HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

Short Course **A**djuvant **V**aginal Cuff Brachytherapy (VCB) in **E**arly Endometrial Cancer Compared to Standard of Care (SAVE)

Lead Org. ID #HCI103841/ IRB# 103841
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PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

Instructions to multi-site Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

_____ _____

Signature of Investigator **Date**

_____

Investigator Name (Print)

_____

Name of Institution

STUDY SUMMARY

Title	**S**hort Course **A**djuvant **V**aginal Cuff Brachytherapy (VCB) in Early **E**ndometrial Cancer Compared to Standard of Care **(SAVE).**
Short Title	VCB in Early Endometrial (SAVE)
Protocol number	IRB #103841
IND	This protocol will not hold an IND
Study Design	Open Label, Randomized trial of 2 fractions of VCB compared to the standard of 3-5 fractions.
Phase	Phase III
Study Duration	2-3 years: 2 years for accrual and 1 year for study treatment and follow up.
Primary Study Objective:	Evaluate the non-inferiority of patient Health Related Quality of Life (HRQOL) in the experimental arm compared to the control arm using the Global Health Status from the EORTC QLQ-C30.
Secondary Study Objectives:	Secondary Objectives 1. Evaluate treatment related HRQOL using the EORTC EN24, question 48 between the two treatment arms. 2. Compare cost effectiveness between the two treatment arms Exploratory Objectives 1. Report vaginal, bowel, and bladder symptoms on HRQOL using the EORTC EN24 the two treatment arms. 2. Evaluate CTCAE v5.0 toxicities and subject compliance 3. Compare local recurrence and document patterns of recurrence 4. Evaluate doses to organs at risk and the prescribed target in the two trial arms and compare them to each other. 5. Compare total distance traveled to the cancer center for study related visits.
Inclusion Criteria	• Histologically confirmed endometrial carcinoma: endometrioid type, serous, and clear cell to include tumors originating in the cervix, but are primarily located in the uterus, and for whom vaginal cuff brachytherapy is indicated. Carcinosarcoma and other sarcomas are

	permitted. FIGO stage I and stage II, with one of the following combinations of stage and grade: 1. Stage IA, grade1 with LVSI, 2, 3 2. Stage IB, grades 1-3 3. Stage II, grades 1-3 • WHO-performance status 0-2 • Written informed consent • Life expectancy > 2 years
Exclusion Criteria:	• Stages of endometrial carcinoma other than defined in inclusion criteria. • Previous pelvic radiotherapy. • Interval between the operation and start of radiotherapy exceeding 16 weeks.
Number of centers:	This study will be conducted at the Huntsman Cancer Institute and up to 5 additional cancer centers.
Number of patients:	108 (Randomized 1:1; 54 to each treatment arm)
Planned duration	2 years of recruitment. 1 year of treatment and follow up. 3 years total.
Study Product, Dose, Route, Regimen and Duration	Experimental Arm: 11Gy will be prescribed to the surface with a minimal treatment length of 3 cm. Two fractions will be given, one week apart. Control Arm options: • 7 Gy at ½ cm x 3 fractions over no more than three weeks. • 5-5.5 Gy at ½ cm x 4 fractions over no more than three weeks. • 6 Gy at the surface of the cylinder x 5 fractions over no more than three weeks.
Statistical Methodology	The primary endpoint will be the Global Health Status from the QLQ-30. The hypothesis to be tested is that the mean Global Health Status will be no more than 15 points lower one month after treatment in the Experimental Arm compared to the Control Arm. The primary non-inferiority analysis will be using a two-sample t test. Additional analyses will evaluate cost effectiveness, toxicity, vaginal, bladder and bowel symptoms affecting HRQOL, doses to organs at risk and the prescribed target, and patterns of recurrence.

1 OBJECTIVES

Hypothesis: A shorter treatment course will not be inferior to patient HRQOL using the Global Health Status from the QLQ-C30 one month after treatment in the two arms.

1.1 Primary Objectives and Endpoint

1.1.1 Evaluate the non-inferiority of patient Health Related Quality of Life (HRQOL) using the Global Health Status from the QLQ-C30 in the 2 arms one month after treatment.

ENDPOINT: Scores determined from patient completed questionnaires will be compared between the two treatment arms one month after treatment completion.

1.2 Secondary Objectives and Endpoint

1.2.1 Compare treatment-related symptoms on HRQOL using EORTC EN24, question 48 between the two treatment arms.

ENDPOINT: Scores determined from patient completed question, “Have you felt less feminine due to your disease or treatment” will be compared between the two treatment arms.

1.2.2 Compare cost effectiveness between the two treatment arms.

ENDPOINT: Cost of procedures will be compared between the two treatment arms.

1.3 Exploratory Objectives and Endpoints:

1.3.1 Report vaginal, bowel, and bladder symptoms on HRQOL using the EORTC EN24 the two treatment arms.

ENDPOINT: “Sexual/vaginal problems", "Gastrointestinal symptoms" and "Urological symptoms" symptom scales from the EORTC EN24.

1.3.2 Evaluate toxicities between the two treatment arms.

ENDPOINT: Patients will be monitored for adverse events using CTCAE V5.0 criteria and the information will be tabulated.

1.3.3 Compare local recurrence and document patterns of recurrence between the two treatment arms. There will be two analyses: A single interim evaluation of patterns of recurrence will be performed after a minimum of 75 patients have been accrued, and the second evaluation will be performed at the end of the study.

ENDPOINT: Patients will have recurring pelvic exams to monitor for disease recurrence. Additionally, after brachytherapy, CT data sets without contours will be sent to HCI for data analysis in an anonymized fashion.

1.3.4 Evaluate and compare doses to organs at risk (bladder, rectum, sigmoid colon, and urethra) and the prescribed target in the two arms.

ENDPOINT: The radiation dose to organs at risk and the prescribed target in each treatment group and explore artificial intelligence approaches to aid in contouring.

1.3.5 Compare total distance traveled to the cancer center for study related visits.

ENDPOINT: Total distance traveled, calculated by multiplying number of study visits by twice the distance to the cancer center. The distance to the cancer center will be calculated as the distance from the patient's zip code and the cancer center zip code

2 BACKGROUND

Endometrial cancer is the most common gynecologic cancer in the western world and primarily affects postmenopausal women. Approximately 85% of patients are diagnosed at an early stage.[1] Additionally, many patients have comorbidities such as obesity, diabetes, and cardiovascular disease. The primary form of treatment is surgery consisting of a total abdominal or laparoscopic hysterectomy and bilateral salpingo-oophorectomy. Major risk factors include stage, age, histologic type, grade, depth of myometrial invasion, and presence of lymphovascular space invasion.[2-5]

Adjuvant radiotherapy for endometrial cancer has been studied in prospective trials for at least four decades. All trials have demonstrated an improvement in local regional control. However, improvement in survival has not been observed in prospective randomized trials in early stage patients. Adjuvant radiotherapy for endometrial cancer has been tailored to specific risks factors. Early-stage endometrial cancer patients have an approximately 95% overall survival rate or a survival rate consistent with the general population.[6] Whereas, patients with deeply invasive, grade 3, stage I tumors have been documented in one study by Creutzberg et. al.[9] to have a 58% overall survival rate.[7] Hence, there is great heterogeneity in prognoses in stage I patients. National Comprehensive Cancer Network (NCCN) guidelines consequently recommend no treatment in general for low-stage patients, adjuvant brachytherapy for patients with intermediate- and high-intermediate-risk disease, and for patients with deeply invasive tumors with high-grade lesions, external beam radiotherapy is an option (NCCN Guidelines 2016). Over the ensuing decades, there has been a shift toward increasing use of vaginal cuff brachytherapy.

In the Norwegian trial published in 1980 by Alders et al., after hysterectomy and postoperative vaginal brachytherapy (60 Gy to the mucosal surface), patients were randomized to observation or external beam.[8] Vaginal and pelvic relapse rates were reduced with adjuvant external beam. However, survival was not improved (89% versus 91% at 5 years). However, the subgroup with grade 3 tumors with deep myometrial invasion showed improved local control and survival after external beam (18% versus 27% cancer-related deaths). In PORTEC-1, 715 patients with stage I endometrial cancer, grade 1 or 2 with deep myometrial invasion, or grade 2 or 3 with superficial invasion less than 50% were randomized after hysterectomy and received external beam, 46 Gy in 2 Gy fractions or no additional treatment.[9] The 10-year local regional relapse rates were 5% in the external beam group and 14% in the control group for a highly statistical advantage for

external beam for local regional control. However, again there is no significant survival difference between the 2 arms. The GOG 99 trial had a similar design; however, patients underwent surgical staging[10]. A high-intermediate-risk group was defined based on the prognostic factors, age, histologic grade, myometrial invasion, and the presence of lymphovascular space invasion. The high-intermediate group (one-third of the study) had a 2-year incidence of relapse in the no adjuvant therapy arm of 27% in contrast to 6% in the low-intermediate group. Radiotherapy resulted in similar hazard reductions for the high-intermediate and low-intermediate groups (58% and 54%), but in absolute terms, the differences were greater in the high-intermediate group with a reduction of 4-year cumulative relapse from 27% to 13% in the radiotherapy group. In the pooled ASTEC/EN5 trials, 905 patients with stage I endometrial cancer were randomly allocated to no adjuvant therapy or external beam radiotherapy.[11] This trial confirmed the results of the PORTEC and GOG 99 trials. In the ASTEC/EN5 trial, brachytherapy was used in 51% of the patients.

In patients who received no adjuvant therapy, the majority of the relapses occurred in the vagina, and hence vaginal brachytherapy has been advocated as a useful method for control of disease.[9, 10] The PORTEC-2 randomized trial compared external beam (46 Gy in 23 fractions) and vaginal cuff brachytherapy (7 Gy in 3 fractions one week apart, prescribed at ½ cm) for patients with high-intermediate-risk features.[12] Four hundred twenty-seven patients were evaluated. There were similar rates of vaginal control between external beam and vaginal cuff brachytherapy in PORTEC-2. The 5-year rates of vaginal relapse were 1.8% for vaginal brachytherapy and 1.6% for external beam radiotherapy in PORTEC-2, and the 5-year rates for local regional relapse (vaginal relapse and pelvic recurrence) were 5.1% and 2.1%, respectively. Quality of life was significantly better in the vaginal brachytherapy arm.[13] Importantly, patients who had brachytherapy reported better social functioning and lower symptoms scores for diarrhea, fecal leakage, the need to stay close to the toilet, and limitation in daily activities due to bowel symptoms. Sexual functioning did not differ between the 2 arms in PORTEC-2. Also, in PORTEC-2, there were no differences in 5-year overall survival between the two arms.

The Sorbe et al., dose seeking trial in stage I endometrial cancer randomized patients between 2.5 Gy and 5.0 Gy in 6 fractions in 8 days prescribed to a depth of 5 mm from the vaginal surface.[14] The trial included 300 patients, and there was one vaginal failure in each arm for a vaginal failure rate of 0.7%. The biologic effective dose was significantly less in the 2.5 Gy x 6 arm in the Sorbe trial compared to PORTEC-2 (Table1).

Table 1.

# of Fx	Dose Per Fx at Surface (Gy/fx)	Total Dose (Gy)	α/β	EQD2 (Gy)	BED (Gy)	Origin
6	6.8[a]	40.8	3	80	133	Sorbe et al.
			10	57	69	
6	3.4[a]	20.4	3	26	44	Sorbe et al.
			10	23	27	

5	6	30	3 10	54 40	90 48	
3	10	30	3 10	78 50	130 60	
3	9.5[a]	28.5	3 10	71 46	119 56	PORTEC2
3	11	33	3 10	92 58	154 69	
2	10	20	3 10	52 33	87 40	
2	11	22	3 10	62 39	103 46	
2	12	24	3 10	72 44	120 53	

EQD2: equivalent dose in 2Gy/fraction
BED: biological effective dose
[a]Originally prescribed at 0.5 cm depth; surface dose estimated assuming using a 3 cm diameter cylinder.

GOG 249 has been presented in abstract form.[15] This trial included 601 patients with stage I and II endometrial cancer with high-intermediate or high-risk features and compared vaginal cuff brachytherapy and 3 cycles of carboplatin-paclitaxel with pelvic external beam. There were no differences in relapse-free survival (84% versus 82%) or overall survival between the 2 arms at a median follow-up of 24 months.

Since completion of these randomized trials, there has been a decrease in external beam radiotherapy and a concomitant increase in vaginal cuff brachytherapy. In the PORTEC-2 trial, Low Dose Radiation (LDR) was permitted, and 30 Gy was specified at a 5 mm depth at a dose rate of 60-65 cGy per hour. Nevertheless, most patients were treated with high-dose-rate brachytherapy in PORTEC-2. Twenty-one Gy was specified at 5 mm depth in 3 fractions of 7 Gy each given 1 week apart. Target length was the upper half of the vagina. It was recommended to choose the active length prescribing at 5 mm depth, 1 cm shorter than the upper half of the vagina resulting in the 100% isodose surface to cross the vaginal mucosa at 50% of the length. In PORTEC-2, grade 3 mucosal toxicity with narrowing or shortening was rare and was identified in 1.9% in the vaginal brachytherapy group compared to 0.5% in the external beam group. Also in the PORTEC-2 trial, physicians recorded more mild-to-moderate vaginal atrophy in the upper vagina in the vaginal brachytherapy group. At 30 months, atrophy was reported in 40% of the patients in the vaginal brachytherapy group, 18% grade 1 and 21% grade 2, but without narrowing or shortening of the vagina. These atrophic changes were without consequences for vaginal or sexual functioning. However, the difference in atrophy compared to external beam radiotherapy questioned if the dose of the mucosa may be higher than required in the PORTEC-2 study. Additionally, vaginal control was 99.3 % in the Sorbe randomized trial and a significantly lower biologic effective dose was used in the 2.5 Gy x 6 arm.[14] Modern

brachytherapy is now image-guided and planning CT scans allow individual planning of dose depth of bladder, rectum, and bowel if they are within 2-3 mm of the cylinder surface.

Rationale for 2 fractions of vaginal cuff brachytherapy of 11 Gy at the surface

Since publication of PORTEC-2, the most common fraction scheme for adjuvant vaginal brachytherapy for endometrial cancer is 7 Gy prescribed at ½ cm (9.5 Gy at the vaginal surface for a 3 cm cylinder) delivered 3 times.[16] This resulted in a vaginal control rate of >98%. Although the grade 3 vaginal toxicity rate was low at 1.9%, vaginal atrophy was reported in 40% of patients at 30 months. In the Sorbe randomized trial a significantly lower biologic effective dose was used and a vaginal control rate of >99% was achieved. Also, 6 Gy prescribed to the surface delivered 5 times was permitted in GOG 0249, an NCI-sponsored trial. The biologic effective dose with this regimen and the Sorbe et al., regimen of 2.5 Gy x 6 is significantly lower than the dose utilized in PORTEC-2 (Table 1). Two fractions of vaginal cuff brachytherapy of 11 Gy at the surface (7.3 Gy at ½ cm) given weekly is a lower biologic effective dose than utilized in PORTEC-2, yet higher than utilized by Sorbe et al where vaginal control was >99%. Thus, lowering the dose compared to PORTEC-2 should result in more convenience, a lower rate of acute and late side effects, and not significantly impact vaginal control.

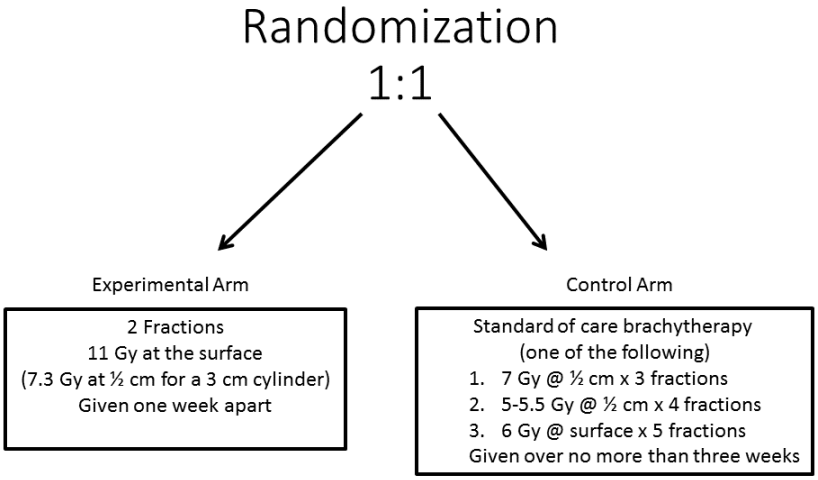
Rationale for short course vaginal brachytherapy

Gynecologic brachytherapy can be a challenging procedure for many women. In one study from the Medical University of Vienna, patients undergoing treatment for cervix cancer feared brachytherapy more than surgery or chemotherapy.[7] Shortening a course of Vaginal Cuff Brachytherapy (VCB) would be convenient for patients. Currently, many women do not receive guideline-suggested treatment especially as they get older. In one study less than half of eligible women received guideline suggested adjuvant radiotherapy.[17] A recent National Cancer Data Base analysis demonstrated that only a third of elderly women with endometrial cancer received standard of care VCB (Torgeson et al unpublished data). Additionally, across the United States there is significant variation in the use of radiotherapy for endometrial cancer.[18] Fewer radiotherapy fractions should permit a higher percentage of women living in rural and frontier areas to receive radiotherapy. Distance from a radiotherapy center has shown to negatively impact compliance for radiation treatment in a number of malignancies.[19] A shorter treatment course will be more patient friendly resulting in greater compliance, be less intensive on radiotherapy resources, be more cost effective, and result in less morbidity. We propose a study of 2 fractions of vaginal cuff brachytherapy of 11 Gy at the surface (7.3 Gy at ½ cm depth) given one week apart. The primary outcome variable is the Global Health Status from the EORTC QLQ-C30. The primary hypothesis is that the Global Health Status from the EORTC QLQ-C30 in experimental arm will be non-inferior to the Global Health Status from the EORTC QLQ-C30 in the control arm. The secondary outcome will evaluate the differences in PROs using the EORTC EN24 for vaginal, bladder, and bowel symptoms, cost effectiveness, toxicities as assessed by CTCAE v5.0, and document patterns of recurrence.

3 STUDY DESIGN

3.1 Description:

This is a phase III, un-blinded, randomized trial comparing an experimental arm and a control arm of vaginal cuff brachytherapy: The experimental arm will treat subjects with 2 fractions of vaginal brachytherapy. The control arm will treat subjects with standard of care vaginal cuff brachytherapy of 3-5 fractions. See schema below: Patients will be randomized 1:1 to the different treatment arms.



3.2 Number of Patients:

108 total patients will be enrolled (54 to each study arm)

3.3 Number of Study Centers

This is a multisite study to be conducted at Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah. Up to 5 additional sites may be included.

3.4 Study Duration

Patient enrollment is expected to take 2 years. Total study duration to be completed in 3 years.

4 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with the enrolling investigators signature in the patient research chart.

Patient No. _____

Patient's Initials: (L,F,M) _____

4.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

4.1.1 _____ Histologically confirmed endometrial carcinoma: endometrioid type, serous, and clear cell to include tumors originating in the cervix, but are primarily located in the uterus, and for whom vaginal cuff brachytherapy is indicated. Carcinosarcoma and other sarcomas are permitted. FIGO stage I and stage II, with one of the following combinations of stage and grade (Appendix A and C):

_____ Stage IA, grade 1 with LVSI, 2, 3

_____ Stage IB, grades 1-3

_____ Stage II, grades 1-3

4.1.2 _____ Patients post hysterectomy and free from residual disease.

4.1.3 _____ WHO/ECOG-performance status 0-2 (Appendix B).

4.1.4 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

4.1.5 Life expectancy of >2 years

4.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

4.2.1 _____ Stages of endometrial carcinoma other than described in Inclusion 4.1.1.

4.2.2 _____ Previous pelvic radiotherapy.

4.2.3 _____ Interval between the hysterectomy and planned start of radiotherapy exceeding 16 weeks.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____ _____ _____

Investigator Signature **Date** **Time**

5 TREATMENT PLAN

5.1 Administration Schedule

Experimental arm: 11Gy will be prescribed to the surface with a minimal treatment length of 3 cm. Two fractions will be given, one week apart. For this instance a week apart indicates an intervening weekend between treatments. Ideally treatments would be 7 days apart. Inspection of the vaginal cuff is required to ensure there is no dehiscence. Dose should be optimized to the cylinder as seen in Figure 1, Appendix D, with dose normalized to 100% at the tip and at the midpoint of the active length. Dose at ½ cm will be recorded also. In cases of fulminant LVSI, the entire vagina may be treated per physician discretion. In most scenarios, the maximal treatment length should not exceed 5 cm. CT simulation shall be performed.

Control arm: One of the following fractions schemes are permitted based on the decision of the treating physician:

- 7 Gy at ½ cm x 3 fractions over no more than three weeks.
- 5-5.5 Gy at ½ cm x 4 fractions over no more than three weeks.
- 6 Gy at the surface of the cylinder x 5 fractions over no more than three weeks.

5.2 Prohibited Concomitant Medications: none

If chemotherapy is going to be used, the preferred sequence is vaginal cuff brachytherapy first.

5.3 Duration of Therapy

Patients in the experimental arm should have treatment completed within two weeks of the first fraction given. Patients in the control arm should have treatment completed within three weeks of the first fraction given.

6 TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting.

6.1 Dose Modifications

No dose modifications will be permitted. If dose to bowel or bladder is felt to be unsafe, evacuation of bowel or bladder is recommended. Treatment may be delayed for up to 2 weeks longer due to medical necessity.

6.2 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

7 STUDY CALENDAR

Examination	Screening[1]	Brachytherapy	Follow-up[6]	Follow-up[6]	Follow-up[6]	Long term Follow-up[6]
			1 month +/- 12 weeks	6 months +/- 12 weeks	12 months +/- 12 weeks	24 and 36 months +/- 12 weeks
Informed consent	X					
Medical history	X					
Eligibility criteria	X					
Vital signs	X		X	X	X	
Physical examination	X		X	X	X	
Pelvic exams	X		X	X	X	
WHO/ECOG performance status	X		X	X	X	
QLQ30 Questionnaire[2]		X	X	X	X	
EN24 Questionnaire[2]		X	X	X	X	
Collection of Cost Data[4]				X		
Collection of Distance Data[7]					X[8]	
Vaginal Cuff Brachytherapy[3]		X				
Adverse Event assessments		X	X	X	X	
Chart Review[5]						X

1. All Pre-study/Screening procedures should be completed less than or equal to 12 weeks before study treatment.
2. Both the QLQ30 and EN24 questionnaires (appendix E and F) should be administered at baseline (prior to the first brachytherapy fraction) and at the 1 month, 6 month, and 12 month follow-up visits.
3. Subjects randomized to the control arm will undergo one of the three treatment options described in section 5 over no more than 3 weeks. Subjects randomized to the experimental arm will undergo the treatment described in section 5 over no more than 2 weeks. See Appendix D for treatment planning and dose reporting form.
4. Collection of cost data for analysis is described in section 8.2
5. The PI will continue to review patient medical charts at 24 and 36 months for disease reoccurrence at one of the following locations: vaginal, pelvic, or distant.

6. In person visits are preferred to allow for exams, so almost all visits will be done on site. If a patient is ill or cannot travel, questionnaires and history may be obtained via telemedicine. Missed exams will be considered deviations.
7. Patient's zip code and the location of the treatment facility will be collected and documented by the study staff.
8. If the information is not collected at the 12 month follow up visit, it will be collected at a subsequent time point or from patient's medical record.

8 CRITERIA FOR EVALUATION AND ENDPOINT

8.1 Primary Objective

Evaluate the non-inferiority of patient HRQOL using the Global Health Status from the QLQ-C30 in the 2 arms one month after treatment.

All patients with a valid baseline and with a follow-up QOL questionnaire at one month post treatment will be included in the analysis. We are accounting for an approximate 5 per cent drop out rate. We anticipate a high compliance rate due to the short follow up interval for the primary endpoint. Patients without valid questionnaires will not be replaced. The baseline questionnaire is considered valid if filled out and dated by the patient before the starting date of trial treatment. Reasons for missing baseline and follow-up questionnaires will be assessed.

For the evaluation of the general quality of life the EORTC (European Organization for Research and Treatment of Cancer) Core questionnaire (QLQ-C30 version 3.0) will be used (Appendix E). The EORTC QLQ-C30 is a multidimensional, cancer-specific quality of life questionnaire developed by the EORTC Study Group on Quality of Life (QOL) for repeated assessments within clinical trials. It is developed in a cross- cultural setting and has been found valid and reliable for quality of life assessments in various cancer populations, irrespective of the specific diagnosis. Optional modules developed for specific diagnostic groups or specific treatment modalities can supplement it. The QLQ-C30 contains five functional scales (physical, cognitive, emotional, social and role functioning), a global health status/quality of life scale, three symptom scales (pain, fatigue and nausea/vomiting), and six single items assessing additional symptoms (dyspnoea, insomnia, loss of appetite, constipation, diarrhoea) and perceived financial impact. For the majority of the QLQ-C30 items a 4-point Likert-type response scale is used. Exceptions are the items for the global quality of life scale (where a 7-point scale is used). All subscale and individual item responses are linearly converted to 0 to 100 scales. A higher score for a functional and global quality of life scales represents a better level of functioning. For the symptom scales and items, a higher score reflects a higher level of symptoms and decreased quality of life.

8.2 Secondary Objectives

Cost-effectiveness (CE) analyses will be explored using cost data (i.e., treatment related costs) for 2 fractions of VCB compared to standard of care brachytherapy (3, 4, or 5 fractions). A payer's perspective will be applied for the analysis because the costs relevant to treatments will be considered. Cost for the intervention will be measured for the cost of therapy. If costs related to the intervention occurs in different years, costs will be adjusted to the most recent year US using the medical component of the Consumer Price Index (CPI). If charged amounts relevant to the treatments are available, they will be converted to costs by using cost-to-charge ratios. We will not compare charges or costs between institutions. There will be no publication of financial data from any individual participating site.

The following data will be collected retrospectively at each patient's six month visit:

- Date of First Service
- Total Professional Fees (reported in US dollars)
- Total Technical Fees (reported in US dollars)

*Subgroup analyses using available cost effectiveness data points, beyond those listed above, may be performed for patients treated at the Huntsman Cancer Institute.

Patient reported HRQOL will be utilized for effect (i.e., effectiveness side). The HRQOL measure will be based on the EORTC QLQ-30 Global Health Status and will be used to calculate Quality Adjusted Life Years (QALYs).

An additional secondary analysis is obtained from EN 24 question 48, “Have you felt less feminine due to your disease or treatment.” The analysis will compare response between the two arms at the one month time point.

8.3 Exploratory objectives

Evaluate CTCAE v5.0 toxicities

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results.

Evaluate and compare doses to organs at risk

Doses to organs at risk including bladder, rectum, sigmoid colon, and urethra, and target in the two trial arms will be evaluated from CT data sets without contours that will be sent to HCI in an anonymized fashion and compared to each other. Artificial intelligence approaches to aid in contouring will be considered. Additionally, the dose to prescribed target in each group will be calculated.

Compare total distance traveled to the cancer center for study related visits.

Total distance traveled, calculated by multiplying number of study visits by twice the distance to the cancer center. The distance to the cancer center will be calculated as the distance from the patient's zip code and the cancer center zip code.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician’s assistant or nurse practitioner).

Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained.

Compare local recurrence and document patterns of recurrence

Local recurrence will be assessed by pelvic exam. Time points for evaluation include screening, one, six, and twelve months via study visits, and via chart review at twenty-four, and thirty-six months post treatment. Imaging may be used at the physician’s discretion depending on the subject’s symptoms. Recurrences in the 2 arms will be assessed according to site: vaginal, pelvic, or distant.

Report vaginal, bowel, and bladder symptoms on HRQOL using the EORTC EN24 the two treatment arms.

In addition to the QLQ C-30 core questionnaire, the EORTC module for endometrial cancer EN24 will be used to descriptively report values for the following symptom scores; **“**Sexual/vaginal problems," "Gastrointestinal symptoms," and "Urological symptoms." Additional questions regarding sexual symptoms and distress will also be reported.

8.4 Stopping Rules

If four discrete subjects present with grade 3 vaginal, rectal, or bladder toxicities considered related to brachytherapy in the experimental arm, it will result in trial closure.

9 STATISTICAL CONSIDERATIONS

Primary Endpoint

The primary objective is to evaluate the non-inferiority of patient Health Related Quality of Life (HRQOL) in the Experimental arm compared to the Control arms one month after treatment. The primary efficacy variable is the

Global Health status from the EORTC QLQ-C30. The EORTC QLQ-C30 is a multidimensional, cancer-specific quality of life questionnaire developed by the EORTC Study Group on Quality of Life (QOL) for repeated assessments within clinical trials. All patients with valid non-missing baseline and one month follow up Global Health Status will be included in the analysis. See below for handling of missing items.

The primary hypothesis is that the Global Health Status is non-inferior in the Experimental Arm compared to the Control Arm. Let μE and μC be the mean Global Health status in the Experimental and Control Arms respectively. The null hypothesis (H0) and alternative hypothesis (H1) are

$$H0: \mu E - \mu C \leq -15 \text{ and } H1: \mu E - \mu C > -15$$

A two sample t test will be used for the primary analysis. As a sensitivity analysis we will be use analysis of covariance with Global Health Status at one month post therapy as Gaussian response variable, treatment group as a fixed effect and baseline Global Health Status as a continuous adjustment variable.

Handling of missing items in the Global Health Status

If at least half the items in the Global Health Status are present then the Global Health Raw Score will be calculated as the average of the items that are present. This method is effectively equivalent to replacing missing items by the average of the items that are present, and is a standard method for treating summary scores with missing items. If more than half the items are missing the Global Health Status will be treated as missing. Subjects with missing Global Health Status will be excluded from the primary analysis. This method provides valid estimates provided data is missing at random (MAR). Sensitivity analyses may be performed with multiple imputation used to impute missing data.

Additional exploratory analysis of the Primary Endpoint

Analysis of the Global Health Status at all time points (baseline, 1 month, 6 month, and 12 months) will use a normal repeated measures model with unstructured covariance matrix. Subjects with missing Global Health Status will be excluded from the analysis. Multiple imputation may be used in a sensitivity analysis. Change from baseline to each of the follow up times will be the focus of the exploratory analysis.

Secondary Endpoints

Vaginal HRQOL evaluation using question 48 of the EORTC EN24: “Have you felt less feminine due to your disease or treatment”. This item has a four point scale. Ordinal logistic regression will be used to analyze this question, with one month value as outcome variable, treatment arm as primary predictor, and the baseline value as covariate. A non-inferiority analysis will be performed with margin equal to 6.1 points, which represents approximately ½ standard deviation. Additional exploratory logistic regression analyses will include the values at all time points (baseline, one month, 6 months and 12 months).

Cost effectiveness. Once parameters are computed: 1) mean differences in cost and effect between treatments, 2) variances for differences in costs and effects, and 3) covariance between effectiveness and cost difference, the incremental cost-effectiveness ratio (ICER) or incremental net benefits summarizing the monetary value of the intervention will be calculated.

$$ICER = \frac{Cost_{2\ Fractions} - Cost_{standard\ care}}{Effect_{2Fractions} - Effect_{standardcare}}$$

A CE acceptability curve will be used to quantify and graphically depict uncertainty in the analysis. To consider uncertainty in parameters, probabilistic sensitivity analysis utilizing Monte Carlo simulation (i.e., second-order simulation) will be conducted. To reflect the uncertainties in costs and in effects, a gamma distribution for costs and a normal distribution for effects will be adopted. And univariate analyses will be conducted to consider an uncertainty of one parameter at a time over a range of 95% confidence interval in cost and effectiveness measures.

Exploratory Endpoints

We will descriptively evaluate patient reported HRQOL regarding bowel, bladder and vaginal symptoms using the validated instrument, EORTC QLQ- EN 24. We will report means, standard deviations, ranges and 95% confidence interval for "Sexual/vaginal problems", "Gastrointestinal symptoms", and "Urological symptoms" symptom scales. All these outcomes will be reported separately for each treatment arm. Doses to organs at risk (including bladder, rectum, sigmoid colon, and urethra) and prescribed target in the two arms of the trial will be analyzed using descriptive statistics such as mean, standard deviation and 95% confidence interval. Comparisons between arms will use exploratory t-tests or non-parametric Wilcoxon tests as appropriate.

Exploratory endpoints will also include CTCAE v5.0 toxicities and patterns of recurrence in the two arms. Recurrences in the two arms will be tabulated as vaginal, pelvic, or distant. We will report counts, proportions, and exact 95% confidence intervals for adverse events. Kaplan-Meier curves and associated confidence intervals will be used to analyze time to recurrence.

The mean, median, standard deviation and interquartile range of total distance traveled will be reported for each study arm. A Wilcoxon rank-sum test will be used to compare the total distance traveled between the arms.

Sample Size Evaluation

We base the sample size on the precision of estimation of the Global Heath Status from QLQ-C30. The hypothesis to be tested is that the mean Global Health Status will be the same or higher one month after treatment in the Experimental Arm compared to the Control Arm. The EORTC QLQ-C30 reference values manual gives the means and SD of the Global Health Status in genitourinary cancer patients as 62.6 ±22.2 points. We assume a standard deviation of 22.2 points for power calculations. Additional assumptions are 1:1 randomization to one of two groups, a true difference of 0 points, a Gaussian response variable, a non-inferiority margin of 15 points, alpha = 0.025 (one sided), and the use of a two sample *t*-test for the primary analysis. A non-inferiority margin of 15 points was chosen for this trial based on a combination of scientific and practical considerations. In a survey of 30 clinical trials, the definition of a clinical meaningful change in quality of life questionnaire data varies widely, with margins up to 10-15 point required for clinical significance (Cocks KT, et al 2008). With these assumptions a total evaluable sample size of 96 will provide 90% power. The planned sample size of 108 randomized equally to two arms allows for a dropout rate of approximately 10%.

10 REGISTRATION GUIDELINES

Patients must meet all of the eligibility requirements listed in Section 4 prior to registration.

Study related screening procedures can only begin once the patient has signed a consent form. Patients must not begin protocol treatment prior to registration.

Treatment should start less than or equal to 10 business days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

Treatment with experimental or control arms will be assigned at the time of enrollment. A randomization code will be created by a biostatistician and given to the Research Compliance Office to maintain and assign treatment to each patient as they are enrolled.

11 DATA REPORTING

11.1 Source documents and access to source data

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. CRFs can be source documents as well as the medical record.

11.2 Quality assurance

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by HCI's RCO, and inspection by local and regulatory authorities.

11.3 Data collection and management responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into OnCore, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

11.4 Study records retention

Study documents should be retained for a minimum of 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the PI, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.5 Monitoring and Auditing

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Centralized monitoring will occur after the first 2, 5, and 10 patients are accrued and treated; then monitoring will occur throughout the trial until 30 days after the last patient has been treated twice yearly. Monitoring will be centralized, with random review of 25% of data, including data reporting and research sample acquisition.

Audits are performed independent of study monitoring. An initial audit will be conducted approximately one year after enrollment begins and annually thereafter. Audits may be conducted more frequently as requested by the Data and Safety Monitoring Committee (DSMC), RCO management, the Principal Investigator (PI), or Clinical Trials Office (CTO) depending on type and complexity of the trial, the level of risks to the trial subjects, and any identified problems or issues. Audit results will be reported to the HCI IRB as required.

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

12 SPECIAL INSTRUCTIONS

12.1 Dosimetric review

Treatment length and active length will be recorded for all patients. CT simulation shall be performed. Dose should be optimized to the cylinder as seen in Figure 1, Appendix D with dose normalized to 100% at the tip and at the midpoint of the active length. Dose at ½ cm will be recorded.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

13.2 Institutional Review

Study will be approved by the Institutional Review Board of University of Utah.

13.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a multicenter, phase III study classified as high risk per the NCI-approved DSM plan. Each high-risk study will be assigned a physician member of the DSMC as medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). Specific notifications will also be issued when a dose-limiting toxicity is encountered and when the MTD dose is defined. Approval of the medical monitor is required for all dose escalations. All serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly. The full committee will also review all toxicities for patients on treatment and less than or equal to 30 days of their last treatment on a quarterly basis.

Each high-risk study will also be assigned a dedicated research compliance officer who will monitor the trial. High-risk studies will be monitored by RCO personnel after the first patient is enrolled and every three months thereafter during active enrollment. The RCO monitor will review the study status and summarize enrollment, toxicities, SAEs, dose escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments that increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. High-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then quarterly thereafter.

An initial audit of high-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of high-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

13.4 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting.

13.4.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Collection of adverse events will begin at start of brachytherapy and continue for 12 months after the start of brachytherapy.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

Adverse events should be evaluated to determine:

1. The severity grade based on CTCAE v.5.0 (grade 1-5).
2. Its relationship to the study treatment(s) (definite, probable, possible, unlikely, not related).
3. Its duration (start and end dates or if continuing at final exam).
4. Action taken (no action taken; study treatment temporarily interrupted; study treatment permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization).
5. Whether it constitutes an SAE.

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 6.1 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

All adverse events will be immediately recorded in the patient research chart.

13.4.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded.

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control).
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.

SAE evaluation will begin after the first treatment and will continue until the first follow up visit, 28 days (+/- 14) after the completion of study treatment. If the patient is unable to attend the first follow up visit, the SAE reporting period will be extended to 56 days after the completion of study treatment.

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

13.5 **SAE Reporting Requirements**

SAEs must be reported to the DSMC, the FDA, and the IRB, according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to HCI-RCO@utah.edu less than or equal to 1 business day of first knowledge or notification of event.

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for this study.
- The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.

For multisite studies the HCI DSMC will notify all participating sites of all unexpected and related SAEs via the Research Compliance Office. The RCO will also notify all investigators at remote clinical sites participating in a multisite trial of any other safety update, including external safety reports, manufacturer's reports and updates to the investigator's brochure.

FDA Notifications:

- This study is IND exempt; therefore, there are no SAE reporting requirements to the FDA.

IRB Notification:

- Events meeting the University of Utah IRB or local IRB reporting requirements will be submitted per local guidelines.

13.6 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

13.7 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The sponsor requires the **prompt reporting** to HCI RCO of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance
- Participating external sites should follow their local IRB requirements regarding the reporting of protocol deviations

13.8 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

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15 APPENDICES

APPENDIX A. FIGO STAGING FIGO 2009 staging for carcinoma of the endometrium

Stage I*	**Tumor confined to the corpus uteri**
stage IA*	No or less than half myometrial invasion
stage IB*	More than half myometrial invasion
Stage II*	**Tumor invades cervical stroma, but does not extend beyond the uterus****
Stage III*	**Local and/or regional spread of the tumor**
stage IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexae
stage IIIB*	Vaginal and/or parametrial involvement
stage IIIC*	Metastasis to pelvic and/or para-aortic lymph nodes
IIIC1*	Positive pelvic lymph nodes
IIIC2*	Positive para-aortic lymph nodes with or without pelvic nodes
Stage IV*	**Tumor invades bladder and/or bowel mucosa, and/or distant metastasis**
stage IVA*	Tumor invasion of bladder and/or bowel mucosa
stage IVB*	Distant metastasis, including intra-abdominal metastases and/or inguinal lymph nodes

Either G1, G2 or G3 (G is FIGO grade) Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II Positive cytology has to be reported separately, without changing the stage.

APPENDIX B. PERFORMANCE STATUS (WHO-ECOG)

Grade 0 Fully active, able to carry out all normal (pre-disease) activity without restriction

Grade 1 Restricted in physically strenuous activity but ambulatory and able to carry out light work, e.g., light house work, office work

Grade 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

Grade 3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

Grade 4 Completely disabled; cannot carry out any self-care; totally confined to bed or chair

APPENDIX C. HISTOLOGIC CLASSIFICATION AND GRADING SYSTEM International Society of Gynecologic Pathologists Classification for Endometrial Carcinomas

- Endometrioid adenocarcinoma
- Mucinous carcinoma
- Serous carcinoma
- Clear-cell carcinoma
- Squamous carcinoma
- Undifferentiated carcinoma
- Mixed types
- Miscellaneous carcinoma
- Metastatic carcinoma

Histologic classification of mixed carcinomas: Mixed serous and endometrioïd carcinomas and mixed clear cell and endometrioid carcinomas should be classified as serous or clear cell carcinomas if they contain at least 10% of a serous or clear cell component, respectively, and otherwise be classified as endometrioid.

International Federation of Gynecology and Obstetrics (FIGO) and Armed Forces Institute of Pathology (AFIP) histologic grading system

G1 tumors have 5% or less of a nonsquamous or nonmorular solid growth pattern
G2 tumors have 6% to 50% of a nonsquamous or nonmorular solid growth pattern
G3 tumors have more than 50% of a nonsquamous or nonmorular solid growth pattern
A higher degree of nuclear atypia (in comparison with the architectural grade) raises the grade of a G1 or G2 tumor by 1.
Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.
Where the treatment plan after hysterectomy is radiation with vaginal cuff brachytherapy without external beam, uterine sarcomas may be included.

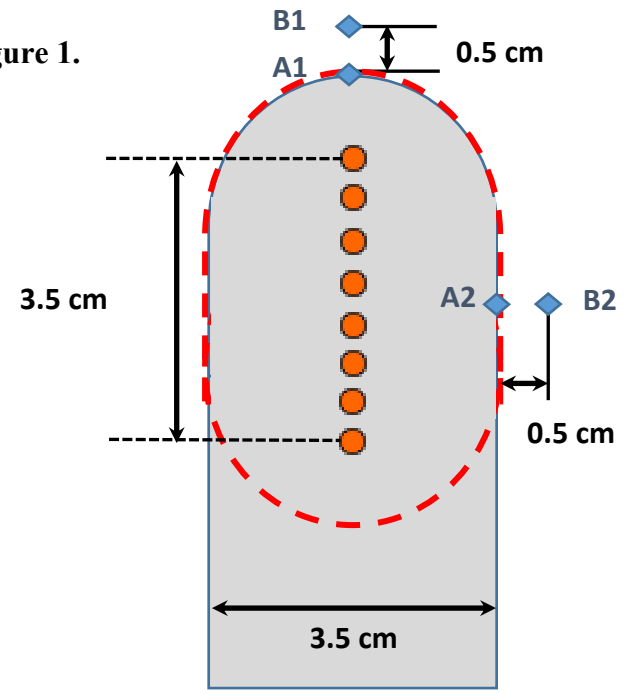
APPENDIX D. VAGINAL BRACHYTHERAPY TREATMENT PLANNING AND DOSE REPORTING FORM

Figure 1 below shows a coronal schematic view of a standard vaginal cylindrical applicator, 3.5 cm in diameter, and 3.5 cm active length. Active length is the distance between the first (most cranial) and the last active source positions. All applicator points A are at the surface of the applicator. Applicator points A1 and A2 are located at the tip and on the side of the cylinder surface, respectively. Applicator points B1, and B2 are at 0.5 cm cranial and parallel to the central axis. Point A2 is half way the active length which, in this case, is 1.75 cm. Depending on the anisotropy of the source used, point A1 can receive a (5-10%) lower dose than the prescribed dose and point A2 a (5-10%) higher dose. The mean dose to points A1 and A2 should be 100%. **A2 and B2 should be measured at the half way point of the active length.**

Planned Treatment	**Do you provide separate plans for each insertion?**
☐ Experimental Arm: 11 Gy at surface x 2 Fractions ☐ Standard of Care Arm: 7 Gy at 0.5 cm x 3 Fractions ☐ Standard of Care Arm: 5-5.5 Gy at 0.5 cm x 4 Fractions ☐ Standard of Care Arm: 6 Gy at surface x 5 Fractions	☐ Yes* ☐ No *If yes, provide a planning form for each fraction

Treatment Start Date	**A1 Dose**	**A2 Dose**
	cGy	cGy
B1 Dose	**B2 Dose**	**Active Treatment Length**
cGy	cGy	cm
Additional Treatment Dates		

Figure 1.



Patient Initials: _____

Study ID: _____

Investigator Signature:

_____

Date: _____

APPENDIX E. QUALITY OF LIFE QUESTIONNAIRE (ENGLISH)

EORTC QLQ-C30 (version 3)

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

Patient Study #: _____

Please fill in your initials: _____

Your birthdate (Day, Month, Year):_____

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

		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 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
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

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
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
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

APPENDIX F. EORTC QLQ – EN24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems.

During the past week:	Not at all	A little	Quite a bit	Very much
1. Have you had swelling in one or both legs?	1	2	3	4
2. Have you felt heaviness in one or both legs?	1	2	3	4
3. Have you had pain in your lower back and / or pelvis?	1	2	3	4
4. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
5. Have you passed urine frequently?	1	2	3	4
6. Have you had leaking of urine?	1	2	3	4
7. Have you had pain or a burning feeling when passing urine?	1	2	3	4
8. When you felt the urge to move your bowels, did you have to hurry to get to the toilet?	1	2	3	4
9. Have you had any leakage of stools?	1	2	3	4
10. Have you been troubled by passing wind?	1	2	3	4
11. Have you had cramps in your abdomen?	1	2	3	4
12. Have you had a bloated feeling in your abdomen?	1	2	3	4
13. Have you had tingling or numbness in your hands or feet?	1	2	3	4
14. Have you had aches or pains in your muscles or joints?	1	2	3	4
15. Have you lost hair?	1	2	3	4
16. Has food and drink tasted differently from usual?	1	2	3	4

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
17. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
18. Have you felt less feminine as a result of your disease or	1	2	3	4

During the past 4 weeks:	**Not at all**	**A little**	**Quite a bit**	**Very much**
19. To what extent were you interested in sex?	1	2	3	4
20. To what extent were you sexually active?	1	2	3	4
Answer these questions only if you have been sexually active during the past 4 weeks:				
21. Has your vagina felt dry during sexual activity?	1	2	3	4
22. Has your vagina felt short and / or tight?	1	2	3	4
23. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
24. Was sexual activity enjoyable for you?	1	2	3	4

Appendix G EORTC QLQ-C30 Spanish Version SPANISH (US)

EORTC QLQ-C30 (versión 3)

Estamos interesados en algunas cosas sobre usted y su salud. Por favor, conteste todas las preguntas usted mismo/a marcando uncirculo el número que major se aplique a su caso. No hay respuestas "correctas" ni "incorrectas". La información que nos proporcione se mantendrá estrictamente confidencial.

Por favor, escriba sus iniciales: _____

Su fecha de nacimiento (día, mes, año): _____

La fecha de hoy (día, mes, año): 31_____

	Para nada	Un poco	Bastante	Extremada-mente
1. ¿Tiene alguna dificultad para realizar actividades que requieran un gran esfuerzo como llevar una bolsa de compras pesada o una maleta?	1	2	3	4
2. ¿Tiene alguna dificultad para salir a caminar por largo tiempo?	1	2	3	4
3. ¿Tiene alguna dificultad para salir a caminar por corto tiempo fuera de la casa?	1	2	3	4
4. ¿Necesita quedarse en cama o en una silla durante el día?	1	2	3	4
5. ¿Necesita ayuda para comer, vestirse, bañarse o ir al baño?	1	2	3	4

Durante la última semana:

	Para nada	Un poco	Bastante	Extremada-mente
6. ¿Estuvo limitado/a al hacer su trabajo u otras actividades diarias?	1	2	3	4
7. ¿Estuvo limitado/a al hacer sus pasatiempos u otras actividades de tiempo libre?	1	2	3	4
8. ¿Le faltó el aire?	1	2	3	4
9. ¿Ha tenido dolor?	1	2	3	4
10. ¿Necesitó descansar?	1	2	3	4
11. ¿Ha tenido problemas para dormir?	1	2	3	4
12. ¿Se ha sentido débil?	1	2	3	4
13. ¿Le ha faltado el apetito?	1	2	3	4
14. ¿Ha sentido náuseas?	1	2	3	4
15. ¿Ha vomitado?	1	2	3	4
16. ¿Ha estado estreñido/a?	1	2	3	4

Por favor, continúe en la página siguiente

SPANISH (US)

Durante la última semana:	**Para nada**	**Un poco**	**Bastante**	**Extremada-mente**
17. ¿Ha tenido diarrea?	1	2	3	4
18. ¿Estuvo cansado/a?	1	2	3	4
19. ¿Interfirió el dolor en sus actividades diarias?	1	2	3	4
20. ¿Ha tenido dificultad para concentrarse en cosas como leer el periódico o ver televisión?	1	2	3	4
21. ¿Se sintió tenso/a?	1	2	3	4
22. ¿Se preocupó?	1	2	3	4
23. ¿Se sintió irritable (enojado/a)?	1	2	3	4
24. ¿Se sintió deprimido/a?	1	2	3	4
25. ¿Ha tenido dificultad para recordar cosas?	1	2	3	4
26. ¿Ha interferido su condición física o su tratamiento médico en su vida familiar?	1	2	3	4
27. ¿Ha interferido su condición física o su tratamiento médico en sus actividades sociales?	1	2	3	4
28. ¿Le ha causado su condición física o su tratamiento médico dificultades económicas?	1	2	3	4

Para las siguientes preguntas, por favor, marque con un círculo el número del 1 al 7 que mejor se aplique a su caso

29. ¿Cómo calificaría su salud en general durante la última semana?

1 2 3 4 5 6 7

Muy mala Excelente

30. ¿Cómo calificaría su calidad de vida en general durante la última semana?

1 2 3 4 5 6 7

Muy mala Excelente

Appendix H EORTC QLQ –EN24 Spanish Translation

SPANISH (US)

EORTC QLQ – EN24

Las pacientes a veces dicen que tienen los siguientes síntomas o problemas. Por favor, indique hasta qué punto ha experimentado estos síntomas o problemas.

Durante la última semana:	**Para nada**	**Un poco**	**Bastante**	**Muchí-simo**
1. ¿Tuvo hinchazón en una o ambas piernas?	1	2	3	4
2. ¿Sintió pesadez en una o ambas piernas?	1	2	3	4
3. ¿Tuvo dolor en la parte baja de la espalda y/o en la pelvis?	1	2	3	4
4. Cuando sintió la necesidad urgente de orinar, ¿tuvo que ir de prisa al baño?	1	2	3	4
5. ¿Orinó con frecuencia?	1	2	3	4
6. ¿Tuvo pérdidas de orina involuntarias?	1	2	3	4
7. ¿Tuvo dolor o ardor al orinar?	1	2	3	4
8. Cuando sintió la necesidad urgente de defecar, ¿tuvo que ir de prisa al baño?	1	2	3	4
9. ¿Tuvo pérdidas de heces involuntarias?	1	2	3	4
10. ¿Se sintió molesta por haber tenido flatulencia (expulsar gases)?	1	2	3	4
11. ¿Sintió retortijones (cólicos) en el abdomen?	1	2	3	4
12. ¿Tuvo sensación de hinchazón en el abdomen?	1	2	3	4
13. ¿Sintió hormigueos o adormecimiento en las manos o en los pies?	1	2	3	4
14. ¿Sintió dolores o molestias en los músculos o articulaciones (coyunturas)?	1	2	3	4
15. ¿Se le cayó algo de pelo?	1	2	3	4
16. ¿Sintió que el sabor de la comida y la bebida es diferente de lo normal?	1	2	3	4

Por favor, continúe en la página siguiente

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SPANISH (US)

Durante la última semana:	**Para nada**	**Un poco**	**Bastante**	**Muchí-simo**
17. ¿Se sintió menos atractiva físicamente a consecuencia de su enfermedad o tratamiento?	1	2	3	4
18. ¿Se sintió menos femenina como consecuencia de su enfermedad o tratamiento?	1	2	3	4

Durante las últimas 4 semanas:	**Para nada**	**Un poco**	**Bastante**	**Muchí-simo**
19. ¿Hasta qué punto estuvo interesada en actividad sexual?	1	2	3	4
20. ¿Hasta qué punto tuvo una vida sexual activa?	1	2	3	4
Conteste las siguientes preguntas solo si usted estuvo activa sexualmente durante las últimas 4 semanas:				
21. ¿Sintió sequedad vaginal durante la actividad sexual?	1	2	3	4
22. ¿Sintió la vagina acortada y/o estrecha?	1	2	3	4
23. ¿Tuvo dolor durante el coito u otra actividad sexual?	1	2	3	4
24. ¿Le resultó placentera la actividad sexual?	1	2	3	4