation-based adjuvant therapy following hysterectomy will be made by the treating physician per local policy. If required, adjuvant therapy is to be administered according to institutional treatment policies and will be recorded on trial case report forms.

8.4 Concomitant Therapy

8.4.1 *Permitted*

Patients may utilize any non-anti-cancer therapies. Use of over-the-counter and complementary therapies is permitted. Complementary therapies should be disclosed to the investigator during the period of time during which the patient is receiving protocol treatment.

8.4.2 *Not Permitted*

Other recognized anticancer therapies (e.g. other chemotherapy, biologic therapies) are not permitted as part of protocol therapy.

9.0 EVALUATION AFTER PROTOCOL AND NON-PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV. The schedule for evaluation after protocol commences as follows:

1. Patients completing simple or radical hysterectomy as per-protocol: the "end of treatment date" is considered the date of surgery.

2. Patients who do not undergo a hysterectomy: the "end of treatment" is considered the date that the decision was made not to have surgery, or the date of the surgical attempt (if applicable).

Patients are to be seen 4-6 weeks after the end of treatment (as defined above) and then again at 3 months after the end of protocol treatment. After this, the visits are q3 monthly for year one, q4 monthly for year two, q6 monthly for year three then q12 months until death or trial completion. At follow up patients will be assessed for local pelvic disease, extra pelvic relapse, and for treatment morbidity. Data collected at each post-treatment follow-up after the end of treatment will include documentation of adverse effects of surgery, status of disease and details of any new post protocol anticancer treatments delivered.

Patients agreeing to inclusion in the Quality of Life and Sexual Health components will complete questionnaires at 3 months, 6 months, 12 months, 24 months, 36 months from end of treatment and at disease recurrence. Patients from Canada, the UK and France agreeing to inclusion in the Health Economics component will complete questionnaires at each follow-up visit from the end of treatment (until disease recurrence) and at the time of disease recurrence. Additional evaluations required at these visits include general performance status, patient weight and Resource Utilization Assessment.

9.1 Evaluation After Completion of Protocol Therapy

The information below is captured using the Follow-Up Report.

Investigations		Timing from the End of Treatment until first disease recurrence or study closure (see definition in Section 9.0)
Physical Exam including:	• performance status • weight • tobacco smoking status	Year One – 4[1] and 12 weeks then q 3 monthly Year Two – q 4 monthly Year Three – q 6 monthly Then q 12 months.
Pelvic exam	• recto-vaginal examination with speculum or colposcopy[2]	Year One – q 3 monthly Year Two – q 4 monthly Year Three – q 6 monthly Then q 12 months.
Radiology	• CT scan of abdomen and pelvis • chest radiograph	As clinically indicated
Adverse Events[3]	• Patients must be evaluated for related adverse events at each follow-up visit.	Year One – 4[1] and 12 weeks then q 3 monthly Year Two – q 4 monthly Year Three – q 6 monthly Then q 12 months.
Resource Utilization Assessment (RUA)	• Supportive care medications, laboratory tests, imaging studies, radiotherapy, transfusions, hospitalization, and outpatient care, including physician, emergency room and home care visits4.	Year One – 4[1] and 12 weeks then q 3 monthly Year Two – q 4 monthly Year Three – q 6 monthly Then q 12 months.
Patient Reported Outcomes	• Quality of Life questionnaire (composed of the QLQ-C30, QLQ-CX24) • Sexual Health questionnaire (composed of the FSDS-R and the FSFI)[4]	At 3 months, 6 months, 12 months, 24 months, 36 months and at first disease recurrence (if applicable).
	• Health Economics questionnaire (composed of the HUI3 and EQ-5D) [5]	Year One – 4[1] and 12 weeks then q 3 monthly Year Two – q 4 monthly Year Three – q 6 monthly Then q 12 months until study closure and at first disease recurrence (if applicable).

1. This visit may be done up to 6 weeks after surgery.
2. A recto-vaginal examination is preferred but not mandatory. A bimanual exam is also acceptable.
3. Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (Appendix V). Only AEs deemed possibly, probably, or definitely related to protocol therapy need to be reported.
4. For patients who consented to this optional study component and/or select GCIG groups .
5. Mandatory for English and French speaking patients from Canada, the UK and select GCIG groups.

9.2 Evaluation After Recurrence

Investigations *Evaluations after pelvic and/or extra pelvic recurrence*		Timing from the date of first recurrence (see Section10.3)
Physical Exam including:	• performance status • weight • tobacco smoking status	At the time of first recurrence* AND Years One to Three – q 6 monthly Then q 12 months until study closure.
Pelvic Exam	• recto-vaginal examination with speculum or colposcopy**	
Radiology	• CT or MRI scan of abdomen and pelvis • chest radiograph	If clinically indicated
Adverse Events***	• Patients must be evaluated for related adverse events at each follow-up visit.	Years One to Three – q 6 monthly Then q 12 months until study closure.
* A full "work-up" for pelvic recurrence is required at the time extra-pelvic recurrence is diagnosed. ** A recto-vaginal examination is preferred but not mandatory. A bimanual exam is also acceptable. *** Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (Appendix V). Only AEs deemed possibly, probably, or definitely related to protocol therapy need to be reported.		

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

As relapse-free survival is an important endpoint in this study, it is vital that it be adequately and precisely documented.

10.1 Definitions

The major parameters of outcome are pelvic recurrence rate at 3 years, pelvic and extra-pelvic relapse-free survival and overall survival.

10.1.1 *Pelvic recurrence rate at 3 years* is defined as a probability of pelvic recurrence within 3 years from randomization A pelvic recurrence is defined as a recurrence within the pelvis, below the pelvic brim and inferior to the L4-L5 vertebral level. Pelvic recurrences will include disease recurrence in the vaginal vault, parametrium and pelvic lymph nodes (including the common iliac nodes).

10.1.2 *Pelvic Relapse-Free Survival* is defined as the date from randomization to the date of first documented reappearance (recurrence) of disease provided that this recurrence is in the pelvis.

10.1.3 *Extra-Pelvic Relapse-Free Survival* is defined as the date from randomization to the date of first documented reappearance (recurrence) of disease provided that this recurrence is outside of the pelvis. An extra-pelvic recurrence is defined as a recurrence outside of the pelvis, including above the pelvic brim and/or superior to the L4-L5 vertebral level. Extra-pelvic recurrences will include the para-aortic lymph nodes.

10.1.4 *Recurrence* is defined as new clinical, imaging or cellular/tissue-based specimen evidence of cervical cancer since study entry.

10.1.5 *Site of First Recurrence* (i.e. para-aortic or supraclavicular lymph nodes, lung, liver, bone, etc.) will be documented.

10.1.6 *Overall Survival* is defined as the time from randomization until death from any cause. For living patients, the date corresponding to the most recent date of patient contact (regardless of whether this date is protocol required) will be used.

10.2 Evidence of Disease Recurrence

Evidence of disease recurrence may be based on clinical, imaging or cellular/tissue based specimen evidence. Ideally, recurrence is based on a cellular or tissue – based analysis. In specific circumstances, imaging tests may provide compelling evidence of disease recurrence and the subsequent management of the patient is based on these results. Rarely, clinical findings unsupported by a specimen-based analysis or definitive imaging are considered to show sufficient evidence of disease recurrence. For the CX.5 protocol, the following policies for determining evidence of disease recurrence will apply:

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

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

iii) Clinical evidence: Clinical-based evidence will be considered sufficient for a diagnosis of recurrent cervical cancer if this evidence is unequivocal (e.g. speculum/colposcopic visualization; a palpable mass) AND is subsequently supported by specimen-based evidence OR unequivocal imaging evidence. When clinical evidence is supported by imaging findings that are considered sufficient to justify recommencing therapy for cervical cancer, the imaging findings will be judged as providing unequivocal evidence of recurrent cervical cancer.

10.3 Dating of First Recurrence

This should always be based on the onset of a sign but never on the onset of a symptom. The date of first detection of a palpable and/or visible lesion is acceptable only when these findings are unequivocal and a diagnosis of tumour involvement is subsequently established by pathological or radiologic confirmation. The diagnosis of recurrent disease by radiographs or scans alone should be dated from the date of the first unequivocally positive record, even if this is determined in retrospect. Initial recording of dates of first recurrence and death should be made as they occur by those who are responsible for the care of the patient. Dates that are based on suspicion alone without unequivocal evidence will be reviewed by the CCTG trial team to establish their accuracy through subsequent behaviour. In addition, the case records of those patients not reported as having recurrent disease will be scrutinized regularly to check that review is continuing and to ensure consistent recording.

10.4 Management Following Recurrence

Patient management following recurrence is at the discretion of the investigator. Protocol follow-up should continue until trial completion.

11.0 SERIOUS ADVERSE EVENT REPORTING

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix V). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting toCCTG.

11.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment (as defined in Section 8) must be reported in an expedited manner (see Section 11.2 for reporting instructions). These include events occurring during protocol treatment and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with known complications.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol treatment cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the CX.5 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours:	Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.
Within10 days:	Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

CX5 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2941

Note: Centres outside of Canada are asked to please refer to their group-specific appendix for additional, detailed instructions regarding SAE reporting.

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the CX.5 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

11.3 Reporting Safety Reports to Investigators

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and relevant information from other clinical trials) that are reportable to regulatory authorities in Canada as reported to theCCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial CX.5 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs will need to be entered into the CCTG trial CX.5 web-based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

Patients may not receive protocol treatment (as defined in Section 8) in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree.
- Request by the patient.

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients do not undergo surgery and/or no longer attend the participating institution.

12.1 Therapy After Protocol Treatment

The management of patients who complete protocol treatment (or who never undergo protocol treatment) is left to the discretion of the Investigator. The visit schedule for those patients who receive other anti-cancer therapy should not be modified as endpoints will be assessed for as long as the patient can be followed and an intent-to-treat analysis will be performed.

12.2 Follow-Up After Protocol Treatment

Follow-up will continue after treatment completion to monitor patients for study endpoints. Participants should be followed by in-person clinic visits to the greatest extent possible. Follow-up assessment by telephone or other remote method is allowed, if permitted by local policy, only in emergency situations (refer to Appendix VIII) or for participants who have permanently ceased follow-up at the recruiting centre but are not lost to follow up. In the latter circumstance, the recruiting centre will remain responsible for procuring and reporting follow-up data per protocol schedule. The recruiting centre should document the reason why in-person follow-up visits are unable to continue at their centre and how relevant study data will be obtained for future follow up periods.

12.3 Lost to Follow Up

Participants will only be declared lost to follow up (LTFU) if there has been a minimum of 3 unsuccessful contact attempts documented over 2 or more years after the last date of successful contact. Required methods of contact include contacting the participant by telephone and searching relevant medical records, if permitted by local site policy. All participant contact attempts must be clearly documented in the patient's medical record.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Review of Diagnostic Imaging and Quality Assurance Procedure

There will be no up-front central radiology review for this study. De-identified MRI scans may be collected by CCTG and reviewed by the CX.5 Radiology Coordinator should the need arise. It is recommended that each site designate a Local Reference Radiologist (LRR) who will be responsible for reviewing the pre-study MRIs for all CX.5 patients; however, this is not mandatory. The description of the MRI specifications outlined in section 5.1.5 was designed to facilitate and standardize the diagnostic imaging for this trial.

13.2 Pathology Quality Assurance

Each CCTG participating centre will identify one Local Reference Pathologist (LRP) who is the designated gynecologic pathologist (on the Participants List). *For non CCTG centres, this process will be described in your cooperative group procedures document.*

The LRP will be responsible for reviewing:

1. The diagnostic pathology specimen for all study patients to confirm their eligibility for the trial. The LEEP/Cone/Biopsy Checklist that is part of the Surgery/Pathology Manual was designed to facilitate and standardize this review.
2. The post-surgical hysterectomy and lymphadenectomy/sentinel node specimens. The Hysterectomy Checklist that is part of the Surgery/Pathology Manual was designed to facilitate and standardize this review.
3. The specimen that diagnoses disease recurrence.

Note: CCTG may require that any or all of the abovementioned specimens be submitted for central pathology review (see section 13.4)

13.3 Surgical Quality Assurance Procedure

13.3.1 *Hysterectomy*

A photograph of the "unpinned" hysterectomy (modified radical or simple) specimen will be submitted as part of the supporting documentation required for the Surgery Report. The CX.5 Study Chair will review these pictures along with other supporting documentation as part of the surgical quality assurance process. Please see the Surgery/Pathology manual for submission details.

13.3.2 *Sentinel Node Mapping Procedure*

It is understood that patients will undergo surgery performed by a trained gynecologic oncologist. Prior to local activation, the site must declare:

1. Whether or not they will be employing sentinel node mapping for their CX.5 patients.
2. Whether each gynecologic oncology surgeon listed on the Participants List has treated at least 10 cervical and/or endometrial cancer patients using the SN mapping technique per the standards outlined in the protocol and this manual.

Then, the first 5 cases for each qualified surgeon performing sentinel node mapping as part of the CX.5 trial must undergo a quality assurance exercise. This exercise will consist of the following steps:

Centre completes all required case report forms (baseline report and surgery form) and

submits the required supporting documentation (de-identified operative and pathology reports)
Note: this is required for ALL patients randomized to CX.5

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Centre provides a de-identified photograph of the preoperative lymphoscintigram and de-identified photographs of the detection of blue sentinel nodes bilaterally.
Please see the Surgery/Pathology manual for submission details.
*Note: this is required for the first **5** patients who undergo SN mapping per surgeon. If lymphoscinitgram is not routinely done at the institution, please contactCCTG.*

↓

CCTG sends a summary of the CRFs, copies of the operative and pathology reports and the SN photographs to the appropriate reviewer.

↓

The reviewer communicates back to CCTG about the status of the review and CCTG then provides the site with the reviewer's comments.
This may require several iterations before the review is complete.

↓

After all 5 cases are reviewed and considered satisfactory, the quality assurance exercise is complete.

Note: it is recommended that this exercise is completed as soon as possible following each surgery so that important feedback may be communicated back to the surgeon before another patient undergoes protocol treatment. It is not expected that this exercise will delay a potential randomization or a patient's surgery; unless under exceptional circumstances.

13.4 Central Pathology Review

There will be no up-front central pathology review for this study; however, tissue samples from procedures that show disease recurrence may be collected for central review by the CX.5 trial Pathology Coordinator should the need arise.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

The primary objective of this study is to compare the pelvic recurrence rate at 3 years of patients with low-risk cervical cancer defined as lesions less than 2 cm, at least 3mm of intact cervical stroma or with less than 50% stromal invasion and randomized to receive simple hysterectomy and pelvic node dissection or radical hysterectomy and pelvic node dissection. Secondary objectives include comparisons of pelvic relapse-free survival, overall survival, extra pelvic relapse-free survival, rate of sentinel node detection, rate of parametrial, margins and pelvic nodes involvement, treatment-related adverse events, and quality of life (including sexual health). Eligible patients will be randomized in a 1:1 ratio to one of the two treatment arms using the minimization method and the following stratification factors: cooperative group, intended use of SN mapping (yes vs. no); stage (IA2 vs. IB1), histological type (squamous vs. adenocarcinoma, adenosquamous) and tumour grade (1-2 vs. 3 vs. not assessable).

14.2 Primary Endpoints and Analysis

Pelvic recurrence rate at 3 years, the primary endpoint of this study, will be estimated by the Kaplan-Meier estimate for the 1-probability of pelvic relapse-free survival (PRFS) at 3 years, where the PRFS is defined as the time from randomization to the time when any documented evidence of recurrence within the pelvic field (see Sections 10.0-10.3). Patients who relapsed outside of the pelvic field or died before the documentation of pelvic relapse will be censored at the time of first documented extra pelvic relapse or death. If the patient is alive without any relapse at the time of final analysis, PRFS will be censored on the date of the last disease assessment. All patients will be included in the analyses in the arms to which they are randomized regardless of whether they receive the assigned treatment (intention-to-treat). Upper limit of a one-sided 95% confidence interval for the difference in the pelvic recurrence rates at 3 years between simple hysterectomy to radical hysterectomy will be calculated based on the Greenwood estimate for the variance of the estimated 3 year PRFS and non-inferiority of simple hysterectomy to radical hysterectomy will be claimed when this upper limit is lower than or equal to 4%. A “per-protocol” sensitivity analysis based on only eligible patients who have received any study treatment and analyzed based on arms they are treated will also be performed for non-inferiority testing.

The experience of PRFS, a secondary endpoint of the study, will be described by the Kaplan-Meier method for all randomized patients in both treatment groups on the base of intention-to-treat. Based on Jung *et al.* (sample size computation for two-sample non-inferiority log-rank test, *[Jung, 2005]*), non-inferiority of simple hysterectomy to radical hysterectomy will be claimed when the upper limit of a one-sided 95% confidence interval for the hazard ratio of simple hysterectomy to radical hysterectomy, derived from a stratified Cox model adjusting for stratification factors at randomization and with a single treatment covariate, is lower than or equal to 2.04. The non-inferiority margin 2.04 for hazard ratio is corresponding to a margin of 4% for the 3 year PRFS between simple hysterectomy and radical hysterectomy when the 3-year PRFS in radical hysterectomy was estimated at 96%. A “per-protocol” sensitivity analysis will also be performed.

Other secondary efficacy endpoints include (1) overall survival, defined as time from randomization to the time of death from any cause. Patients who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last contact date; and (2) extra pelvic relapse-free survival free survival, defined as time from randomization to the time of first documented relapse outside the pelvic field. Patients who had pelvic relapse or died before extra pelvic relapse will be censored at time of pelvic relapse or death. Patients who are alive without any recurrent disease at the time of the final analysis will be censored at their last disease

assessment dates. Analyses for these secondary efficacy endpoints will be done using similar methodology for PRFS. For the rest of the secondary endpoints, the rate of sentinel node detection and rate of parametrial, margins and pelvic nodes involvement, they will be compared between two arms using a Fisher's exact test.

All patients who have received study treatment will be included in the adverse events analysis based on arms they are treated. Adverse events will be graded using the NCI Common Toxicity Criteria Version 4.0. The incidence of adverse events will be summarized by type of adverse event and severity. A Fisher's exact test will be used as needed to compare adverse events between the two arms.

14.3 Sample Size and Duration of Study

It is estimated that the pelvic recurrence rate at 3 years for the radical hysterectomy is around 4% and we would consider simple hysterectomy is non-inferior to radical hysterectomy if its pelvic recurrence rate at 3 years is 8% orless, With 350 patient randomized to each of the two treatment arms, the study will have around 85% power to conclude the non-inferiority at 0.05 level when the pelvic recurrence rate at 3 years is the same in the two arms. Final analysis will be performed when the last patient randomized has been followed for 3 years.

14.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by Central Office. Their frequencies will be reported annually at investigators' meetings. In addition adverse events will be reviewed by the DSMC every 6 months and also by the Safety Conference Committee according to CCTG policy. As well, the annual report will include number of cases in each arm with positive nodes (abandoned protocol treatment).

14.5 Interim Analysis

No interim analysis will be performed.

14.6 Analysis for Quality of Life

The quality of life and sexual health of patients in this study will be assessed by respectively EORTC QLQ-C30 core questionnaire with its module QLQ-CX24, the Female Sexual Function Index (FSFI), and the Female Sexual Distress Scale (FSDS-R). The EORTC QLQ-C30 and QLQ-CX24 are self-administered cancer specific questionnaires with multi-dimensional scales. QLQ-C30 consists of both multi-item scales and single item measures, including five functional domains, a global quality of life domain, three symptom domains, and six single items, while QLQ-CX24 has three multi-item subscales: symptom experience, body Image, and sexual/vaginal functioning, and five single items pertaining to menopausal symptoms, lymphedema, lower back pain, tingling and numbness, and sexual enjoyment. FSFI is a 19-item self-report measure of female sexual function that provides scores on six domains of sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain) as well as a total score. The FSDS-R is a 13-item unidimensional measure of sexually-related distress. Scoring of the quality of life and sexual health data will be completed following the procedures recommended by the EORTC Study Group on Quality of Life and other published algorithms.

The quality of life and sexual health data will be analyzed to look for statistically and clinically significant differences between two treatment arms. Questionnaire compliance rates will first be ascertained for each group at each measurement time point. Mean scores at baseline and the change scores from baseline at each follow-up assessment time point will be calculated for each subscale and summary scores and compared between two arms by Wilcoxon test. The profile of change scores over time between two treatment arms will be compared using linear mixed models.

The basic hypotheses in QOL and sexual health data analysis are, on average, women managed with simple hysterectomy had lower change scores from baseline on QLQ-CX24 symptom subscale and FSDS-R total score and higher change scores from baseline on FSFI total score relative to women in the radical hysterectomy group. Based on estimates of pooled standard deviations of 13.5, 10 and 21 respectively for change scores on QLQ-CX24 symptom subscale and FSDS-R and FSDS-R total score, we need respectively a total of 120, 130 and 560 women with QOL and sexual health assessments to detect respectively 7, 5, 5 points difference between two treatment arms with 80% power and two-sided 0.05 level in these subscale and scores.

14.7 Economic Analysis

Cost-effectiveness and cost-utility analyses will be performed based on respectively cost per life-year gained and cost per quality adjusted life year gained. The mean and standard deviation of cost-effectiveness and cost-utility ratio will be calculated and the bootstrap method will be used to derive the confidence intervals.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc

15.1.1 The results of this study will be published. Normally, authorship includes the naming of individual authors. As per CCTG authorship policies, publication of the final analysis of the primary outcome includes:

- The first author will generally be the chair of the study.
- The second author will normally be the CCTG Senior Investigator and the last (Senior) author will be the CCTG Gynecology Committee Chair. The CCTG Authorship policy indicates criteria that must be satisfied by the Disease Site Committee Chair in order to be recognized as Senior Author. When the time frame and duration of a study preclude the Site Chair from meeting these criteria, the CCTG Senior Investigator will normally be the senior Author.
- The CCTG Senior Biostatistician will normally be the second last (Co-senior) author.
- Additional authors, as allowed by journal policies, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair. Normally, these authors will include those investigators forming the CCTG Trial Committee.
- Each participating centre is to identify a reference pathologist. **The reference pathologists are considered contributing investigators and will be identified as individuals in relevant publications.** Typically such recognition is placed within an appendix, including supplementary online appendices.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.
- In the event of a separate paper dealing with the economic outcomes, the first author will generally be the Committee on Economic Analysis liaison on the trial committee.

For Intergroup trials, such as CX.5, a member of a cooperative group that has contributed at least 5% to the total accrual will be included. An additional member from that group will be included for each additional increase of 10% to the total accrual (i.e. 2 authors for > 15%, 3 authors for > 25%, etc.). Each cooperative group will be asked to identify the author(s) to be named.

For separate papers dealing with secondary endpoints, the first author will generally be the CCTG investigator named as responsible for that endpoint (e.g. QoL, economics, etc.). For subset analyses, the first author will be assigned on a prospective basis in a manner consistent withCCTG's policies, which state: "*The nature of a cooperative group requires that collaborations be nurtured. The most prestigious of authorship positions (First Author, Senior Author) must therefore be appropriately distributed among the individuals eligible for these positions across the reports associated with a project. Similarly, positions of Other Contributing Authors should be distributed to account for contributions to a project, including trial accrual.*" These principles include the recognition of investigators based with collaborating cooperative groups.

15.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write a manuscript describing the results of the study within a reasonable time of its completion. If, after a period of six months following the analysis of study results, the draft is not substantially complete, the CCTG Central Office reserves the right to make other arrangements to ensure timely publication.

15.2.1 *Dissemination of Trial Results*

CCTGwill inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG web site (http://www.ctg.queensu.ca).

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the CCTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Supporting groups and agencies will be acknowledged.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

All institutions outside of Canada should refer to their group-specific appendix for additional instructions regarding regulatory requirements.

16.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It isCCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

16.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in an CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

For institutions outside of Canada, please refer to your group-specific appendix for additional detailed instructions regarding informed consent.

16.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by theCCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

16.5 Retention of Patient Records and Study Files

All essential documents must be maintained in accordance with ICH-GCP.

In accordance with GCP 4.9.5, essential documents must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. In most cases, this will be for 10 years following the completion of the trial (10 years post final analysis, last data collected, or closure notification to REB, whichever is later) at the centre, or until notified by CCTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

For international participating regions, local regulatory guidance should be followed with respect to duration of records retention, unless otherwise contractually dictated.

16.6 Centre Performance Monitoring

For CCTG centres, this study is eligible for inclusion in the CTTG Centre Performance Index (CPI). Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

16.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at CCTG participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable). Other GCIG groups are to follow their Standard Operating Procedures for on-site monitoring.

The above mentioned documentation, in addition to any submitted source documents, may be accessed remotely in the event of a public health emergency either through remote access to Electronic Medical Records or through a secure file sharing portal.

For institutions outside of Canada, please refer to your group-specific appendix for additional details regarding on-site monitoring.

16.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, is to be found in Appendix IV.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except the QoL questionnaires. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Randomization and Data Management Guidebook" posted on the CX.5 area of the CCTG web-site (www.ctg.queensu.ca).

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-random-ization	4-6 weeks after the end of treatment	After end of treatment - q 3 months for year one, q 4 months for year 2, q 6 months for year 3, then annually	After Recurrence[1]
Physical				
Height	X			
Weight	X	X	X	X
Performance Status	X	X	X	X
Medical, surgical and obstetrical history	X			
Co-morbidities	X			
Tobacco smoking history	X	X	X	X
Pelvic Exam: Recto-vaginal examination with speculum or colposcopy [2]	X		X	X[3]
Radiology				
Chest CT or Chest X-Ray	X	*As clinically indicated*		
Abdominal/Pelvic CT				
Pelvic MRI	X[4]			
Other Investigations				
LEEP/Cone biopsy	X			
Pregnancy Test	X[5]			
Adverse Events				
Adverse Events	X	X[6]	X[6]	X[6]
Quality of Life				
Quality of Life questionnaire *(composed of the QLQ-C30, QLQ-CX24)* Sexual Health questionnaire *(composed of the FSDS-R and the FSFI)*[7]	X		X[8]	
Economic Analysis[9]				
Health Economics questionnaire *(composed of the HUI3 and EQ-5D)*	X		X[10]	
Resource Utilization Assessment		X	X	

1. This column also applies to those patients who do not receive protocol therapy (i.e. do not undergo a radical or simple hysterectomy).
2. A recto-vaginal examination is preferred but not mandatory. A bimanual exam is also acceptable.
3. For patients whose 1st recurrence is extra-pelvic recurrence, a pelvic exam is mandatory until pelvic recurrence is seen.
4. Pelvic MRI is not required for patients with stage IA2 disease who underwent a LEEP or cone.
5. Pregnancy test may be repeated again prior to surgery as per local policy.
6. Only AEs deemed possibly, probably, or definitely related to protocol therapy need to be reported.
7. For patients who consented to this optional study component.
8. Quality of Life and Sexual Health questionnaires are required at month 3, 6, 12, 24 and 36 and first disease recurrence
9. For patients in Canada, the UK and France only.
10. Health Economics questionnaire is also due at the time of first disease recurrence.

APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III - 2009 FIGO NOMENCLATURE

Table 1: Carcinoma of the cervix uteri: FIGO nomenclature (2009)

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤ 5 mm and largest extension ≤ 7 mm.
IA_1	Measured stromal invasion of ≤ 3.0 mm in depth and horizontal extension of ≤ 7.0 mm.
IA_2	Measured stromal invasion of > 3.0 mm and not > 5.0 mm with a lateral extension of not > 7.0 mm.
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA. *
IB_1	Clinically visible lesion ≤ 4.0 cm in greatest dimension.**
IB_2	Clinically visible lesion > 4.0 cm in greatest dimension.
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.
IIA	Without parametrial invasion but extension to the upper two thirds of the vagina.
IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension.
IIA2	Clinically visible lesion > 4.0 cm in greatest dimension.
IIB	With obvious palpable parametrial invasion.
Stage III	The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney.
IIIA	Tumour involves lower third of the vagina, with no extension to the pelvic wall.
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV.
IVA	Spread of the growth to adjacent organs.
IVB	Spread to distant organs.

* *All macroscopically visible lesions – even with superficial invasion – are allotted to stage IB carcinomas. The involvement of vascular / lymphatic spaces should not change the stage allotment.*

** *For the purposes of the CX.5 trial, "low-risk" IB_1 lesions must be ≤ 10mm in stromal invasion and must be ≤ 20mm in maximum dimension.*

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except the quality of life questionnaire, sexual health questionnaire and the health economics questionnaire. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "CCTG EDC Generic Data Management Guidebook" posted on the CX.5 area of the CCTG web-site (www.ctg.queensu.ca).

The electronic CRFs to be used in this trial, through the EDC system, are as follows:

Electronic Folder	Required	To be completed electronically	De-Identified Supporting Documentation Required[1]
Eligibility Checklist	Prior to randomization	At the time of randomization	
Baseline Report LEEP/cone/biopsy Checklist	Prior to protocol surgery	Within 6 weeks after randomization	• Consent form signature pages (Canadian patients only) • Copies of pathology reports (from initial diagnosis and LRP review) and radiology reports[2] • PROs[3]
Surgery Report	4-6 weeks after protocol surgery	Within 8 weeks after surgery	• Operative report • Pathology report • Photograph of hysterectomy specimen for surgical QA[4] • Lymphocintogram and photographs for SN mapping QA[5]
Adjuvant Therapy Report	Upon the completion of adjuvant therapy	Within 8 weeks after the completion of adjuvant therapy	--
Follow-Up Report	Year One – q 3 monthly[6] Year Two – q 4 monthly Year Three – q 6 monthly Then q 12 months until study closure.[7]	Within 8 weeks of the visit date	• Pelvic exam notes • Radiology reports (if done) • Pathology/cytology/surgical reports (if done) • PROs[3]
Recurrence Report	At the time of first pelvic and/or extra-pelvic disease recurrence	Within 8 weeks of the date of recurrence	• Pelvic exam notes • Radiology reports (if done) • Pathology/cytology/surgical reports (if done) • PROs[3]
Short Follow-up Report	q 6 monthly from the date of the most recent recurrence	Within 8 weeks of the visit date	• Pelvic exam notes (if done) • Radiology reports (if done) • Pathology/cytology/surgical reports (if done)
Death Report	At the time of patient death	Within 8 weeks of patient death	Autopsy report (if done)
SAE Report[8]	At the time of the event	See section 11.0	

1. Supporting Documentation should be uploaded into the EDC system Supporting Document Upload Tool after the eCRF has been submitted electronically.
2. Original diagnostic specimen and/or MRI images may be requested for central review purposes (see Section 13).
3. Patient Reported Outcomes (QoL, Sexual Health, Health Economics) for applicable patients should be uploaded into the EDC system Supporting Document Upload Tool after the eCRF has been submitted electronically.
4. See Section 13 and the Surgery/Pathology manual for full details.
5. For sites performing SN mapping (see Section 13 and the Surgery/Pathology manual).
6. The reporting period for the first Follow-Up Report will start from the date of the 4-6 week post-surgery visit and collect data up until the date of the first follow-up visit.
7. Calculated from the date of protocol surgery.
8. See section 11.0 Serious Adverse Event Reporting for details.

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self-report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, she should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing her that the questionnaire was not completed. Ask the patient if she is willing to complete one:
If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if she is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if she is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then she is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **CX.5**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (3)

☐ Prior to randomization

☐ At the time of first recurrence

After surgery prior to recurrence:

☐ 3 months ☐ 6 months ☐ 12 months

☐ 24 months ☐ 36 months

☐ Other _____ (specify)

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (C)

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very Poor						Excellent

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

1	2	3	4	5	6	7
Very Poor						Excellent

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

EORTC QLQ-CX24 QUESTIONNAIRE

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

During the past week:	Not At All	A Little	Quite a Bit	Very Much
31. Have you had cramps in your abdomen?	1	2	3	4
32. Have you had difficulty in controlling your bowels?	1	2	3	4
33. Have you had blood in your stools (motions)?	1	2	3	4
34. Did you pass water/urine frequently?	1	2	3	4
35. Have you had pain or a burning feeling when urinating?	1	2	3	4
36. Have you had leaking of urine?	1	2	3	4
37. Have you had difficulty emptying your bladder?	1	2	3	4
38. Have you had swelling in one or both legs?	1	2	3	4
39. Have you had pain in your lower back?	1	2	3	4
40. Have you had tingling or numbness in your hands or feet?	1	2	3	4
41. Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
42. Have you had discharge from your vagina?	1	2	3	4
43. Have you had abnormal bleeding from your vagina?	1	2	3	4
44. Have you had hot flushes and/or sweats?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
47. Have you felt dissatisfied with your body?	1	2	3	4

During the *past 4 weeks*:	Not At All	A Little	Quite a Bit	Very Much
48. Have you worried that sex would be painful?	1	2	3	4
49. Have you been sexually active?	1	2	3	4

Answer the following questions only if you have been *sexually active* during the *past 4 weeks*:	Not At All	A Little	Quite a Bit	Very Much
50. Has your vagina felt dry during sexual activity?	1	2	3	4
51. Has your vagina felt short?	1	2	3	4
52. Has your vagina felt tight?	1	2	3	4
53. Have you felt pain during sexual intercourse or any other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable to you?	1	2	3	4

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

Sexual Health Questionnaire (FSDS-R & FSFI) – ENGLISH

CCTG Trial: **CX.5**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (3)

☐ Prior to randomization

☐ At the time of first recurrence

After surgery prior to recurrence:

☐ 3 months ☐ 6 months ☐ 12 months

☐ 24 months ☐ 36 months

☐ Other _____ (specify)

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

FSDS-R QUESTIONNAIRE - FEMALE SEXUAL DISTRESS SCALE-Revised
CCTG CX.5

INSTRUCTIONS

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST 30 DAYS INCLUDING TODAY*. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.

* **AT BASELINE ONLY**: If there has been a period of no sexual activity (whether with a partner or on your own) because of a recent medical procedure, please complete this with the most recent 4-week period that did include sexual activity.

Example: How often did you feel: Personal responsibility for your sexual problems.

NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
0	1	2	3	4

HOW OFTEN DID YOU FEEL:		NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
1.	Distressed about your sex life	0	1	2	3	4
2.	Unhappy about your sexual relationship	0	1	2	3	4
3.	Guilty about sexual difficulties	0	1	2	3	4
4.	Frustrated by your sexual problems	0	1	2	3	4
5.	Stressed about sex	0	1	2	3	4
6.	Inferior because of sexual problems	0	1	2	3	4
7.	Worried about sex	0	1	2	3	4
8.	Sexually inadequate	0	1	2	3	4
9.	Regrets about your sexuality	0	1	2	3	4
10.	Embarrassed about sexual problems	0	1	2	3	4
11.	Dissatisfied with your sex life	0	1	2	3	4
12.	Angry about your sex life	0	1	2	3	4
13.	Bothered by low sexual desire	0	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

FSFI QUESTIONNAIRE - CCTG CX.5
Female Sexual Function Index (FSFI) ©

These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible using the scale to the right. Your responses will be kept completely confidential. If you choose not to answer a particular question, please proceed to the next question.

In answering these questions, the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation, and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

Circle only one item per question.

Question		Response options (please circle)
1.	Over the past 4 weeks, how satisfied have you been with your overall sexual life?	5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied & dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
2.	Over the past 4 weeks, how often did you feel sexual desire or interest?	5 = Almost always or always 4 = Most times (more than ½ the time) 3 = Sometimes (about ½ the time) 2 = A few times (less than ½ the time) 1 = Almost never or never
3.	Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?	5 = Very high 4 = High 3 = Moderate 2 = Low 1 = Very low or none at all

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Question		Response options (please circle)
4.	Over the past 4 weeks, did you engage in sexual activity of any kind with a partner and/or by yourself (masturbation)?	0 = No sexual activity (neither with a partner nor by myself) 1 = Sexual activity with a partner only 1 = Sexual activity by myself only 1 = Sexual activity both with a partner and by myself

If you selected "0 = No sexual activity (neither with a partner nor by myself)", please skip remaining questions on this questionnaire. If you selected any other response, please continue.

5.	Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?	X = No sexual activity 5 = Almost always or always 4 = Most times (more than ½ the time) 3 = Sometimes (about ½ the time) 2 = A few times (less than ½ the time) 1 = Almost never or never
6.	Over the past 4 weeks, how would you rate your level of sexual arousal ("turned on") during sexual activity or intercourse?	X = No sexual activity 5 = Very high 4 = High 3 = Moderate 2 = Low 1 = Very low or none at all
7.	Over the past 4 weeks how confident were you about becoming sexually aroused during sexual activity or intercourse?	X = No sexual activity 5 = Very high confidence 4 = High confidence 3 = Moderate confidence 2 = Low confidence 1 = Very low or no confidence
8.	Over the past 4 weeks, how *often* have you been satisfied with your sexual arousal (excitement) during sexual activity or intercourse?	X = No sexual activity 5 = Almost always or always 4 = Most times (more than ½ the time) 3 = Sometimes (about ½ the time) 2 = A few times (less than ½ the time) 1 = Almost never or never
9.	Over the past 4 weeks, how *often* did you become lubricated ("wet") during sexual activity or intercourse?	X = No sexual activity 5 = Almost always or always 4 = Most times (more than ½ the time) 3 = Sometimes (about ½ the time) 2 = A few times (less than ½ the time) 1 = Almost never or never

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Question	Response options (please circle)
10. Over the past 4 weeks, how *difficult* was it for you to become lubricated ("wet") during sexual activity or intercourse?	X = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
11 Over the past 4 weeks, how *often* did you maintain your lubrication ("wetness") during sexual activity or intercourse?	X = No sexual activity 5 = Almost always or always 4 = Most times (more than ½ the time) 3 = Sometimes (about ½ the time) 2 = A few times (less than ½ the time) 1 = Almost never or never
12. Over the past 4 weeks, how *difficult* was it to maintain your lubrication ("wetness") during sexual activity or intercourse?	X = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
13. Over the past 4 weeks, when you had sexual stimulation, how *often* did you reach orgasm (climax)?	X = No sexual activity 5 = Almost always or always 4 = Most times (more than ½ the time) 3 = Sometimes (about ½ the time) 2 = A few times (less than ½ the time) 1 = Almost never or never
14. Over the past 4 weeks, when you had sexual stimulation, how *difficult* was it you to reach orgasm (climax)?	X = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
15. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?	X = No sexual activity 5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied & dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Question	Response options (please circle)
16. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?	X = No partner 5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied & dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
17. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?	X = No partner 5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied & dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
18. Over the past 4 weeks, how often did you experience discomfort or pain *following* vaginal penetration?	X = Did not attempt penetration 5 = Almost always or always 4 = Most times (more than ½ the time) 3 = Sometimes (about ½ the time) 2 = A few times (less than ½ the time) 1 = Almost never or never
19. Over the past 4 weeks, how often did you experience discomfort or pain *during* vaginal penetration?	X = Did not attempt penetration 5 = Almost always or always 4 = Most times (more than ½ the time) 3 = Sometimes (about ½ the time) 2 = A few times (less than ½ the time) 1 = Almost never or never
20. Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain *during or following* vaginal penetration?	X = Did not attempt penetration 5 = Very high 4 = High 3 = Moderate 2 = Low 1 = Very low or none at all.

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VII - HEALTH UTILITIES ASSESSMENT

Introduction

Note: Health Utilities Assessment applies to Canadian and UK centres only. Patients from these centres should complete the quality of life assessment before the health utilities assessment.

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival, progression free survival, and quality of life into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Health utility and quality of life assessments provide different but complementary information.

- Health utility is a measure of preference for a given health state that acknowledges the risk and uncertainty of outcomes in choices patients face and in clinical decision-making.
- They can be used as a weighting factor to adjust survival by quality of life.
- Depending on whether a disease-specific or generic quality of life instrument is used, often only utility assessments may be able to compare patient groups with different diseases.
- Only utilities provide a single meaningful measure that can be incorporated in health policy and health economic analyses.

Health utilities data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients and populations
- to evaluate the extent of change in health benefits of an individual, group, or population across time
- to evaluate new treatments, technologies, and patient management strategies
- to support approval of new drug applications or patient management strategies
- to try to provide the best value for health care dollars within and across diseases and health
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Health Utilities Questionnaire

The instructions below are intended as a guide for the administration of the Health Utilities Questionnaire

1. Preamble

   Health utilities data are collected for research purposes, and will not be used for the patient's individual medical care. The assessment is in the form of a self-report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

- pre-randomization or pre-registration (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g. psychological distress, social disruption, symptoms, side-effects, *et cetera*.

The Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that she prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The health utilities questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, she should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The health utilities questionnaire should be given to the patient before being seen by the doctor, at every follow-up visit, as required by the protocol schedule in section 9.1 or until deterioration to ECOG PS 4 or hospitalization for end-of-life-care.

To minimize missing health utilities data, if the patient is no longer attending clinic during the scheduled follow-up period, the patient should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. To facilitate this, ensure that after randomization all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic. If the patient has deterioration to ECOG PS 4 or hospitalization for end of life care they need not be contacted for questionnaire completion.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If…

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Four situations are described below. In these cases, it is beneficial if health economics data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if she is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if she is willing to complete a questionnaire over the phone. If the patient agrees, read out questions 1-5 and range of possibilities, and record the answers. The visual analogue scale should not be completed in this case. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

D. The patient is no longer attending clinic during the scheduled follow-up period.

Should the patient no longer be attending clinic, she should be contacted by phone to ask her to complete the questionnaire and mail it to the clinic. To facilitate this, ensure that after randomization all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was received should be recorded on the questionnaire. The date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic. If the patient has deterioration to ECOG PS 4 or hospitalization for end of life care they need not be contacted for questionnaire completion.

6. Waiving the Health Utilities Component

The only time that we will not require a patient to complete the health utilities questionnaires is if she is not literate in either English or French. In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Health Utilities Questionnaire

If a patient speaks and reads English or French, but does not wish to complete the questionnaires then she is NOT eligible and should NOT be put on study.

8. Inability to Complete Health Utilities Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the HUI3 assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Health Utilities Questionnaire – **ENGLISH**

CCTG Trial: CX.5

This page to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (3)

☐ Prior to randomization

☐ At the time of first recurrence

After surgery prior to recurrence:

☐ 3 months ☐ 6 months ☐ 9 months ☐ 12 months

☐ 16 months ☐ 20 months ☐ 24 months

☐ 30 months ☐ 36 months

☐ Other _____ (specify)

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __ (yyyy mmm dd)

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Health Utilities Index Mark 3 (HUI3) Questionnaire

CCTG: CX.5

This questionnaire contains a set of questions which ask about various aspects of your health. When answering these questions please think about your health and your ability to do things on a day-to-day basis, during the past week. For each question, please select one answer that best describes your level of ability or disability during the past week. Please answer all the questions yourself by circling the letter (a, b, c, …) beside the answer that best applies to you. Choose the best single response that applies to you. There are no right or wrong answers; what we want is your opinion about your abilities and feelings. To define the past week period, please think about what the date was 7 days ago and recall the major events that you have experienced during this period. Please focus your answers on your abilities, disabilities and how you have felt during the past week.

You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

---

1. Which one of the following best describes your ability, during the past week, to see well enough to read ordinary newsprint?

   a. Able to see well enough without glasses or contact lenses.

   b. Able to see well enough with glasses or contact lenses.

   c. Unable to see well enough even with glasses or contact lenses.

   d. Unable to see at all.

2. Which one of the following best describes your ability, during the past week, to see well enough to recognize a friend on the other side of the street?

   a. Able to see well enough without glasses or contact lenses.

   b. Able to see well enough with glasses or contact lenses.

   c. Unable to see well enough even with glasses or contact lenses.

   d. Unable to see at all.

3. Which one of the following best describes your ability, during the past week, to hear what was said in a group conversation with at least three other people?

   a. Able to hear what was said without a hearing aid.

   b. Able to hear what was said with a hearing aid.

   c. Unable to hear what was said even with a hearing aid.

   d. Unable to hear what was said, but did not wear a hearing aid.

   e. Unable to hear at all.

4. Which one of the following best describes your ability, during the past week, to hear what was said in a conversation with one other person in a quiet room?

   a. Able to hear what was said without a hearing aid.

   b. Able to hear what was said with a hearing aid.

   c. Unable to hear what was said even with a hearing aid.

   d. Unable to hear what was said, but did not wear a hearing aid.

   e. Unable to hear at all.

5. Which one of the following best describes your ability, during the past week, to be understood when speaking your own language with people who do not know you?

   a. Able to be understood completely.

   b. Able to be understood partially.

   c. Unable to be understood.

   d. Unable to speak at all.

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

6. Which one of the following best describes your ability, during the past week, to be understood when speaking with people who know you well?

   a. Able to be understood completely.

   b. Able to be understood partially.

   c. Unable to be understood.

   d. Unable to speak at all.

7. Which one of the following best describes how you have been feeling during the past week?

   a. Happy and interested in life.

   b. Somewhat happy.

   c. Somewhat unhappy.

   d. Very unhappy.

   e. So unhappy that life was not worthwhile.

8. Which one of the following best describes the pain and discomfort you have experienced during the past week?

   a. Free of pain and discomfort.

   b. Mild to moderate pain or discomfort that prevented no activities.

   c. Moderate pain or discomfort that prevented some activities.

   d. Moderate to severe pain or discomfort that prevented some activities.

   e. Severe pain or discomfort that prevented most activities.

9. Which one of the following best describes your ability, during the past week, to walk? Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

   a. Able to walk around the neighbourhood without difficulty, and without walking equipment.

   b. Able to walk around the neighbourhood with difficulty; but did not require walking equipment or the help of another person.

   c. Able to walk around the neighbourhood with walking equipment, but without the help of another person.

   d. Able to walk only short distances with walking equipment, and required a wheelchair to get around the neighbourhood.

   e. Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and required a wheelchair to get around the neighbourhood.

   f. Unable to walk at all.

10. Which one of the following best describes your ability, during the past week, to use your hands and fingers? Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

    a. Full use of two hands and ten fingers.

    b. Limitations in the use of hands or fingers, but did not require special tools or the help of another person.

    c. Limitations in the use of hands or fingers, independent with use of special tools (did not require the help of another person).

    d. Limitations in the use of hands or fingers, required the help of another person for some tasks (not independent even with use of special tools).

    e. Limitations in the use of hands or fingers, required the help of another person for most tasks (not independent even with use of special tools).

    f. Limitations in the use of hands or fingers, required the help of another person for all tasks (not independent even with use of special tools).

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

11. Which one of the following best describes your ability, during the past week, to remember things?

    a. Able to remember most things.

    b. Somewhat forgetful.

    c. Very forgetful.

    d. Unable to remember anything at all.

12. Which one of the following best describes your ability, during the past week, to think and solve day to day problems?

    a. Able to think clearly and solve day to day problems.

    b. Had a little difficulty when trying to think and solve day to day problems.

    c. Had some difficulty when trying to think and solve day to day problems.

    d. Had great difficulty when trying to think and solve day to day problems.

    e. Unable to think or solve day to day problems.

13. Which one of the following best describes your ability, during the past week, to perform basic activities?

    a. Eat, bathe, dress and use the toilet normally.

    b. Eat, bathe, dress or use the toilet independently with difficulty.

    c. Required mechanical equipment to eat, bathe, dress or use the toilet independently.

    d. Required the help of another person to eat, bathe, dress or use the toilet.

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

14. Which one of the following best describes how you have been feeling during the past week?

    a. Generally happy and free from worry.

    b. Occasionally fretful, angry, irritable, anxious or depressed.

    c. Often fretful, angry, irritable, anxious or depressed.

    d. Almost always fretful, angry, irritable, anxious or depressed.

    e. Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help.

15. Which one of the following best describes the pain or discomfort you have experienced during the past week?

    a. Free of pain and discomfort.

    b. Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.

    c. Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities.

    d. Frequent pain or discomfort; frequent disruption of normal activities. Discomfort required prescription narcotics for relief.

    e. Severe pain or discomfort. Pain not relieved by drugs and constantly disrupted normal activities.

16. Overall, how would you rate your health during the past week?

    a. Excellent.

    b. Very good.

    c. Good.

    d. Fair.

    e. Poor.

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

17. How did you complete the questionnaire? Please select the one answer that best describes your situation.

    a. By myself, without any help from anyone else.

    b. By myself, except someone else circled the answers on the questionnaire form for me.

    c. With the help of someone else.

    d. This questionnaire was completed by a family member, without help from the subject or patient.

    e. This questionnaire was completed by a nurse or other health professional, without help from the subject or patient.
    Please specify type of health professional: _____

    f. This questionnaire was completed by another person, without help from the subject or patient.

    Please specify relationship to subject or patient: _____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

EQ-5D Questionnaire

CCTG: CX.5

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

1. **Mobility**
   a. I have no problems in walking about ☐
   b. I have some problems in walking about ☐
   c. I am confined to bed ☐

2. **Self-Care**
   a. I have no problems with self-care ☐
   b. I have some problems washing or dressing myself ☐
   c. I am unable to wash or dress myself ☐

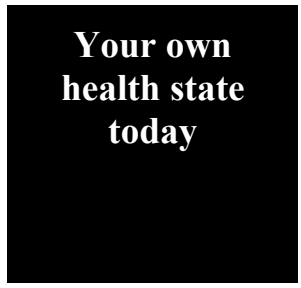
3. **Usual Activities** *(e.g. work, study, housework, family or leisure activities)*
   a. I have no problems with performing my usual activities ☐
   b. I have some problems with performing my usual activities ☐
   c. I am unable to perform my usual activities ☐

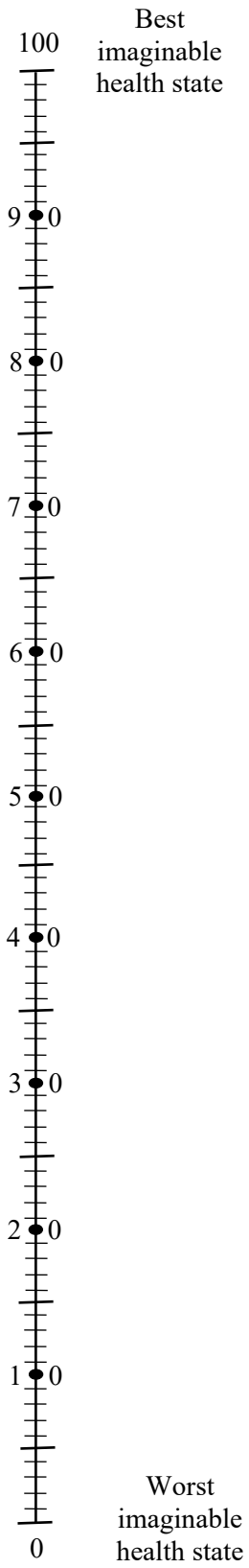
4. **Pain/Discomfort**
   a. I have no pain or discomfort ☐
   b. I have moderate pain or discomfort ☐
   c. I have extreme pain or discomfort ☐

5. **Anxiety/Depression**
   a. I am not anxious or depressed ☐
   b. I am moderately anxious or depressed ☐
   c. I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

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





Please check to make sure you have answered all questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____
Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VIII - COVID-19 AND EMERGENCY SITUATIONS AND COMPLIANCE

Management of Protocol Variances in Emergency Situations

Compliance with the trial protocol should be ensured to every extent possible. However, specific variances from the protocol that occur as a result of efforts to minimize or eliminate hazards and protect the safety and well-being of patients are permissible in emergency situations.

In these rare circumstances, minor deviations that do not impact patient safety or willingness to participate or trial integrity, which have been justified and documented in the medical record by the QI/SI will not be considered to be REB reportable deficiencies requiring action, but must be reported to CCTG (e.g. in Electronic Data Capture (EDC) or using trial specific deviation logs as directed by CCTG) within 4 weeks of the end of the Emergency Situation, and to your REB at the next amendment or annual approval.

Centres should also discuss these reporting requirements with their local REB and review the trial website for additional guidance specific to the trial.

Minor Protocol Deviations:

- Missed or delayed protocol mandated visits or investigations on treatment or in follow up.
- Changes in study drug distribution (e.g. drug distributed remotely or IV drug given at satellite site), providing permitted by local SOPs, or written procedure established and is approved by CCTG or acceptable per further instruction from CCTG. Note there will be no exceptions for injectable/IV investigational agents as must be administered at participating site.
- Alternative methods for safety assessments (e.g. telephone contact, virtual visit, alternative location for assessment).
- Patient care and evaluations provided by non-research staff, providing overseen by QI/SI who must make all treatment decisions and ensure that all required information and results will be reported to allow central data submission. Includes physical exam, clinical laboratory tests, research blood collections that can be shipped centrally, imaging, non-investigational drug therapy*, standard radiation therapy, surgery, and other interventions that do not require protocol-specified credentialing*. *Must be approved by CCTG or acceptable per further instruction from CCTG.
- Re-treatment following extended treatment delays if protocol specifies that excessive delays require discontinuation, providing other protocol requirements for discontinuation have not been met and either discussed with CCTG or acceptable per further instruction from CCTG.

Note:

- Applicable only to COVID-19 and other CCTG designated emergency situations.
- No waivers will be given for eligibility, including performance of protocol mandated tests/imaging.
- Deficiencies will be issued if patients are enrolled when trial is on accrual hold, for unreported Serious Adverse Events as well as changes in drug distribution/administration and/or re-treatment after extended treatment delays when not discussed and approved by CCTG or acceptable per further instruction from CCTG.
- Deviations or changes that are believed to impact patient safety, compromise the study integrity or affect willingness to participate are still considered Major Protocol Violations and must be reported to CCTG and your REB. These include more than a minimal delay in protocol therapy administration.

1.0 Remote Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating centres during the duration of study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

The above mentioned documentation may be accessed remotely in the event of a public health emergency either through remote access to Electronic Medical Records or through a secure file sharing portal.

LIST OF CONTACTS

	Contact	Tel. #	Fax #
STUDY SUPPLIES Forms, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Selene MillerStudy Coordinator CCTGEmail: smiller@ctg.queensu.ca	613-533-6430	613-533-2941
	or: Dr. Lois Shepherd Senior Investigator CCTGEmail: lshepherd@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Marie Plante Study Chair Email: marie.plante@crhdq.ulaval.ca		
SERIOUS ADVERSE EVENTS (SAEs)	Selene Miller Study Coordinator CCTGEmail: smiller@ctg.queensu.ca	613-533-6430	613-533-2941